CORSO DI FORMAZIONE AIDS PER DIRIGENTI MEDICI – XII ANNUALITA' – 2014

NUOVE TERAPIE ANTI HV NELLE COINFEZIONI

Dott. Salvatore Martini

UOS Diagnosi e Terapia Immunodeficienza Acquisita

COINFEZIONI HIV/VIRUS EPATITICI

- EPIDEMIOLOGIA DELLE COINFEZIONE HIV/HBV
- HAART IN PZ CON COINFEZIONE HIV/HBV
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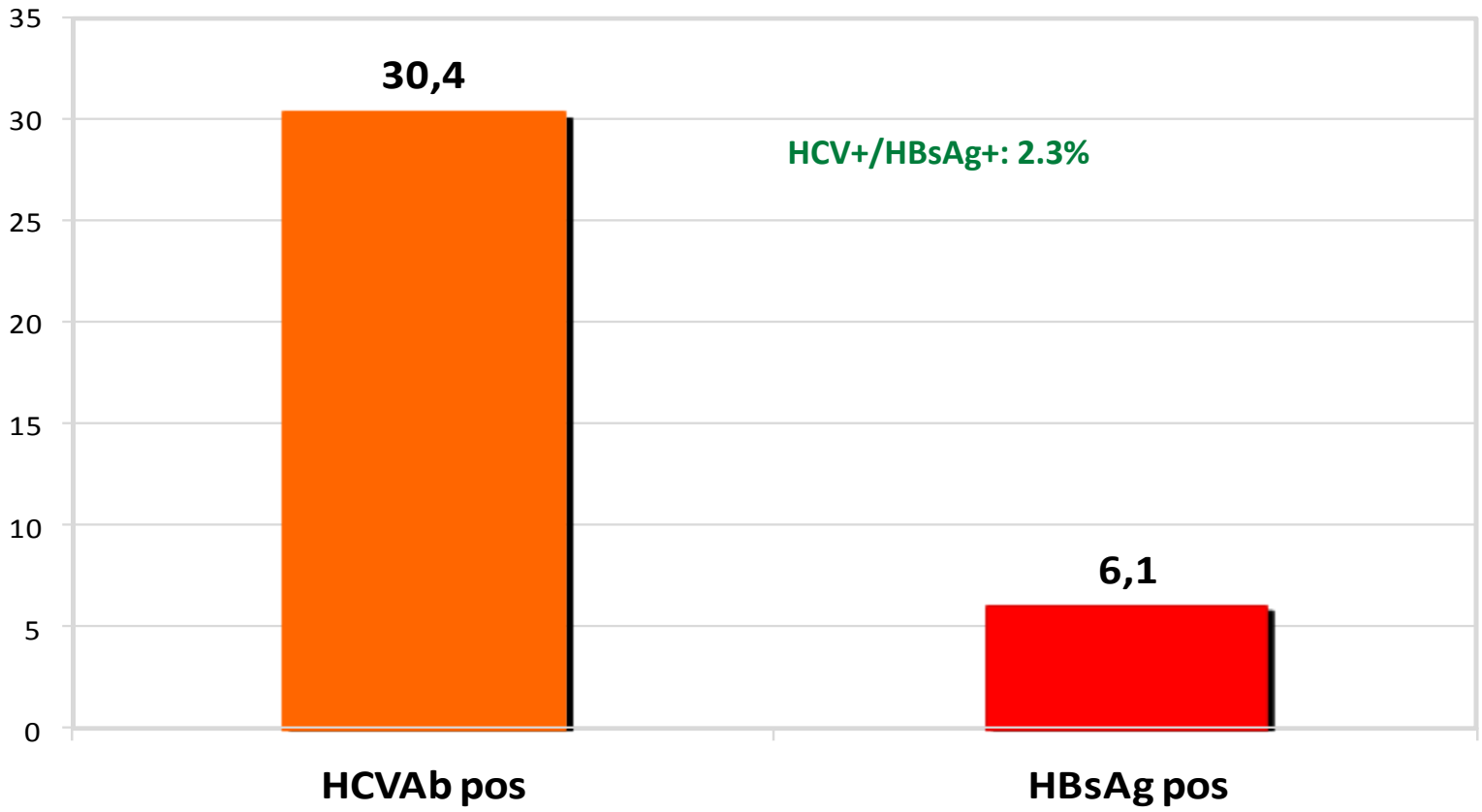
- HAART IN PZ CON COINFEZIONE HIV/HCV
- HAART E NUOVI DAA ANTI-HCV
- OPZIONI FUTURE

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

HBsAg and HCV Ab positivity in 10,665 patients



for 2014, 6 months

Icona Foundation cohort: data at enrolment on 11,978 patients (ctd)

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

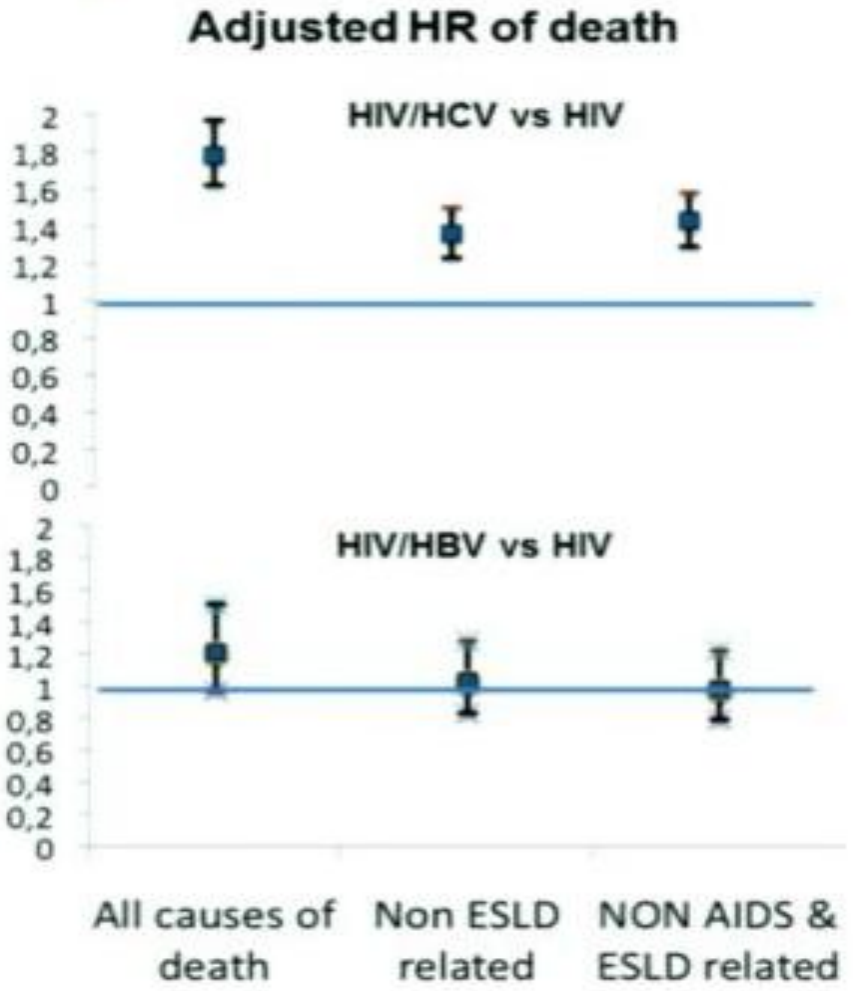
		1997-1999	2000-2002	2003-2005	2006-2008	2009-2010	2011-2014	TOTAL
	CD4+/mmc, median	424	382	376	384	396	360	402
	HIV-RNA cps/mL, median	19800	28605	29400	24155	27455	23542	26525
	AIDS at enrolment, n (%)	472 (11.7%)	200 (13.8%)	106 (16.3%)	108 (12.1%)	111 (8.7%)	302 (8.1%)	1299 (10.8)
	Known HIV seroconversion, n (%)	940 (23.4%)	305 (21.1%)	180 (27.6%)	194 (21.9%)	400 (30.8%)	1071 (29.0%)	3090 (25.7)
	HCVAb+, %	**50.1%**	**29.0%**	**21.8%**	**12.7%**	**8.3%**	**7.8%**	**30.4%**
	HBsAg+, %	**5.8%**	**5.2%**	**5.2%**	**5.2%**	**3.7%**	**3.6%**	**6.1%**
Reason for being naive:	Newly diagnosed	1067 (26.5%)	727 (50.4%)	381 (58.6%)	472 (53.4%)	1251 (50.7%)	1411 (55.9%)	5309 (44.3)
	Treatment not reccomended by guidelines	1499 (37.3%)	379 (26.3%)	145 (22.3%)	227 (25.7%)	340 (26.2%)	682 (18.4%)	3272 (27.3)
	First contact to care	621 (15.4%)	206 (14.3%)	80 (12.3%)	135 (15.2%)	188 (14.4%)	600 (16.2%)	1830 (15.2)
	Patient decision	568 (14.1%)	88 (6.1%)	26 (4%)	24 (2.7%)	48 (3.7%)	126 (3.4%)	880 (7.3)
	Perceived poor adherence	237 (5.8%)	26 (1.8%)	16 (2.4%)	13 (1.4%)	36 (2.7%)	43 (1.1%)	371 (3.0)
	Not available	8 (0.1%)	9 (0.6%)	1 (0.1%)	9 (1.1%)	64 (2.5%)	193 (7.6%)	284 (2.3)
	Clinical contraindication	17 (0.4%)	5 (0.3%)	1 (0.1%)	3 (0.3%)	2 (0.1%)	4 (0.1%)	32 (0.2)

Hepatitis C in HIV: from screening to treatment, a revolution

Dr Karine Lacombe, M.D., PhD
INSERM UMR-S1136, IPLESP
SMIT St Antoine, AP-HP
Université Pierre et Marie Curie, Paris VI

HCV within 30 years of HIV infection: clinical consequences

- Retrospective, longitudinal analysis of the French National Hospital DRG-based information system.
- Of 69,913 HIV-infected patients 2,366 deaths occurred in 247,484 patient-years.
- Overall mortality was higher in 8,283 (7.5%) HIV/HCV patients vs to 59,476 (2.8%) HIV patients (HR 1.79,P<0.0001) & in 2,154 (3.9%) HIV/HBV patients (HR 1.21,P=0.09)
- Non-liver-related mortality as well as non-liver, non-AIDS-related mortality were higher in HIV/HCV coinfected patients (HR 1.36, P<0.0001 and HR 1.43, P<0.0001, respectively).



Mallet V. CROI 2014

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Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali
e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

Novembre 2013

Forza delle raccomandazioni e livello delle evidenze

Le raccomandazioni sono state accompagnate dalla specifica del livello di forza della raccomandazione e del livello di qualità della evidenza a supporto delle stesse, basato su un *grading* espresso dalle lettere A, B, e C (forza della raccomandazione, rispettivamente "Fortemente raccomandato", Moderatamente raccomandato", "Opzionale") e dai numeri I, II, e III (livello delle evidenze, rispettivamente "I dati sono ricavati da almeno uno studio controllato e randomizzato con potenza sufficiente o da metanalisi di studi controllati", "I dati sono ricavati da ricerche non randomizzate o da studi osservazionali di coorte", "Raccomandazione basata su rassegne casistiche o sul consenso di esperti").

Tabella 2 - Quando iniziare la Terapia antiretrovirale di combinazione (cART) in corso di epatiti croniche da HBV e HCV

T CD4+	MOTIVAZIONE	AZIONE	OBIETTIVO	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
< 500 cellule/μL (indipendentemente dalla viremia)	Accelerazione progressione di epatiti croniche sia da HBV sia da HCV.	Inizio della cART.	Ottenere T CD4+ > 500 cellule/μL e HIV-RNA soppresso.	• Se CD4+ ≤ 500 cellule/μL: [AII] • Se CD4+ ≤ 350 cellule/μL: [AI]	[5, 7-12]
> 500 cellule/μL	• Pro inizio: effetto diretto di HIV sulla progressione della fibrosi epatica. • Contro inizio: esposizione prolungata a cART associata a più elevata mortalità (per epatopatia o a accelerata progressione della malattia epatica).	Inizio della cART.	Ottenere HIV-RNA soppresso.	[BII]	[12 -18]
• Nei pazienti in cui è indicata la terapia dell'epatite cronica B, è consigliabile iniziare una cART indipendentemente dal numero di T CD4+ e dagli altri parametri, somministrando Tenofovir come parte di un regime antiretrovirale attivo, in alternativa, in presenza di particolari pattern di resistenza di HBV, tenofovir con un altro nucleosidico attivo su HBV (Telbivudina o Entecavir) in aggiunta ad altri due antiretrovirali [5,7-12, 41] [AII].					

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Tabella 4 – Avvertenze per la gestione dei fallimenti e strategie alternative

PAZIENTI CON...	AVVERTENZE	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Coinfezione da HBV	L'interruzione della somministrazione farmaci antiretrovirali con attività su HBV deve essere attuata solo quando strettamente necessaria e deve essere seguita da un attento *follow up* in tutti i pazienti portatori di HBsAg o di anticorpi anti-HBc per il rischio di riattivazioni anche fatali, specie quando il paziente presenti una malattia epatica avanzata.	[AII]	[42,43]
Indicazione a terapia anti-HBV	• Qualora si debba interrompere una terapia con tenofovir per tossicità o per motivi legati alla ricerca della migliore terapia anti-HIV possibile, occorre somministrare adefovir ai dosaggi efficaci per controllare HBV [AIII]. • Evitatare l'impiego di telbivudina o entecavir come unico farmaco anti-HBV specie in soggetti già esposti a XTC per l'elevato rischio di resistenza.	[AII] [AII]	[5,7,9-11] [5,7,9-11]

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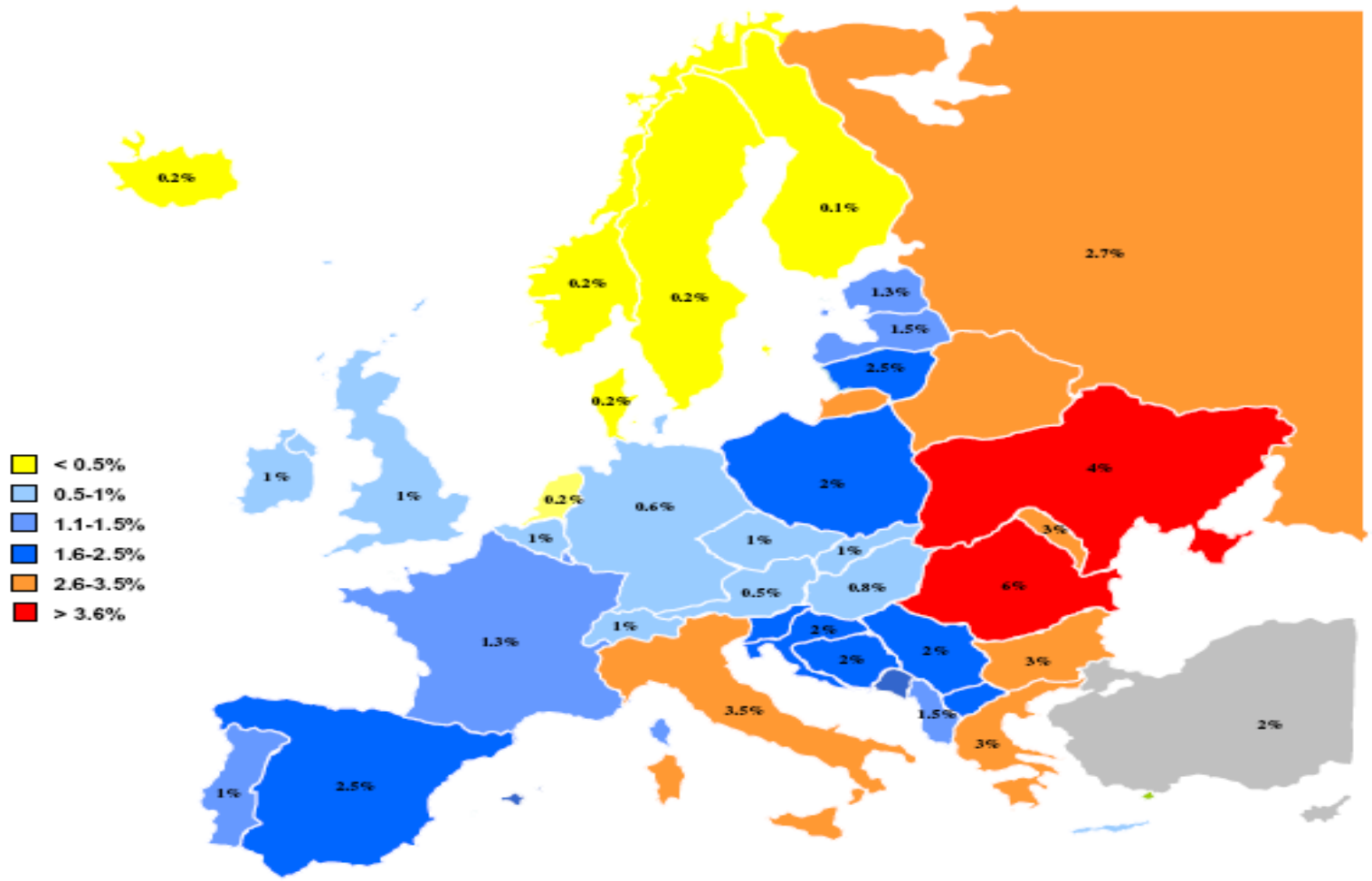
HCV Chronic infection: an European and Italian problem….

Europe has a significant population that is HCV/HIV co-infected. Though they represent a small proportion of all HCV-positives, they tend to have more advanced liver injury and (to date) have exhibited disappointing response rates to antiviral therapy.

Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection. (EASL guidelines 2014).



In Italia: HCV

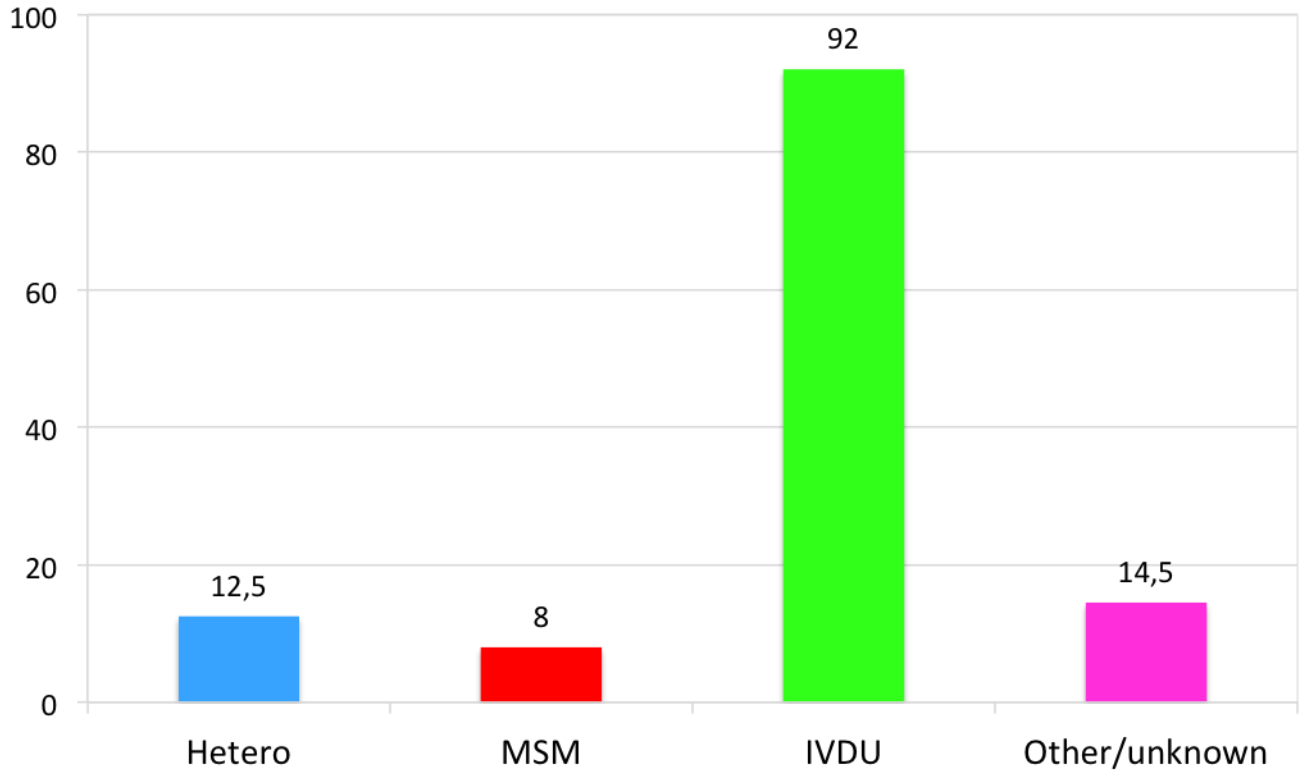
In Italia non è mai stato condotto uno studio di prevalenza dell'infezione da virus dell'epatite C rappresentativo dell'intera popolazione

Dagli studi (locali) disponibili, emerge che:

- Prevalenza di HCV RNA è >3% nei soggetti nati prima del 1950 e aumenta progressivamente con l'età, mentre è considerevolmente più bassa nelle generazioni più giovani, in assenza di tossicodipendenza: > 1.500.000 di infetti
- Prevalenza è più alta nelle aree Meridionali e Insulari rispetto a Centro e del Nord, con prevalenza che varia dall'8% al 2%.
- HCV è la causa principale di epatiti croniche, cirrosi, tumori epatici, trapianti di fegato (>65%).
- Aumento popolazione immigrata (dal 2004 al 2010 più che raddoppiata: attualmente circa 10% della popolazione) con problematiche sociali, culturali e sanitarie (ad esempio molte persone provengono da Paesi ad alta endemia di virus B e C) → scenari epidemiologici nuovi
- Quale epidemiologia nel 2020-30?

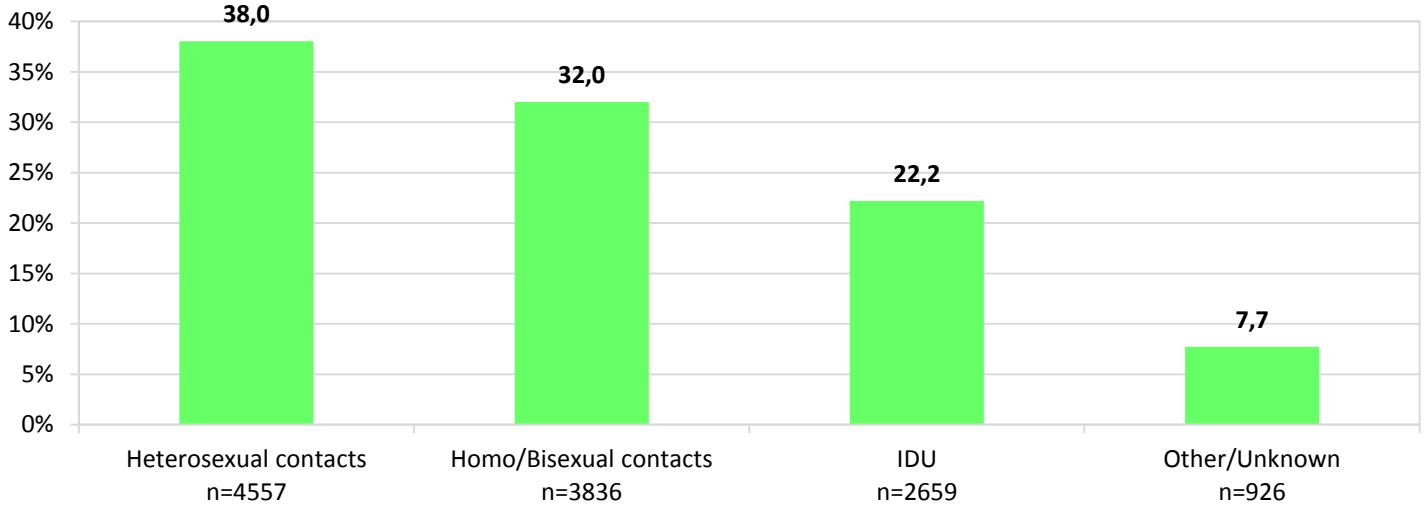
Ministero della Salute
D.G. Prevenzione
Ufficio V – Malattie infettive e profilassi internazionale

Mode of HIV transmission according to HCV Ab status N=10665

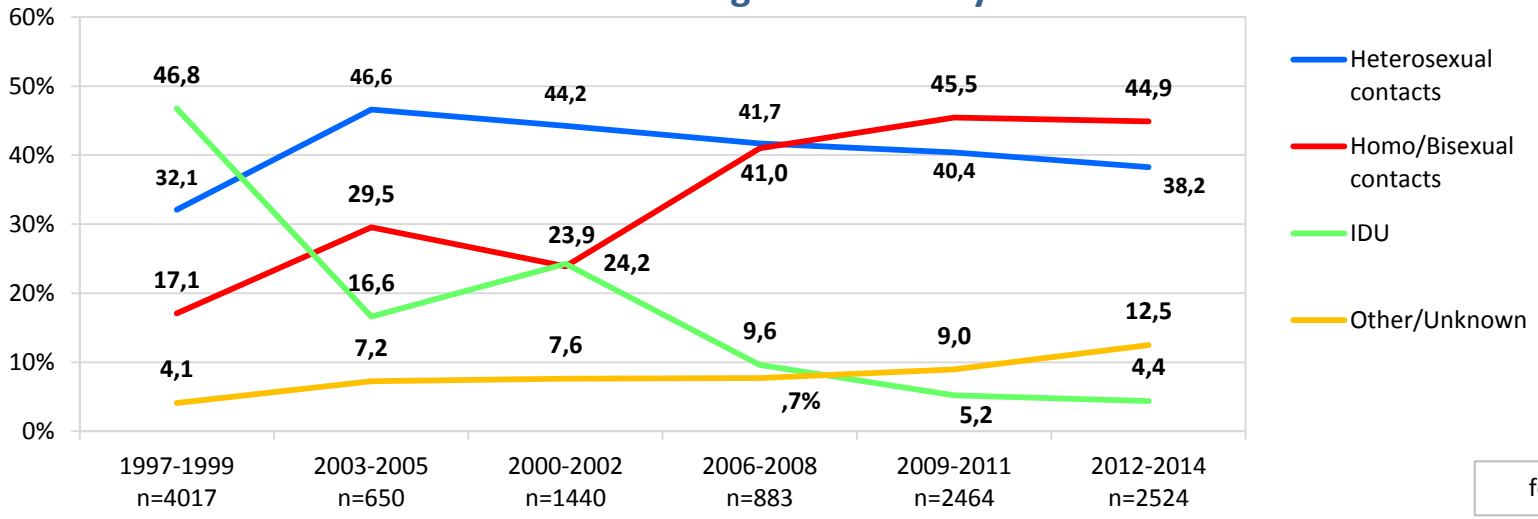


for 2014, 6 months

Mode of HIV transmission



Mode of HIV transmission according to calendar year of enrollment



for 2014, 6 months

Proportion of HCV genotypes in 1257 patients

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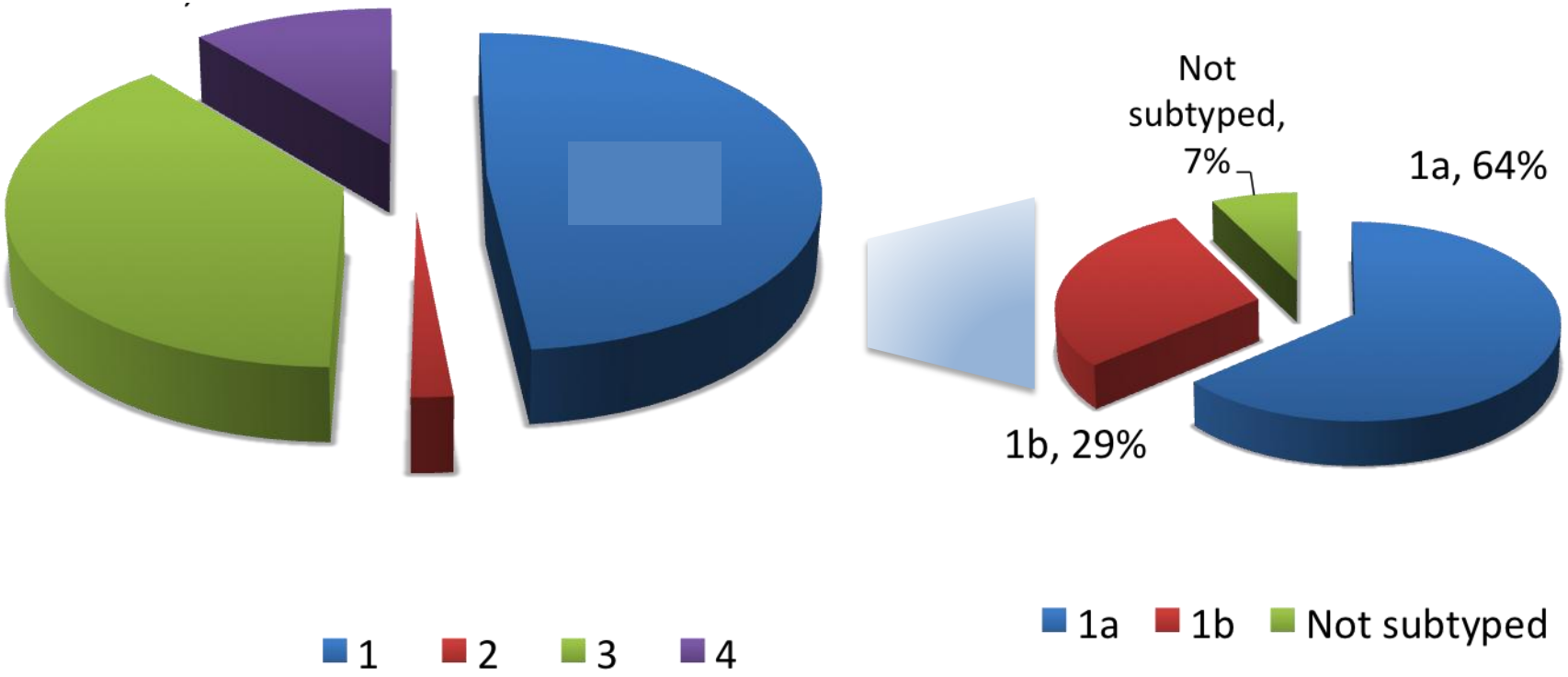
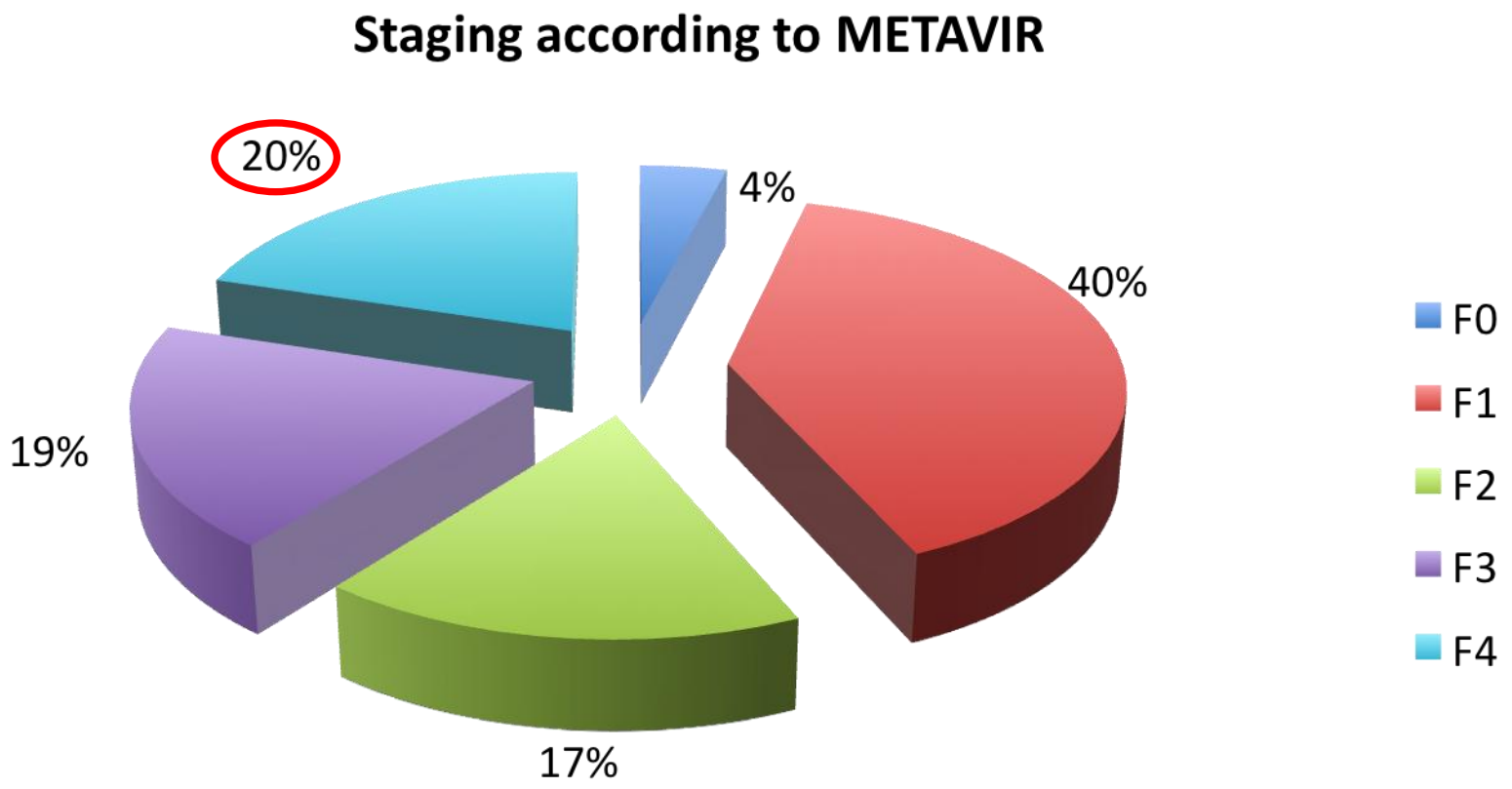
ITALIAN COHORT NAIVE ANTIRETROVIRALS



Distribution of Fibrosis stages in 744 HIV+ patients treated for HCV in the OPERA Cohort

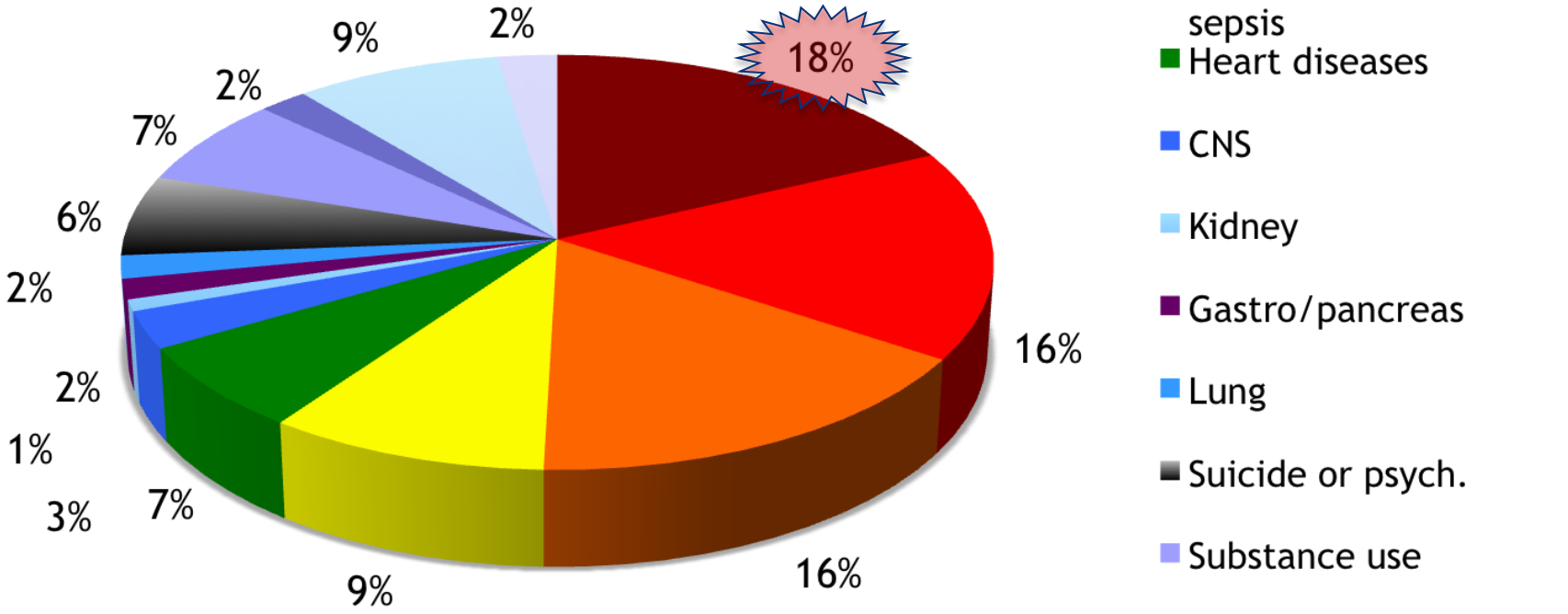


Fibrosis staging by liver biopsy in 547 and by fibroscan in 197
0-7 Kpa: F1; 7,1-11 F2; 11,1-16,5: F3; > 16,5 F4

Puoti M et al., ICAR 2012

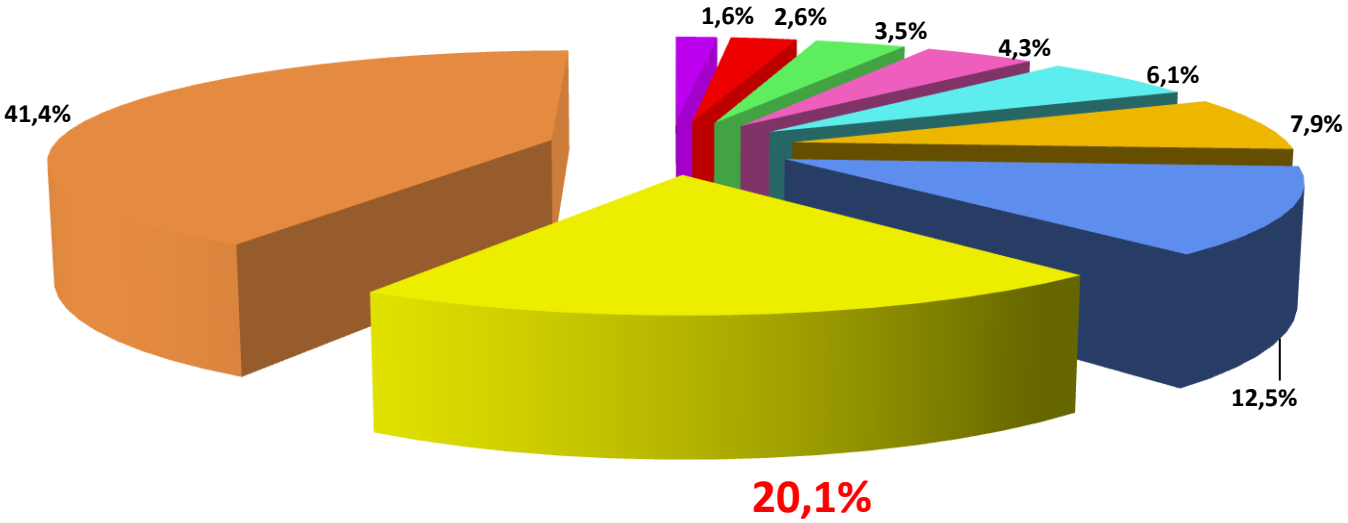
Liver diseases rank in the first most-common causes of death in HIV-infected persons

Causes of death in the Swiss HIV Cohort study 2005-09



Weber R et al HIV Medicine (2013), 14, 195–207

Cause of death, n=623



Il paziente co-infetto HIV-HCV

- Evoluzione più rapida della infezione da HIV
- Evoluzione più rapida della malattia epatica HCV correlata
- Minore risposta ad alcuni trattamenti antiretrovirali (monoterapia con PI/r)

Score di semplificazione

Criteri esclusione: 1) Bassa aderenza 2) Fallimenti precedenti PI 3) HBV+

PARAMETRI	0	1	2	3
CD4 nadir cells/mmc	<100	100-200	200-400	>400
CD4 baseline cells/mmc	<200	200-400	400-600	>600
Viremia non rilevabile, mesi	< 6	6 - 12	12-24	>24
Coinfezione HCV-HIV	si	no		
Viremia residua, cp HIV-RNA/ml	20-40	10-20	1-10	<1
HIV-DNA, copie10^6 PBMCs	>400	100-400	10-100	<10
HIV-RNA baseline, cp HIV-RNA/ml	>10^6	10^6-5x10^5	5x10^5-10^5	<10^5

Score >13: monoterapia PI/rtv
Score 10-13: PI/rtv + 3TC
Score < 10: HAART

HIV/HCV coinfection: pathogenesis

HIV/HCV coinfection leads to accelerated hepatic fibrosis progression, with higher rates of cirrhosis, liver failure and liver death than does HCV mono-infection.

Impact of HCV on HIV

- Impaired Th1 function in HIV infection affects appropriate immune response to HCV
- Conflicting clinical results
- More rapid progression to AIDS or death for HCV genotype 1
- Increasing HIV RNA and decreasing CD4 more likely in co-infected pts

Impact of HIV on HCV Infection

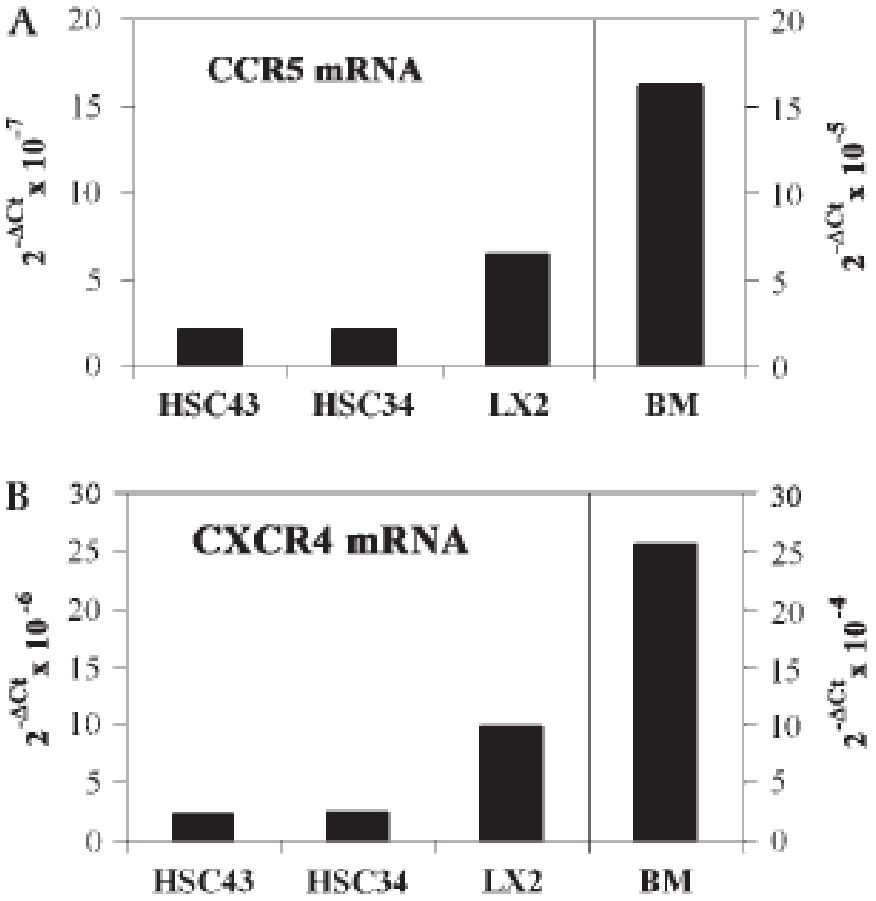
- Increased HCV-RNA titers[1]
- More rapid progression to:[1]
  - Cirrhosis
  - End-stage liver disease
  - Death
- Lower response to PegIFN-ribavirin treatment[1]

- **Biologic basis incompletely understood, but may be related to:**
  - **Impaired T-cell responses to HCV[2]**
  - **HIV's effect on hepatic cells[3]**
  - **Amplified microbial translocation, which might promote hepatic fibrosis[4]**

1. Singal AK, et al. *World J Gastroenterol.* 2009;15:3713-3724. 2. Miller M, et al. Clin Infect Dis 2005;41:713-720. 3. Eyster M, et al. JAIDS 1993;6(6):602-610. 4. Balagopal A, et al. Gastroenterology 2008;135(1):226-33.

HIV infection of Hepatic Stellate Cells can also lead to HSC activation

Transcripts for the chemokine receptors CCR5 and CXCR4, which bind gp120, were detectable in human hepatic stellate cells (HSCs).

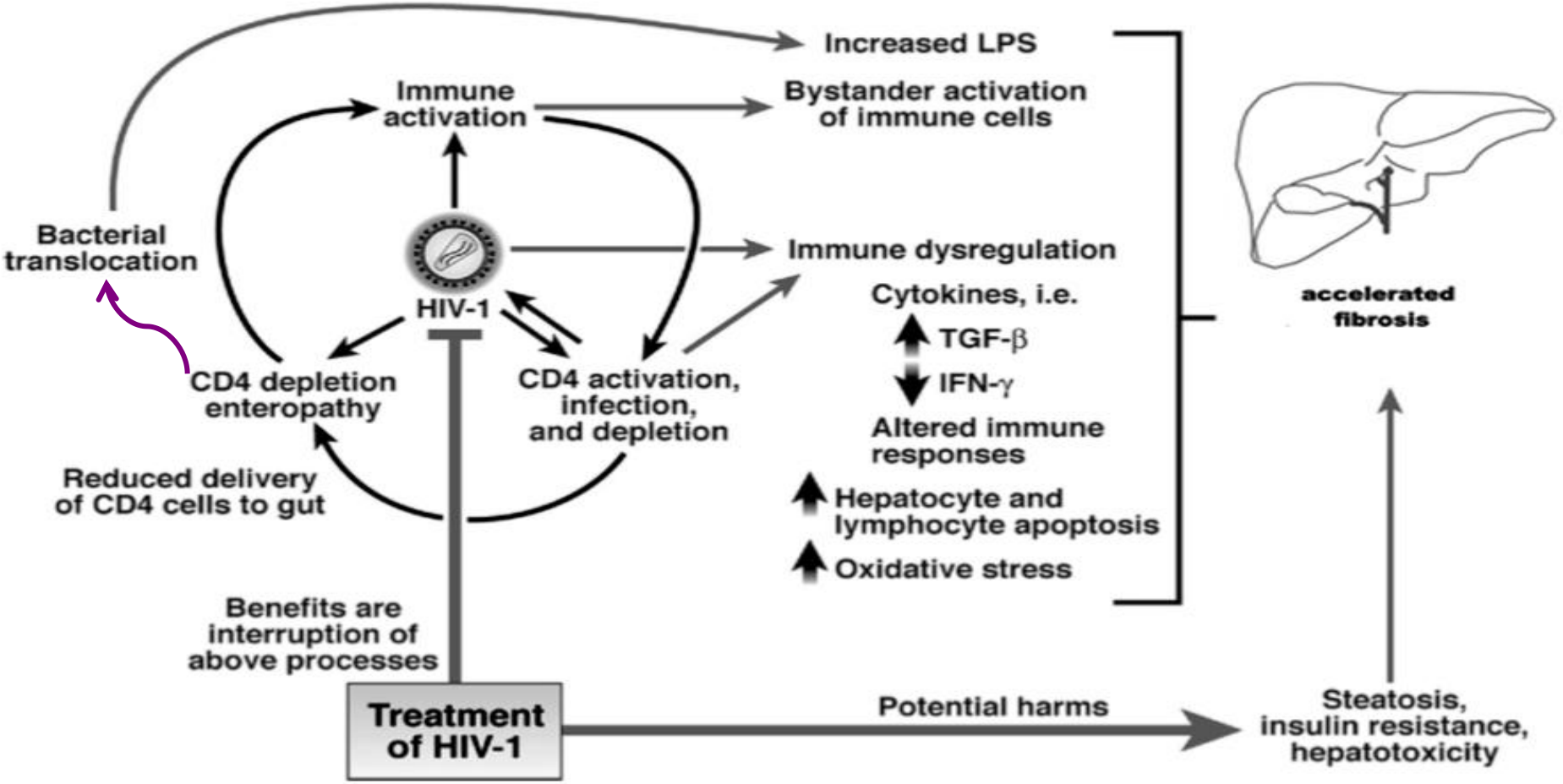


Expression of the HIV co-receptors, CCR5 and CXCR4, in human hepatic stellate cells (HSCs).

Total RNA was isolated from two primary HSC lines, the stable human HSC line, LX-2, and from human bone marrow (BM), as indicated. Expression of CCR5 and CXCR4 was assessed by real-time PCR.

The scales on the right side refer to data obtained with bone marrow RNA.

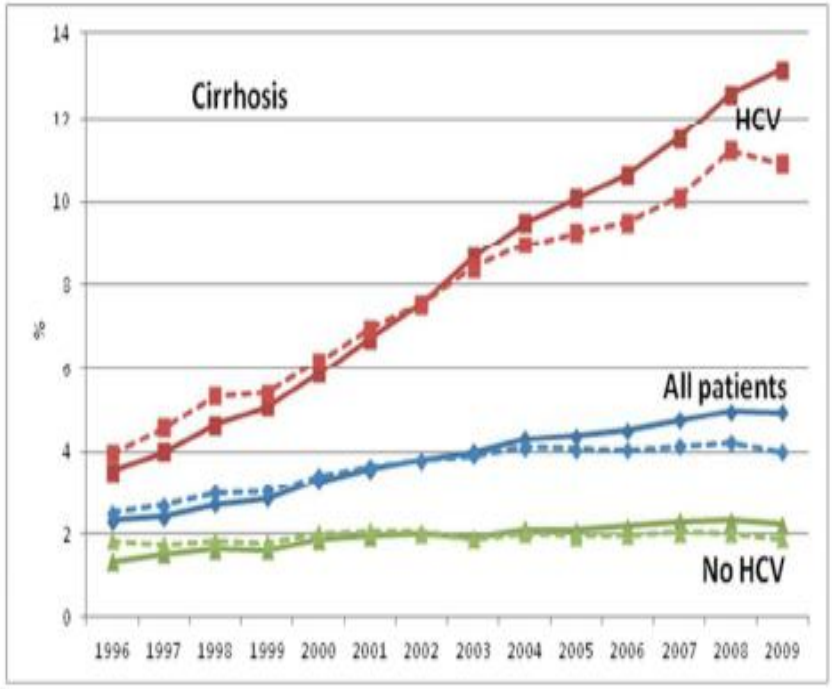
Influence of HIV-1 replication and its treatment on the liver in HCV coinfection

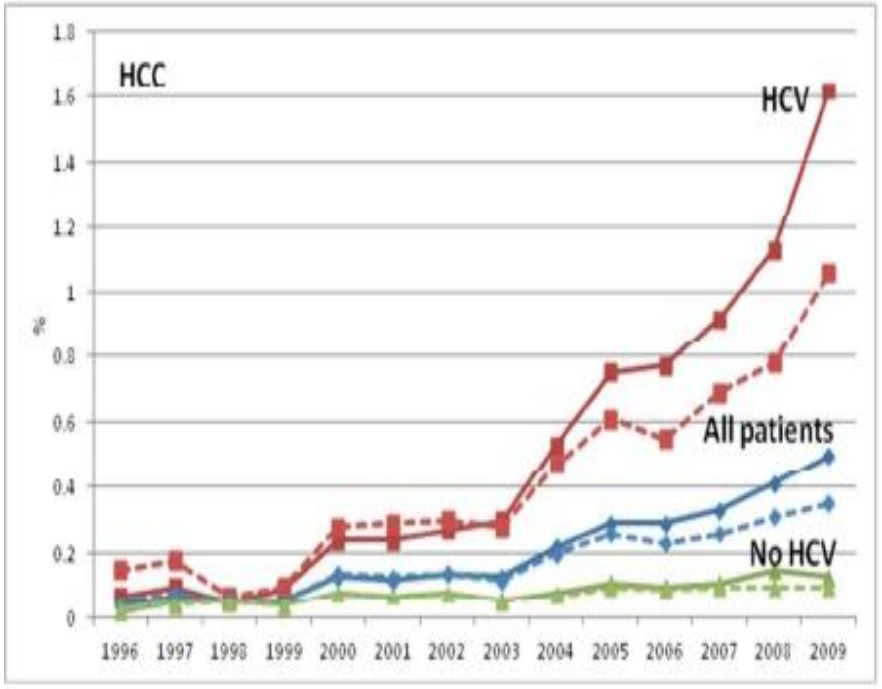


Kim RY and Chung RT GASTROENTEROLOGY 2009;137:795– 814

The prevalence of cirrhosis and hepatocellular carcinoma in patients with HIV infection

Patients received care in the Veterans Affairs (VA) healthcare system - 1996-2009 n=24,040





The prevalence of cirrhosis and HCC has increased dramatically among HIV-infected patients driven primarily by the HCV epidemic.

Ioannou GN Hepatology.

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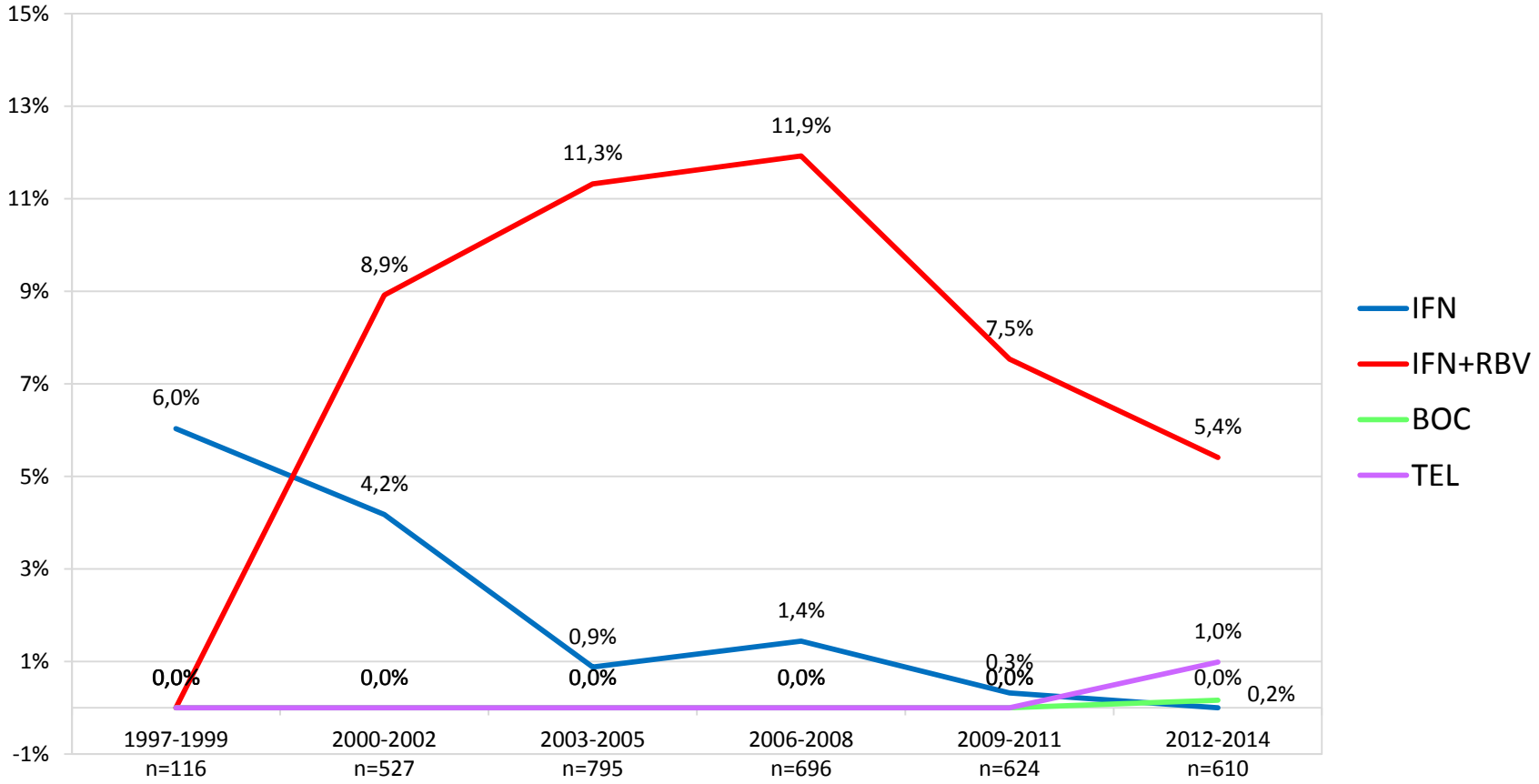
Proportion of HCVAb+/HCV-RNA+ patients starting any anti-HCV treatment for the first time, according to period of starting



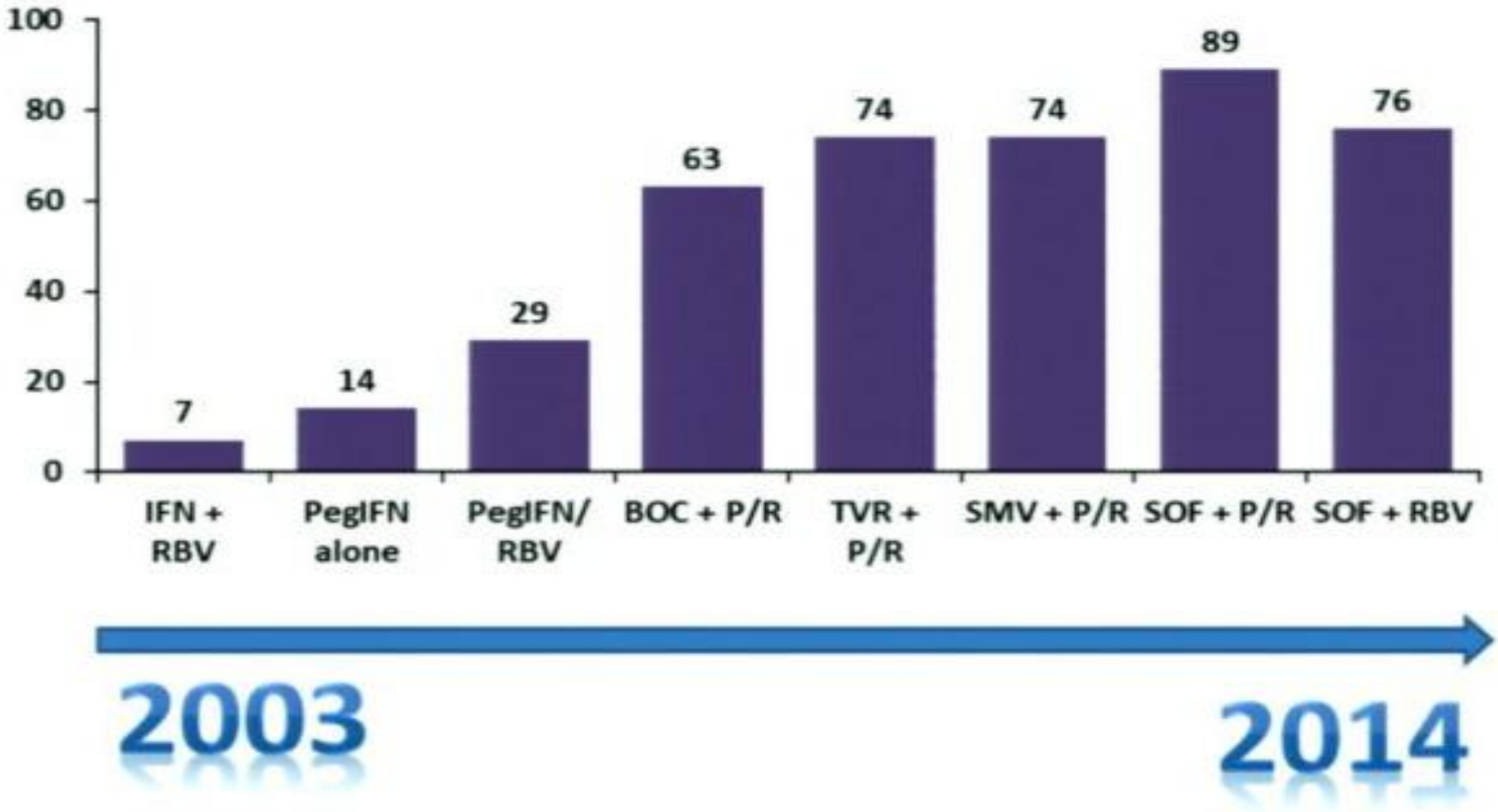
for 2014, 6 months

Trattamento del paziente co-infetto HIV-HCV

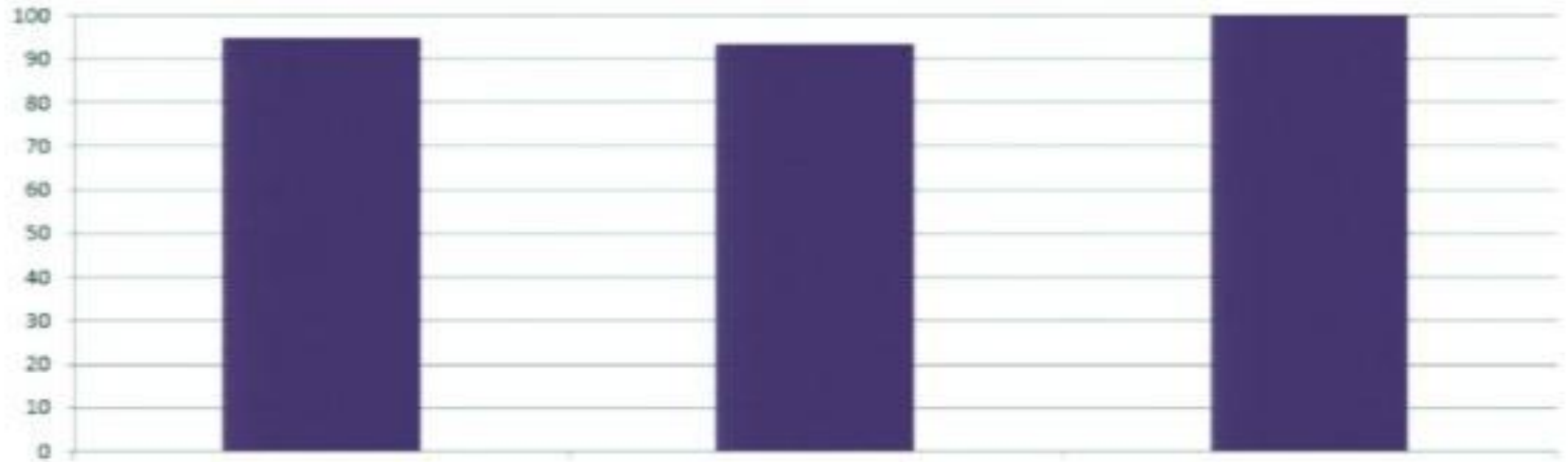
- E’ giusto rinviare il trattamento HCV per attendere i nuovi farmaci?

- Il paziente HIV rientra nelle categorie prioritarie per i trattamenti con i nuovi farmaci ?

Progression in treatment efficacy

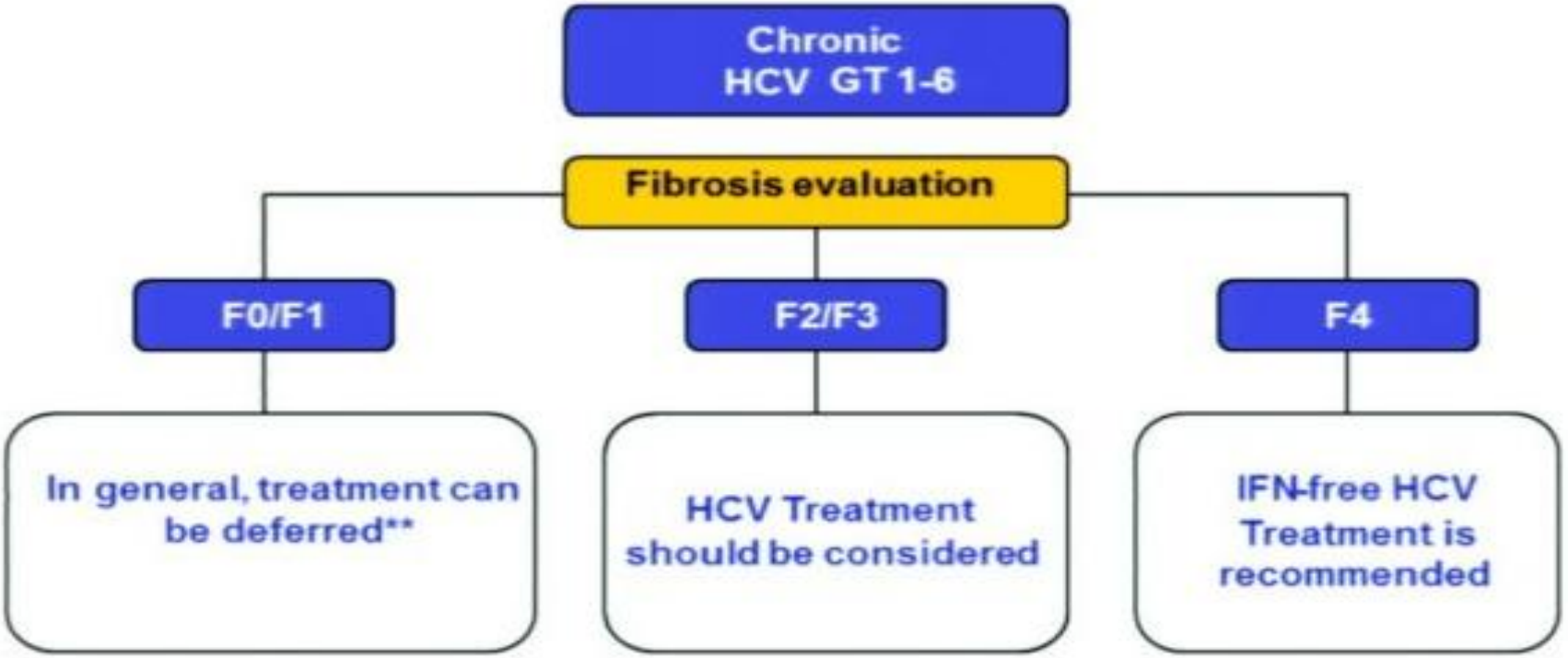


Future IFN-free options



➔ **Need to translate RCTs results and assess tolerance in real-life settings + define best strategies in most difficult to treat patients (GT 3, NR, cirrhotics…)**

EACS Guidelines, Nov 2014 update



**Monitor fibrosis stage annually, preferably with two established methods. Consider Treatment, if rapid progression.

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HAART IN HIV/HCV

Serve dunque ottimizzare la HAART nel coinfetto HIV/HCV ?

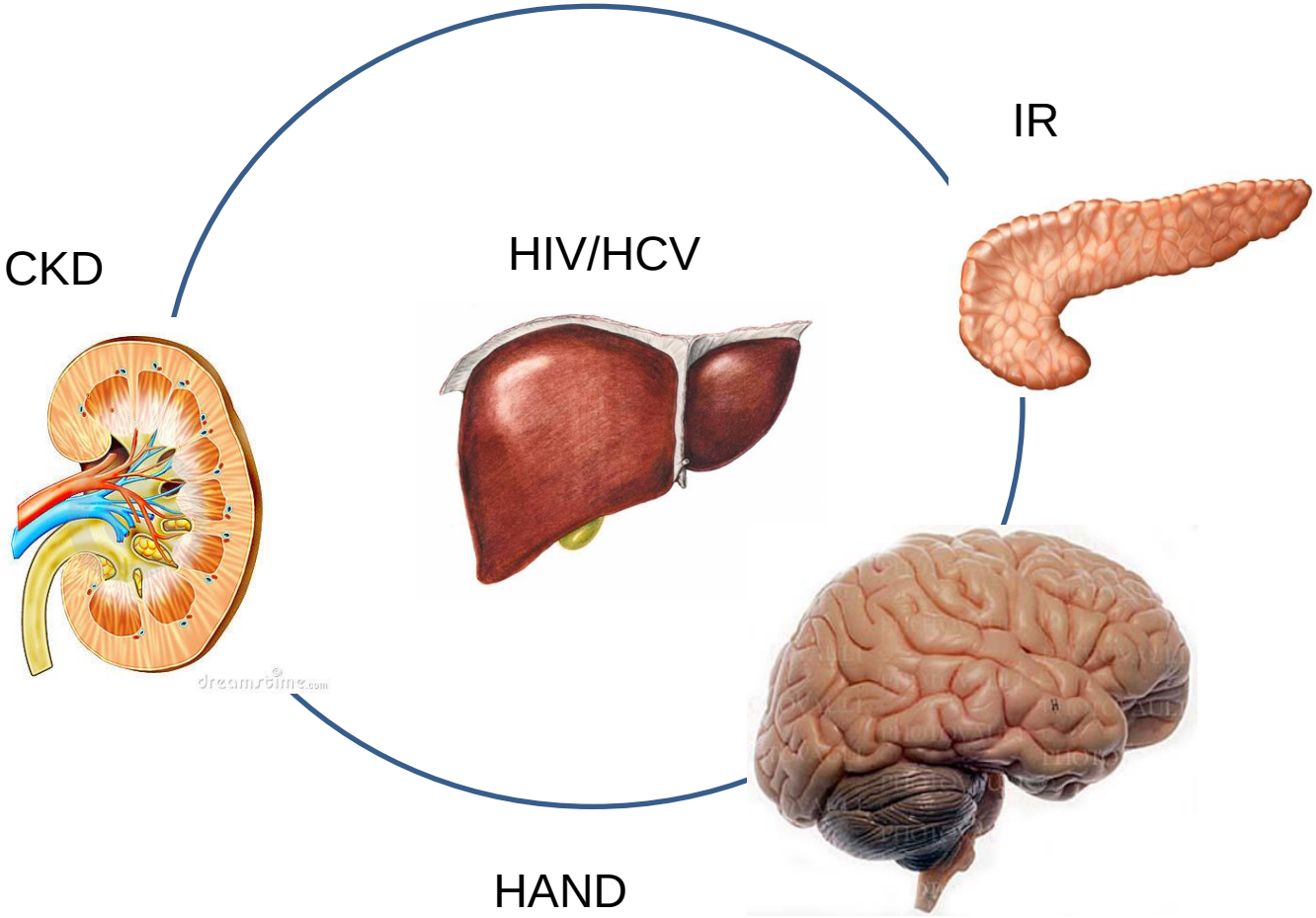
Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

Novembre 2013

Tabella 3b – Avvertenze per il terzo farmaco ("Anchor")

PAZIENTI CON...	AVVERTENZE	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Coinfezione da virus epatite	Evitare Nevirapina (specie se genere F con T CD4+ > 250 cellule/μL e di genere M con T CD4+ > 400 cellule/μL), Tipranavir per rischio di "*flares*" di epatite in soggetti con epatite cronica.	[BII]	[5,7-12]
Indicazione a terapia anti-HCV	• In assenza di DAA anti-HCV, impiegare preferenzialmente IP a basso impatto sulla sensibilità all'insulina o farmaci alternativi agli IP (NNRTI o INI).	[CIII]	[17, 26-30]
	• Non somministrare Telaprevir con LPV/r, DRV/r, fAPV/r causa interazioni.	[BIII]	[31-36]
	• Somministrare Telaprevir con ATV/r, EFV (però Telaprevir al dosaggio 1125 mg ogni 8 ore), Etravirina, Rilpivirina, INI (compreso Stribild®).	[BIII]	[31-36]
	• Boceprevir. Molte interazioni con IP e NNRTI. Non significative con INI. Nessun dato con Stribild®. Fare riferimento alle interazioni nella Tabella specifica.	[BIII]	[33,37-40]
	• Prima dell'inizio con DAA anti-HCV, è indicato uno switch a regime cART che minimizzi/annulli le potenziali interazioni.	[BIII]	[31-40]
Pazienti con cirrosi	• Evitare nevirapina e tipranavir in soggetti con insufficienza epatica moderata o grave (*Child-Pugh* B o C).	[BI]	[5,7-12]
	• Enfuvirtide non ha controindicazioni e non richiede correzioni di dosaggio.	[BI]	[5,7-12]
	• Se *Child-Pugh* ≥ 7, impiegare con cautela EFV, LPV/r, RAL, MVC.	[BIII]	[5,7-12]

IL RUOLO SISTEMICO DELLA COINFEZIONE HIV/HCV



HIV/HCV coinfection: disease progression and complication

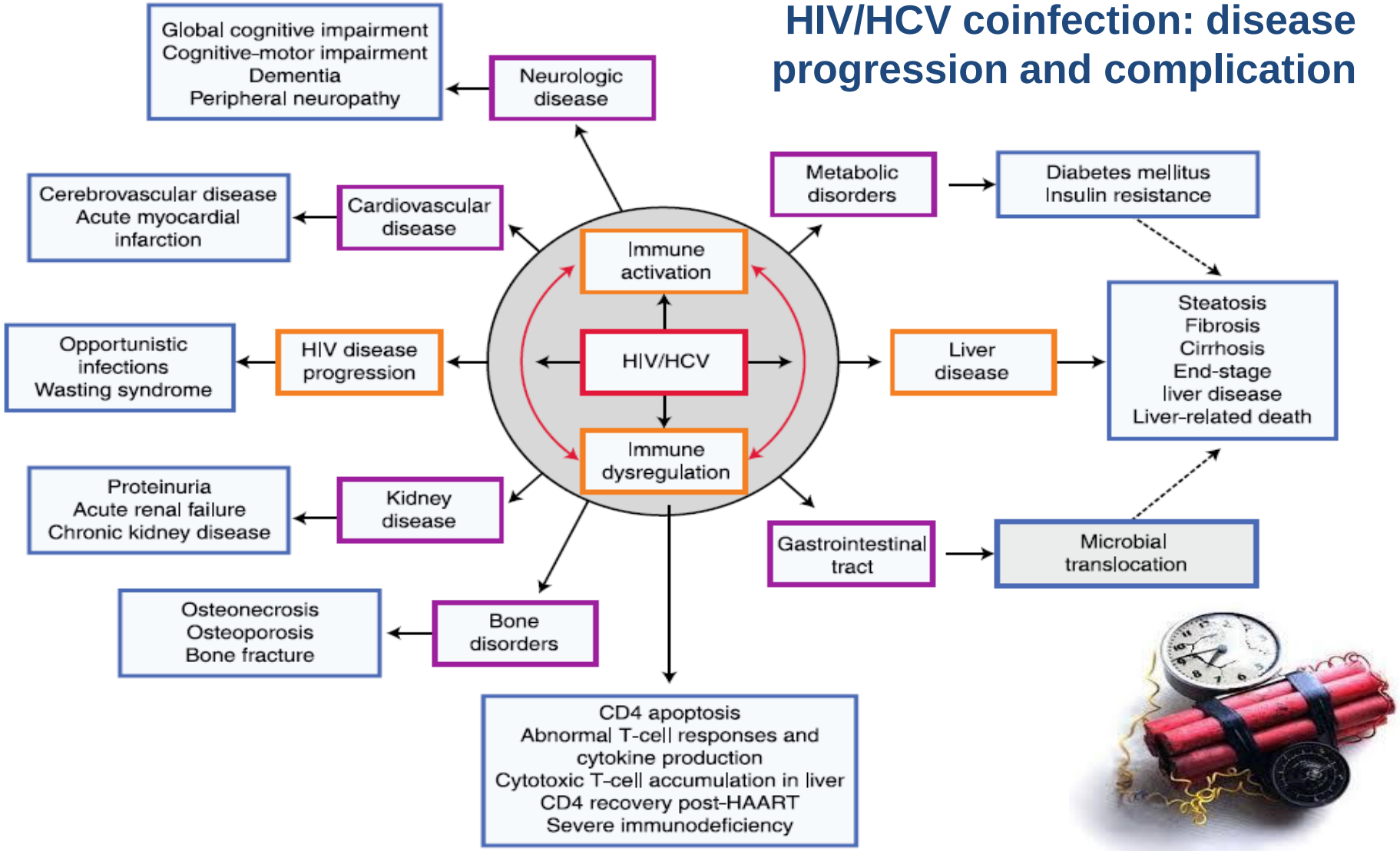


Fig. 1 Pathogenesis of HIV/HCV co-infection: Immune activation and dysregulation, effects on HIV and HCV disease progression, and complications in multiple organ systems

HAART IN HIV/HCV

VANNO VALUTATI 3 TARGET DELLA HAART IN HCV:

- **EFFICACIA VIRO-IMMUNOLOGICA**

- **TOLLERABILITA'**
  epatica
  cardiovascolare
  renale
  ossea
  neurologica
  metabolica

- **RIDOTTE DDI CON I NUOVI DAAs**

Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy

Norbert Bräu et al.

HIV/HCV-coinfected patients with undetectable HIV RNA through HAART have a slower FPR than those with any HIV RNA level and an FPR similar to HCV-monoinfected individuals.

Journal of Hepatology
Volume 44, Issue 1 , Pages 47-55, January 2006

HAART IN HIV/HCV

VANNO VALUTATI 3 TARGET DELLA HAART IN HCV:

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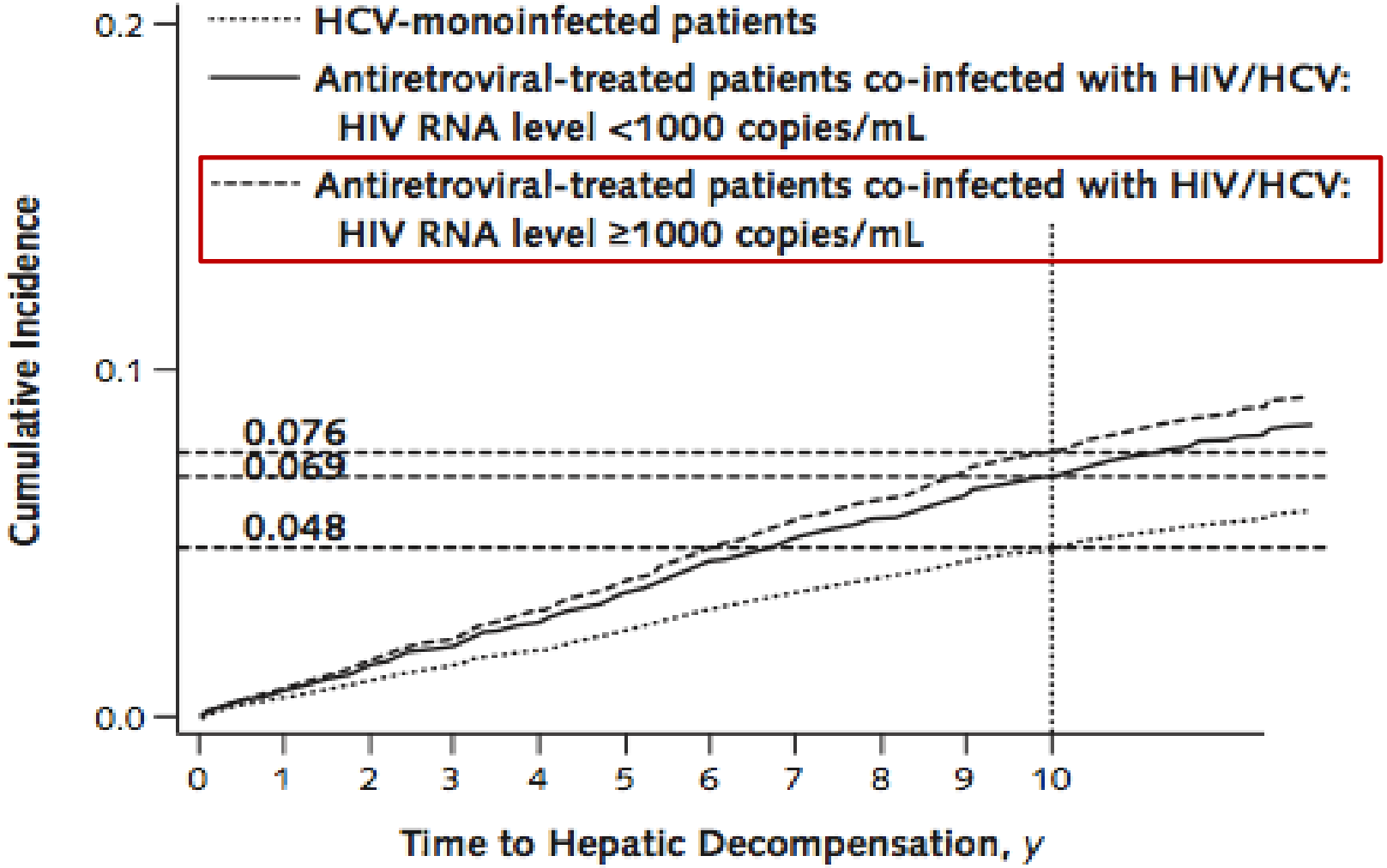
  metabolica

- **RIDOTTE DDI CON I NUOVI DAAs**

Hepatic Decompensation in Antiretroviral-Treated Patients Co-Infected With HIV and Hepatitis C Virus Compared With Hepatitis C Virus–Monoinfected Patients



Ann Intern Med. 2014;160:369-379.

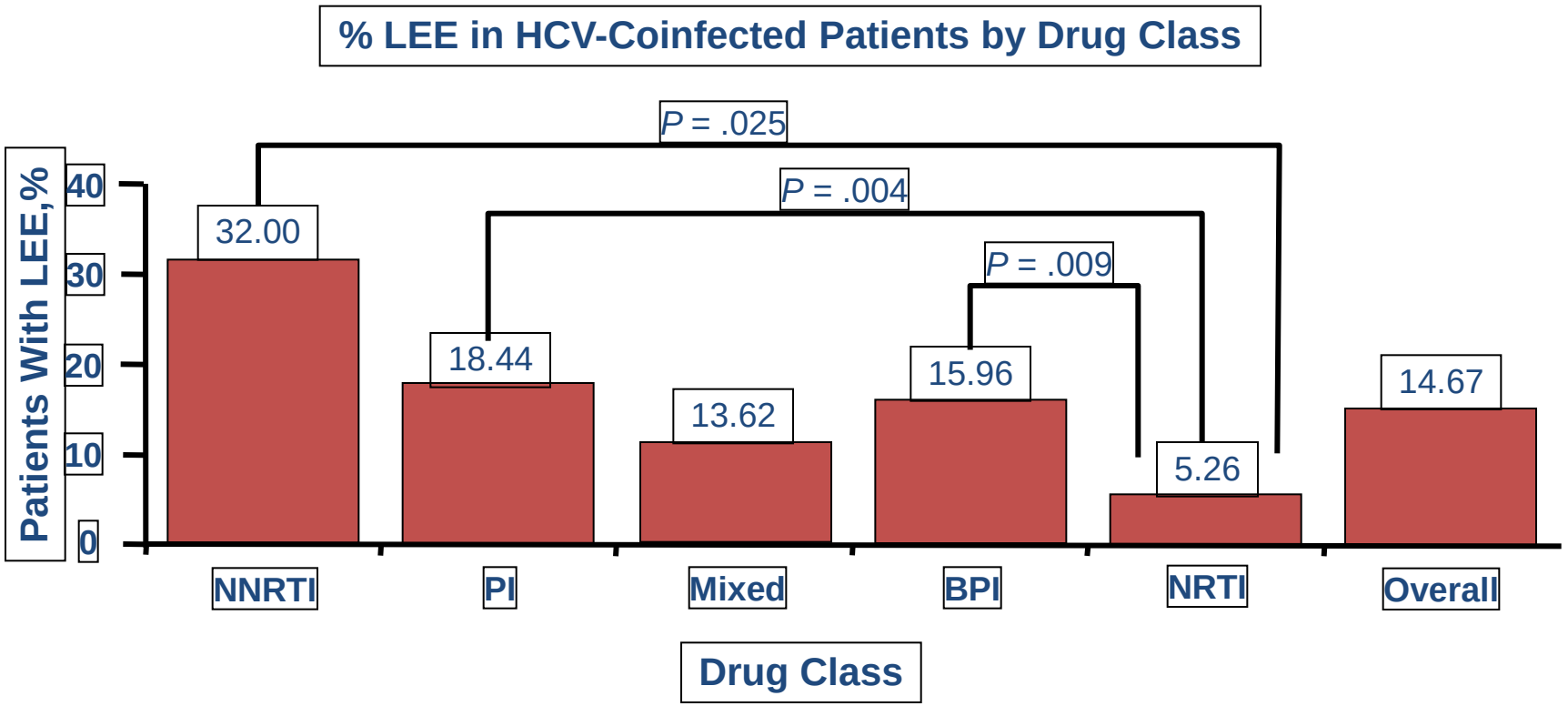
Coinfezione HIV-HCV
quali i regimi "liver friendly"…?

Nella gestione dei coinfetti HIV/HCV sarebbe da evitare l'uso di:

- **d-drugs (Acidosi lattica)**
- **AZT(< Hb) e ABC(< SVR) nei pazienti trattati con PegIFN + Riba**
- **NVP(flares epatitici)**
- **TPV(flares epatitici)**

HAART and Liver Enzyme Elevations

- Meta-analysis of 20 publications of HIV-infected patients HCV coinfection
- Grade 2 or higher liver elevations noted



Benhamou Y, et al. CROI 2006. Abstract 88.

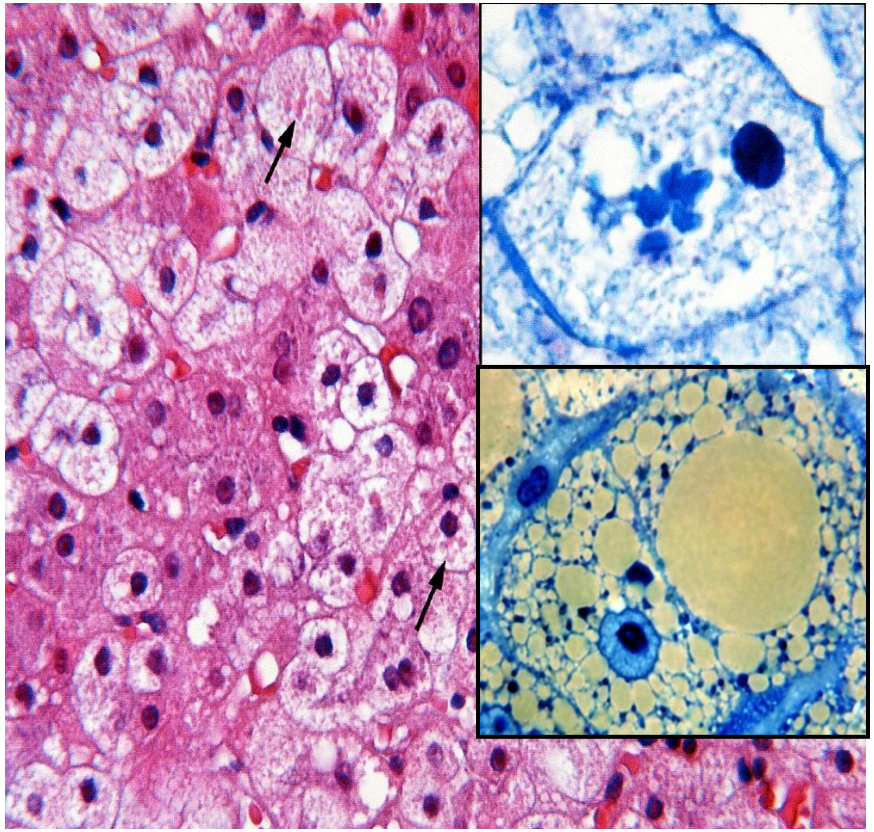
Drugs available for HIV therapy

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

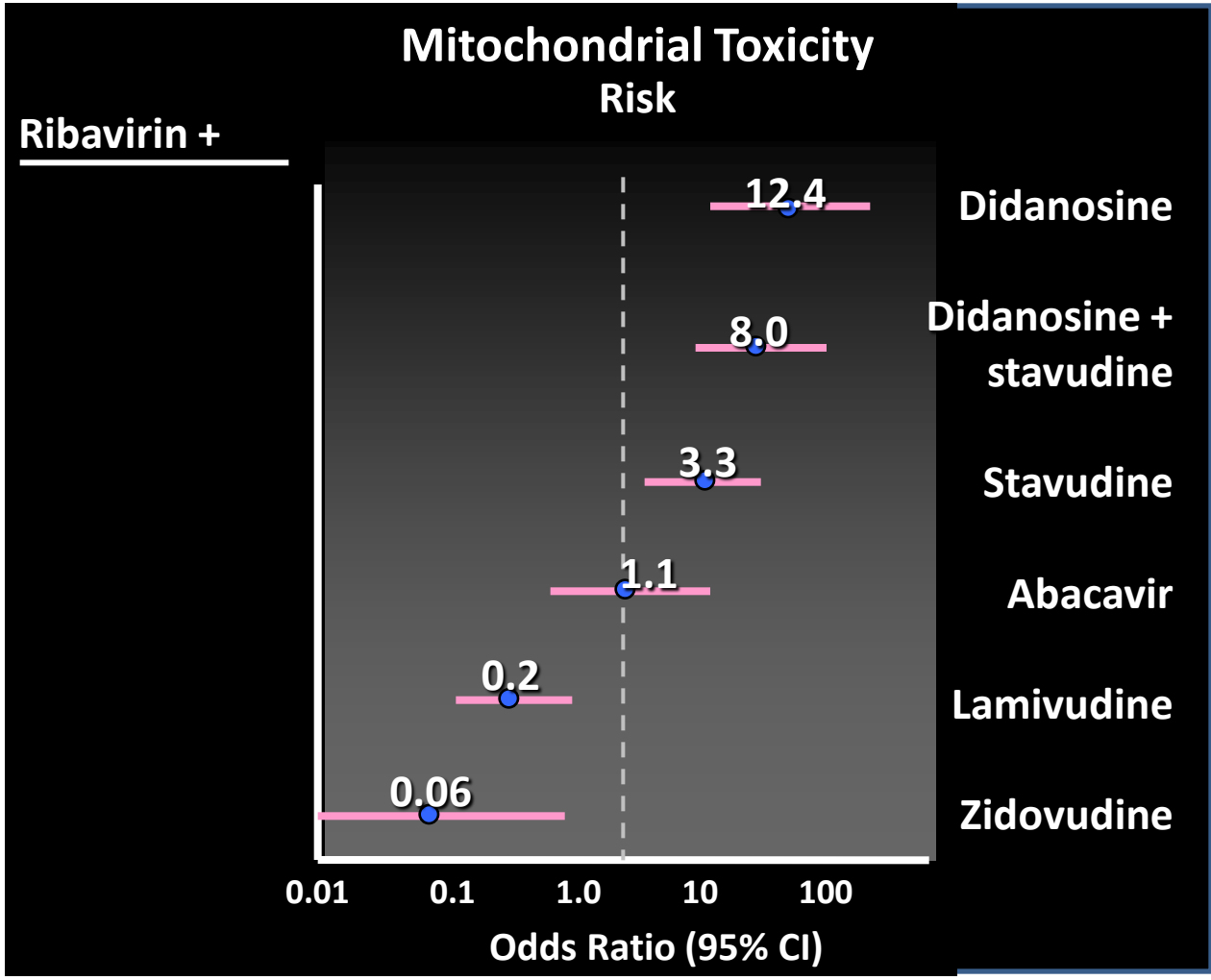
Mitochondrial toxicity

Il mtDNA svolge la propria replicazione mediante l'azione di un enzima, la DNA-polimerasi-γ, che viene in diversa misura inibito dagli NRTI: la potenza inibitoria degli NRTI varia a seconda del singolo farmaco, essendo più elevata per le cosiddette**"D-drugs"** (zalcitabina, didanosina e stavudina) e più blanda per le "non–D drugs" (lamivudina, zidovudina e abacavir)



Risk of Mitochondrial Toxicity: NRTI + Ribavirin in HIV/HCV-Coinfected Patients

- US FDA Adverse Event Reporting System (2002)
  - HIV/HCV patients
    - Ribavirin + NRTIs
- 31 cases (58 adverse events) suggestive of mitochondrial toxicity
  - Pancreatitis and/or increased lipase (n=21)
  - Lactic acidosis (n=20)
  - Elevated LFTs (n=8)
  - Hepatic steatosis (n=6)
  - Elevated creatinine, neuropathy, multiorgan failure (n=1 each)



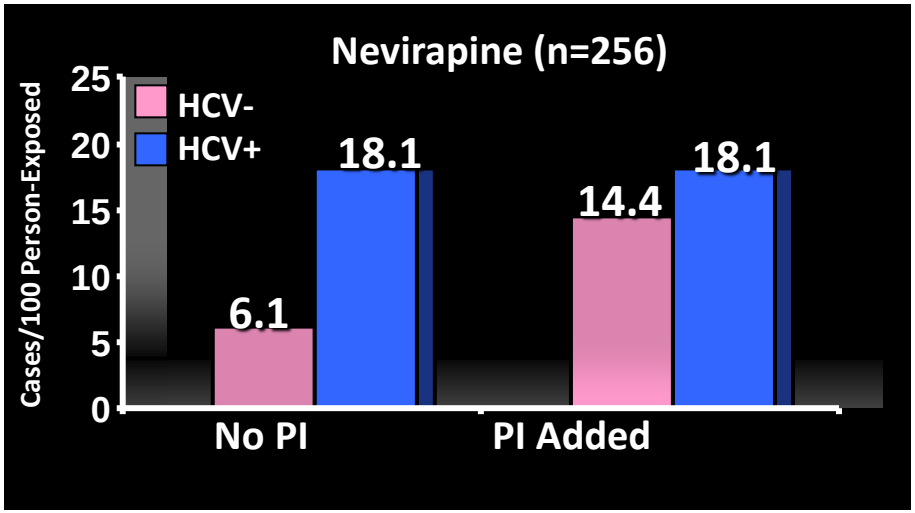
Drugs available for HIV therapy

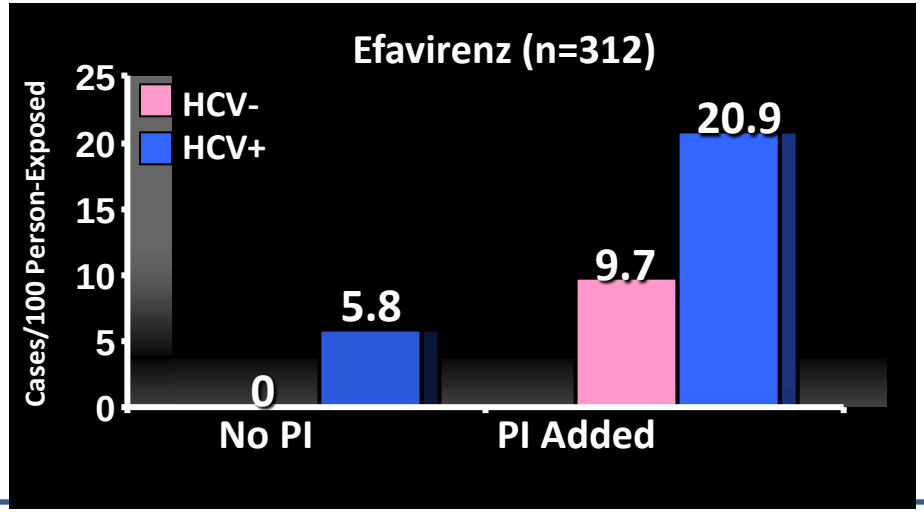
NNRTIs

- Efavirenz
- Nevirapine
- Etravirine

Incidence of Severe Hepatotoxicity of NNRTIs in Hepatitis Coinfection

- Prospective study on the incidence severe hepatotoxicity (grade 3 or 4 AST/ALT)
  - Johns Hopkins HIV cohort (n=568)
  - HCV (43%) and HBV (7.7%)
- Overall incidence of severe hepatotoxicity
  - Nevirapine: 15.6%
  - Efavirenz: 8.0%
- **Hepatotoxicity risk was significantly greater in:**
  - **Hepatitis coinfection**
  - **NNRTI + PI**



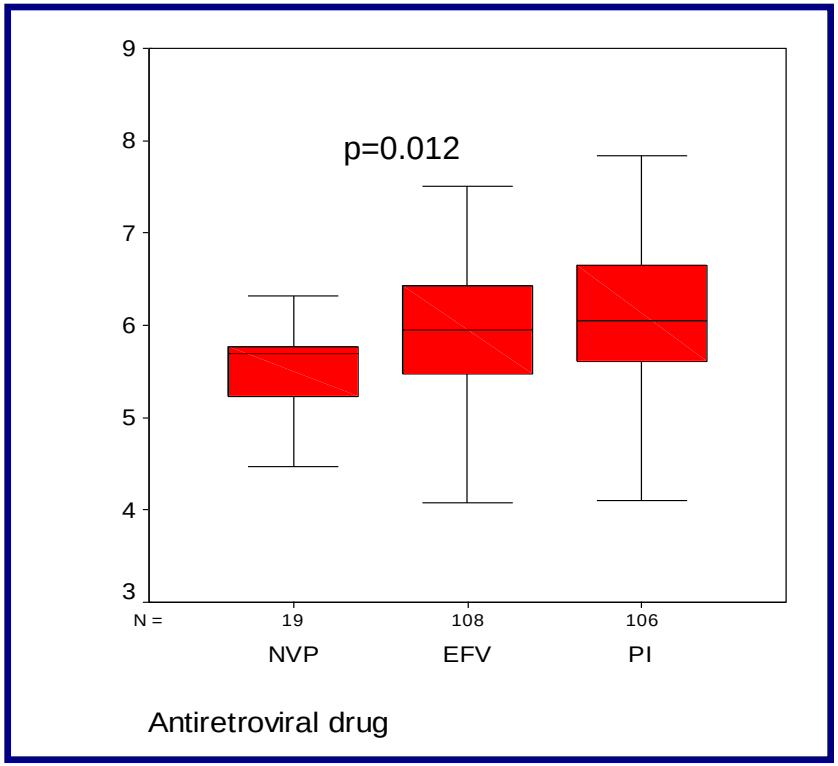


Discussion

Impact of NVP on HCV-RNA viral load

- It has been shown that HCV patients receiving NNRTIs, especially NVP, have lower HCV-RNA levels.
- HIV can induce HCV replication through TGF-beta1, which is produced in the liver in response to proinflamatory cytokines.
- NVP has been associated with higher decreases in levels of TNF-alpha receptor than other antiretroviral drugs, which might decrease TGF-beta1 secretion in the liver and reduce HCV replication.

HCV-RNA level among individuals receiving PI-, EFV- or NVP-based ART



1) Bani-Sadr F et al. AIDS 2007; 21: 1645
2) Mata R et al. EACS Conference 2009, Cologne, Germany.
3) Lin W et al. Gastroenterology 2008; 134:803–811
4) Virgili N et al. J Acquir Immune Defic Syndr 2009; 50: 552-553

284

Hepatic safety and tolerability of etravirine: pooled 96-week analysis of DUET-1 and DUET-2

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[1]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [2]Kaiser Permanente, Los Angeles, CA, USA; [3]San Raffaele University, Milan, Italy; [4]Tibotec BVBA, Mechelen, Belgium; [5]Tibotec Inc., Yardley, PA, USA

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Abstract

Background

DUET-1 and DUET-2 are identically designed, randomized, double-blind, Phase III trials that assessed the efficacy and safety of etravirine (ETR; TMC125) in HIV-1-infected, treatment-experienced patients. We report pooled 96-week hepatic safety data.

Methods

Patients with HIV-1 RNA ≥5000 copies/mL, documented genotypic NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations were randomized to ETR 200mg bid or placebo, both with a background regimen (BR) of darunavir/ritonavir (DRV/r) + NRTI(s) ± enfuvirtide (ENF). Patients co-infected with chronic hepatitis B and/or C were allowed to enroll if clinically stable, not expected to require hepatitis treatment during the trial, and had baseline aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels <5x upper limit of normal (ULN). Hepatic adverse events (AEs) and laboratory parameters were assessed.

Results

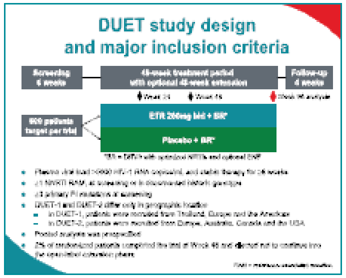
One thousand, two hundred and three patients (12.4% co-infected with hepatitis B and/or C) were evaluated. Median treatment duration was 26 weeks longer in the ETR group (96 vs 69.6 weeks for placebo). Total patient-years exposure (PYE) was higher in the ETR group (895.4 vs 766.7 for placebo). Incidence of hepatic AEs was comparable between the two groups (see table below). Incidence of serious hepatic AEs and treatment-emergent grade 3/4 ALT/AST elevations was low in both groups. No hepatic AE-related deaths occurred.

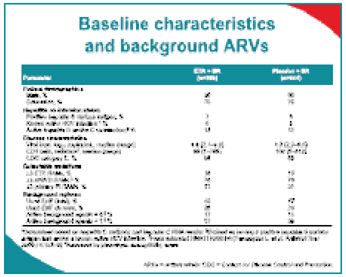
	Overall incidence, n (%)		Incidence adjusted for difference in exposure time, number of patients/100 PYE	
	ETR + BR (n=599)	Placebo + BR (n=604)	ETR + BR (n=599)	Placebo + BR (n=604)
AE				
Any hepatic AE	52 (9)*	43 (7)	5.8	5.6
Grade 3 or 4 hepatic AEs	25 (4)	18 (3)	2.8	2.3
Serious hepatic AEs	10 (2)	9 (1)	1.1	1.2
Any hepatic AE leading to discontinuation	8 (1)	4 (1)	0.9	0.5
Treatment-emergent grade 3 or 4 hepatic laboratory abnormalities				
ALT increase (>5.1x ULN)	26 (4)	14 (2)	2.9	1.8
AST increase (>5.1x ULN)	23 (4)	15 (2)	2.6	2.0

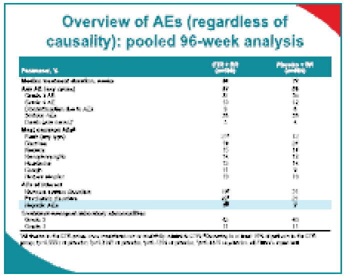
*p value vs placebo = 0.3370 (Fisher's exact test)

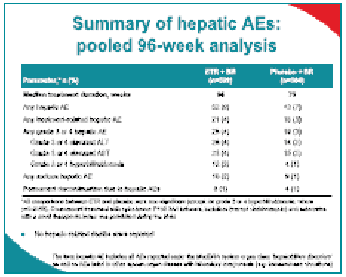
Conclusions

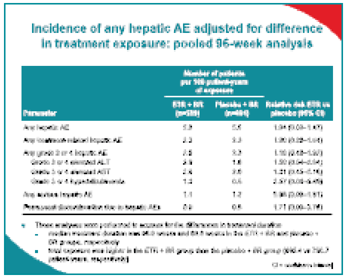
In treatment-experienced patients, the frequency of hepatic events with ETR was generally comparable to placebo through 96 weeks in DUET-1 and DUET-2. Discontinuation due to hepatic AEs with ETR was low and comparable with placebo.

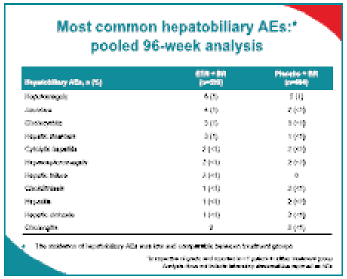


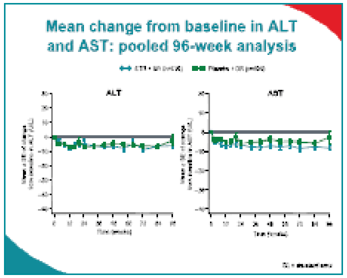


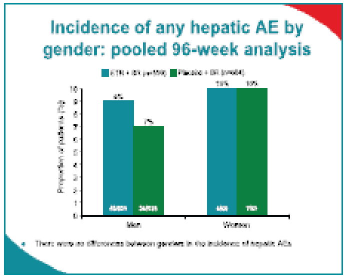


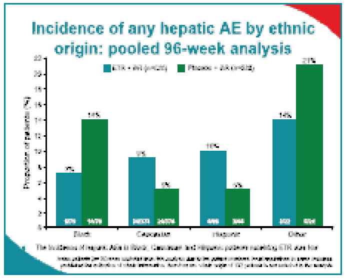


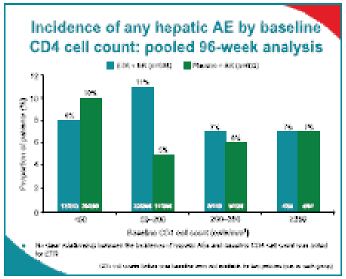


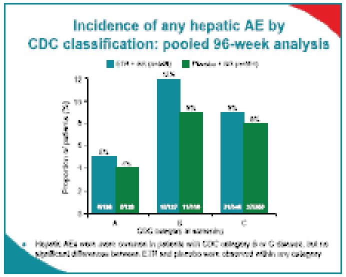


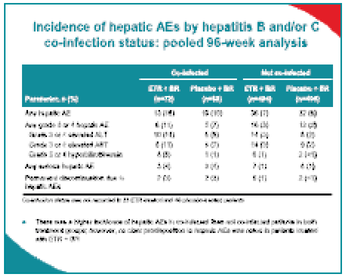












Conclusions

- In treatment-experienced patients, the incidence of hepatic AEs with ETR + BR was generally low and comparable with placebo + BR through 96 weeks
  - when adjusted for the difference in treatment exposure, the incidence of hepatic AEs was similar in both treatment groups
- Discontinuation due to hepatic AEs was low and comparable in both groups
  - there were no hepatic-related deaths
- The incidence of hepatic AEs was generally low and comparable between ETR + BR and placebo + BR regardless of
  - gender
  - ethnic origin
  - baseline CD4 cell count
  - screening CDC category
- The incidences of hepatic AEs were higher in patients with hepatitis B and/or C co-infection in both the ETR and placebo groups; however, ETR + BR did not appear to increase hepatic risk in these patients

Acknowledgments

- We express our gratitude to the patients who participated in the studies, as well as the study center staff, the data safety and monitoring board, clinical event adjudication panels, Virco, Tibotec personnel and the following principal investigators.

DUET-1

Argentina: HA Ariza, J Benetucci, P Cahn, LM Calanni, LI Cassetti, J Corral, DO David, A Krolewiecki, MH Losso, P Patterson, RA Teijeiro; **Brazil:** CA da Cunha, B Grinsztejn, EG Kallas, JV Madruga, EM Netto, JH Pilotto, M Schechter, J Suleiman, A Timerman; **Chile:** J Ballesteros, R Northland; **Costa Rica:** AA Alvilés Montoya, G Herrera Martinez, A Solano Chinchilla; **France:** M Dupon, C Katlama, JM Livrozet, P Morlat, G Pialoux, C Piketty, I Poizot-Martin; **Mexico:** J Andrade-Villanueva, G Reyes-Terán, J Sierra-Madero; **Panama:** A Canton, A Rodriguez, N Sosa; **Puerto Rico:** JO Morales Ramirez, JL Santana Bagur, R Soto-Malave; **Thailand:** T Anekthananon, P Mootsikapun, K Ruxrungtham; **USA:** M Albrecht, N Bellos, R Bolan, P Brachman, C Brinson, F Cruickshank, R Elion, WJ Fessel, R Haubrich, T Hawkins, S Hodder, P Hutcherson, T Jefferson, H Katner, C Kinder, M Kozal, J Lalezari, J Leider, D McDonough, A Mills, K Mounzer, J Nadler, D Norris, W O'Brien, G Pierone, K Raben, B Rashbaum, M Rawlings, B Rodwick, P Ruane, J Sampson, S Schrader, A Scribner, M Sension, D Sweet, B Wade, D Wheeler, A Wilkin, T Wilkin, T Wills, M Wohlfeiler, K Workowski

DUET-2

Australia: J Chuah, D Cooper, B Eu, J Hoy, C Workman; **Belgium:** N Clumeck, R Colebunders, M Moutschen; **Canada:** J Gill, K Gough, P Junod, D Kilby, J Montaner, A Rachlis, B Trottier, CM Tsoukas, S Walmsley; **France:** C Arvieux, L Cotte, JF Delfraissy, C Katlama, PM Girard, B Marchou, JM Molina, D Vittecoq, Y Yazdanpanah, P Yeni; **Germany:** K Arasteh, S Esser, G Fätkenheuer, H Gellermann, K Göbels, FD Goebel, H Jäger, JK Rockstroh, D Schuster, S Staszewski, A Stoehr; **Italy:** A Antinori, G Carosi, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, S Rusconi, L Sighinolfi, F Suter; **The Netherlands:** PHJ Frissen, JM Prins, BJA Rijnders; **Poland:** A Horban; **Portugal:** F Antunes, M Miranda, J Vera; **Spain:** P Domingo, B Clotet, G Garcia, JM Gatell, J González-Lahoz, J López-Aldeguer, D Podzamczer; **UK:** P Easterbrook, M Fisher, M Johnson, C Orkin, E Wilkins; **USA:** B Barnett, J Baxter, G Beatty, D Berger, C Borkert, T Campbell, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, JE Gallant, RN Greenberg, C Hicks, DT Jayaweera, S Kerkar, N Markowitz, C Martorell, C McDonald, D McMahon, M Mogyoros, RA Myers Jr, G Richmond, S Schneider, H Schrager, P Shalit, FP Siegal, L Sloan, K Smith, S Smith, P Tebas, LS Tkatch, W Towner

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Presented at the 47th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, Pennsylvania, USA, October 29–November 1 2009.

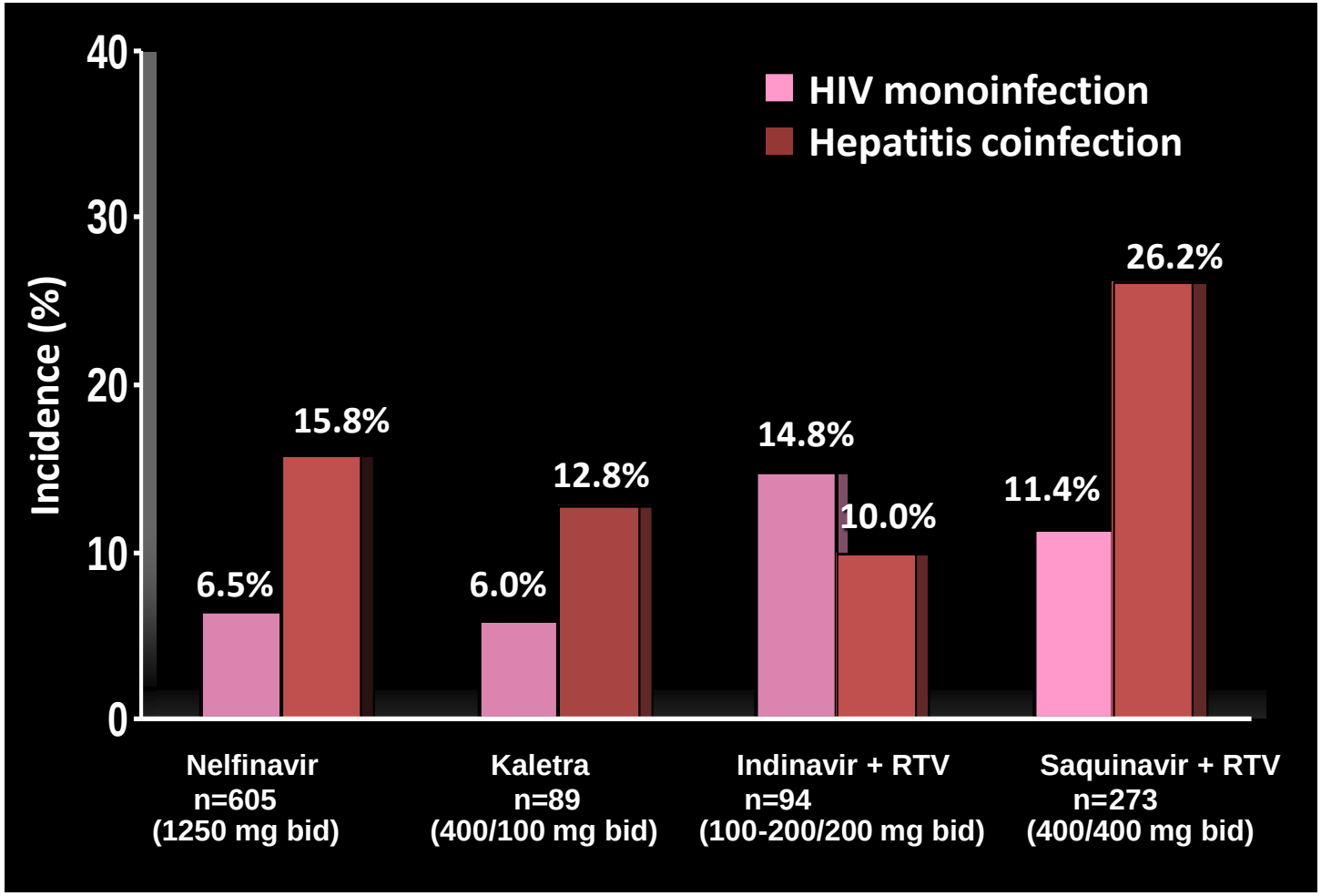
This poster is available on-line at www.tibotec.com

Drugs available for HIV therapy

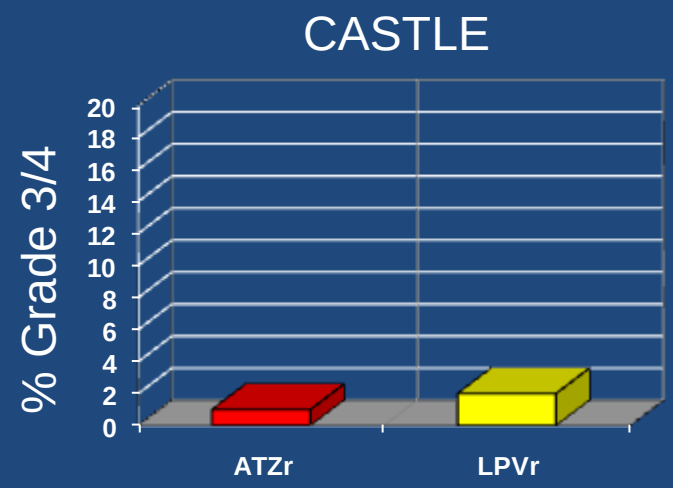
Protease Inhibitors

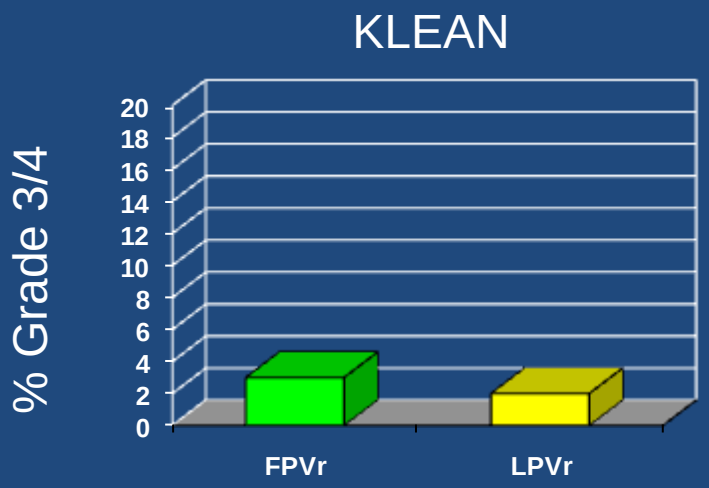
- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

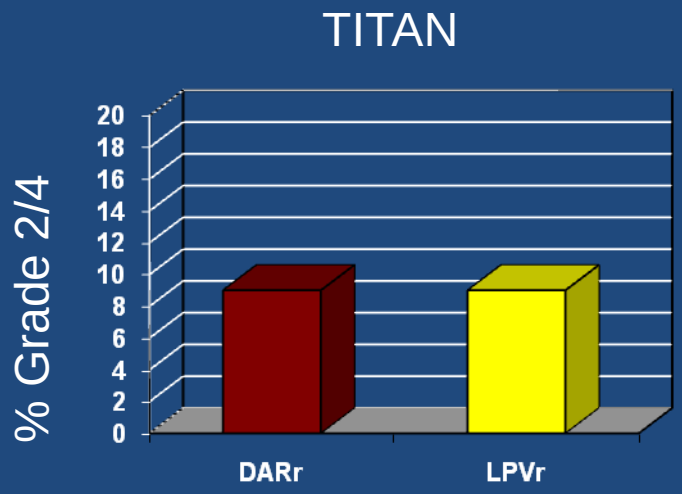
Incidence of Severe Hepatotoxicity During Therapy With PI-Based Regimens

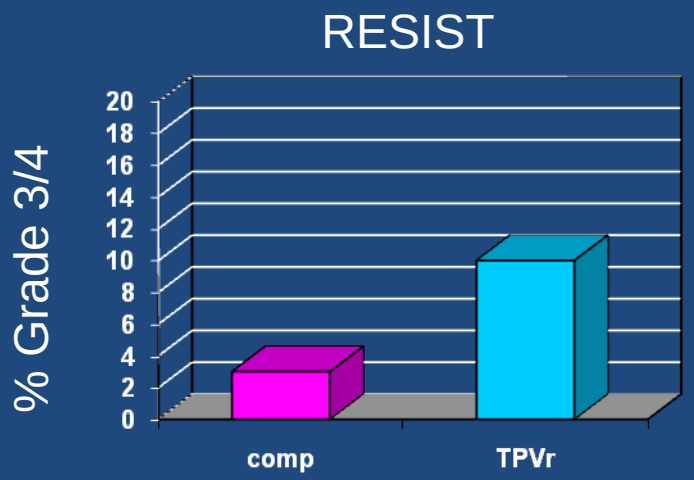


Hepatotoxicity with Newer PIs









Drugs available for HIV therapy

New Classes

- **R5 Inhibitors**

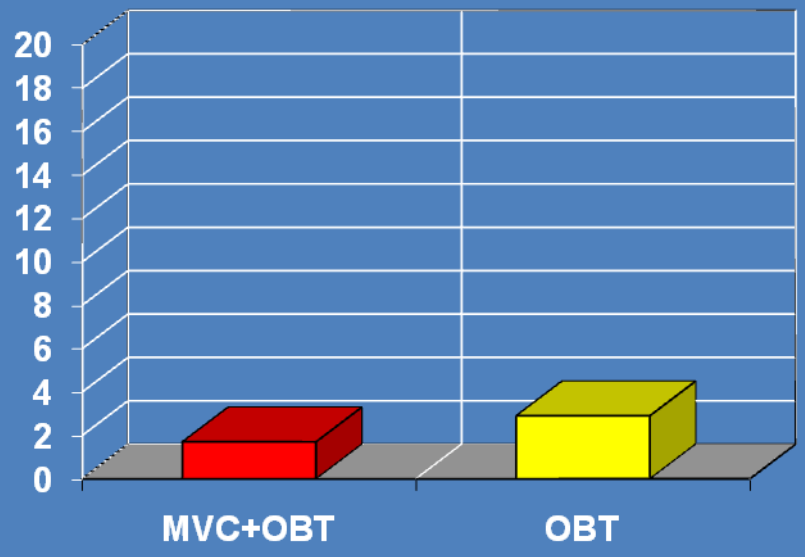
  Maraviroc

- **Integrase Inhibitors**

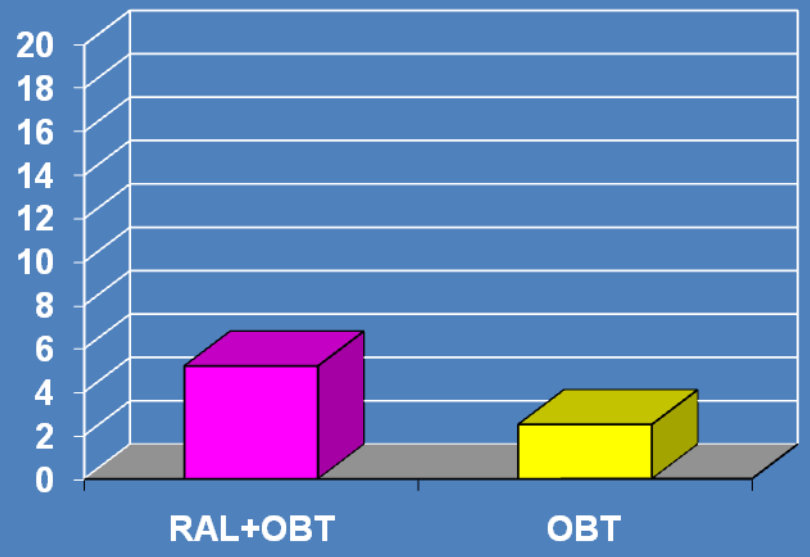
  Raltegravir

Hepatotoxicity and New Agents

Motivate 1 and 2



Benchmark 1



Rates of Grade ¾ rises in ALT

Principali tossicità riferibili alle diverse classi e ai singoli farmaci emersi dagli studi registrativi o da importanti studi di coorte

	RASH IPERSENSIBILITÀ	GASTROINTESTINALE	TOSSICITÀ EPATICA	CARDIOVASCOLARE	OSSA/MUSCOLI	TOSSICITÀ RENALE	SISTEMA NERVOSO	LIPODISTROFIA	ALTERAZIONI METABOLICHE
NRTI			X					X	X
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X
ddI		X	X	X			X		X
3TC									
FTC									
ABC	X			X			X		
TDF					X	X			
NNRTI	X								
EFV	X		X				X		X
NVP	X		X						
ETV	X								
RPV*	X						X		
IP		X		X	X			X	X
IDV		X	X	X		X		X	X
SQV		X							
LPV		X		X					X
FPV	X	X		X					X
ATV			X			X			
DRV		X							
TPV			X				X		X
Inibitori della fusione									
ENF	X								
Inibitori integrasi									
RAL					X		X		
Inibitori CCR5									
MVC			X						

* Approvazione FDA, in attesa approvazione EMA e AIFA

CENTRO NAZIONALE AIDS
In collaborazione con
Ministero della Salute

HAART IN HIV/HCV

VANNO VALUTATI 3 TARGET DELLA HAART IN HCV:

- **EFFICACIA VIRO-IMMUNOLOGICA**

- **TOLLERABILITA'**
  epatica
  cardiovascolare
  renale
  ossea
  neurologica
  metabolica

- **RIDOTTE DDI CON I NUOVI DAAs**

Atherosclerosis risk in HIV-infected patients: The influence of hepatitis C virus co-infection

Background: The influence of hepatitis C virus (HCV) infection on atherosclerosis risk in HIV-infected patients has not been adequately evaluated in real-life situations.

Objectives and methods: **We compared indexes of early atherosclerosis evaluated by echo-Doppler ultrasound** (***presence of plaque in carotid or femoral arteries***) in **18 HCV–HIV co-infected patients** versus **22 HIV mono-infected patients**.

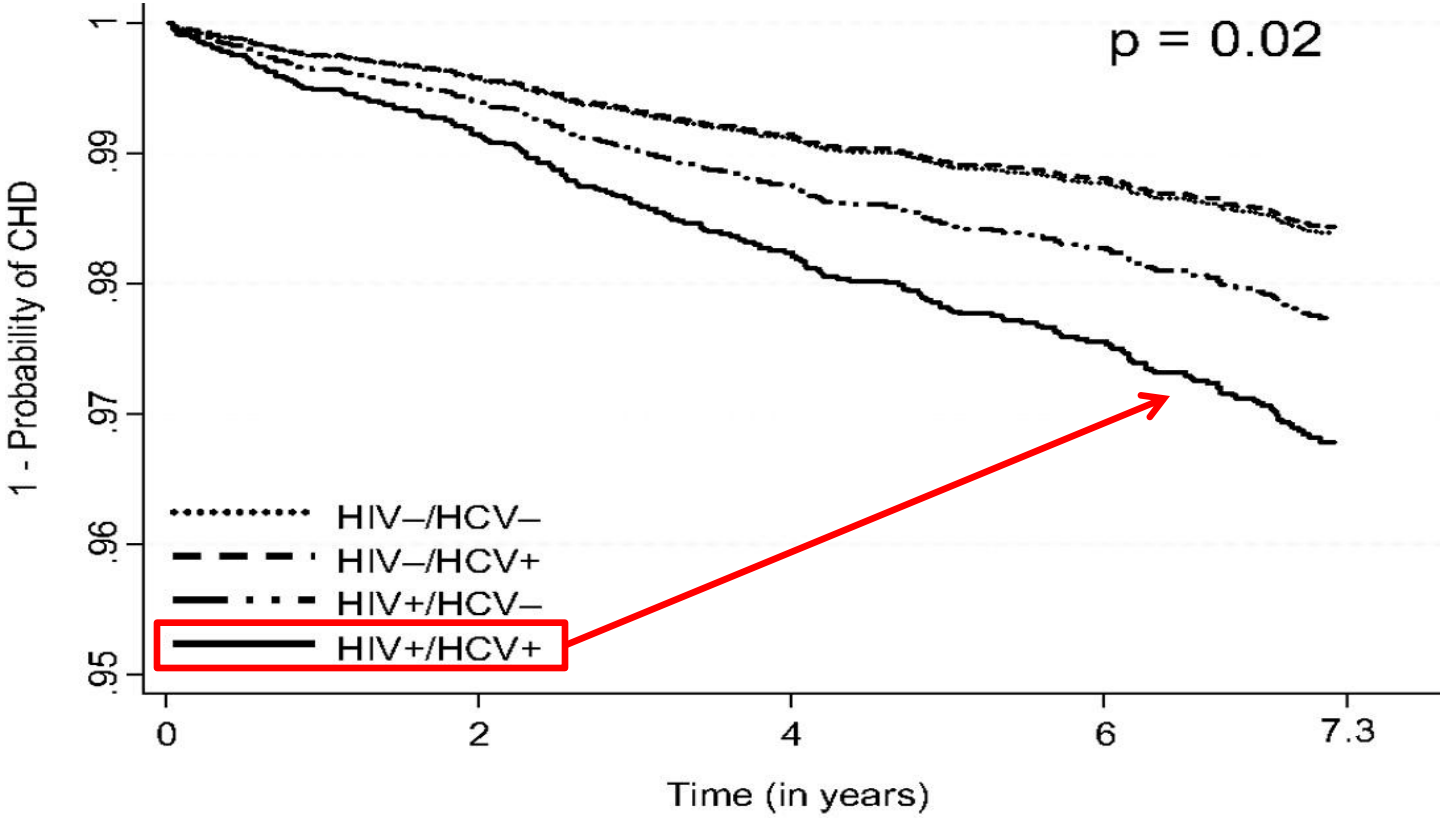
Results**: Prevalence of subclinical carotid plaque was significantly higher in HCV–HIV co-infected patients (p = 0.04)**, despite of the fact LDL-cholesterol and blood pressure (BP) were lower in the co-infected patients (p = 0.003). HCV chronic infection (OR = 10; IC: 1.5–72; p = 0.02) was an independent risk factor.

Conclusion: This cross sectional study suggests that **HCV infection might be an independent cardiovascular risk factor in HCV–HIV co-infected patients**. HCV infection might be considered as not only a liver infection but also as a metabolic disease in HIV patients, justifying regular cardiovascular surveillance.

Circulation: Cardiovascular Quality and Outcomes

American Heart Association.

The Risk of Incident Coronary Heart Disease Among Veterans With and Without HIV and Hepatitis C



No. at risk					
HIV-/HCV-	5453	5212	4898	4435	2918
HIV-/HCV+	701	685	648	575	398
HIV+/HCV-	1687	1532	1379	1208	932
HIV+/HCV+	738	655	566	477	353

Freiberg M et al. Circ Cardiovasc Qual Outcomes 2011;4:425-432

Principali tossicità riferibili alle diverse classi e ai singoli farmaci emersi dagli studi registrativi o da importanti studi di coorte

	RASH IPERSENSIBILITÀ	GASTROINTESTINALE	TOSSICITÀ EPATICA	CARDIOVASCOLARE	OSSA/MUSCOLI	TOSSICITÀ RENALE	SISTEMA NERVOSO	LIPODISTROFIA	ALTERAZIONI METABOLICHE
NRTI			X					X	X
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X
ddI		X	X	X			X		X
3TC									
FTC									
ABC	X			X			X		
TDF					X	X			
NNRTI	X								
EFV	X		X				X		X
NVP	X		X						
ETV	X								
RPV*	X						X		
IP		X		X	X			X	X
IDV		X	X	X		X		X	X
SQV		X							
LPV		X		X					X
FPV	X	X		X					X
ATV			X			X			
DRV		X							
TPV			X				X		X
Inibitori della fusione									
ENF	X								
Inibitori integrasi									
RAL					X		X		
Inibitori CCR5									
MVC			X						

* Approvazione FDA, in attesa approvazione EMA e AIFA

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In collaborazione con
Ministero della Salute

HAART IN HIV/HCV

VANNO VALUTATI 3 TARGET DELLA HAART IN HCV:

- **EFFICACIA VIRO-IMMUNOLOGICA**

- **TOLLERABILITA'**
  epatica
  cardiovascolare
  renale
  ossea
  neurologica
  metabolica

- **RIDOTTE DDI CON I NUOVI DAAs**

COINFEZIONE HIV/HCV E CKD

- Patients with chronic HCV infection were at higher risk of CKD
- Higher HCV-RNA levels were associated with an increased risk of CKD
- The risk of CKD was similar in anti-HCV negative patients and anti-HCV+ patients with resolved infection
- HCV genotype was not significantly associated with risk of CKD

EuroSIDA

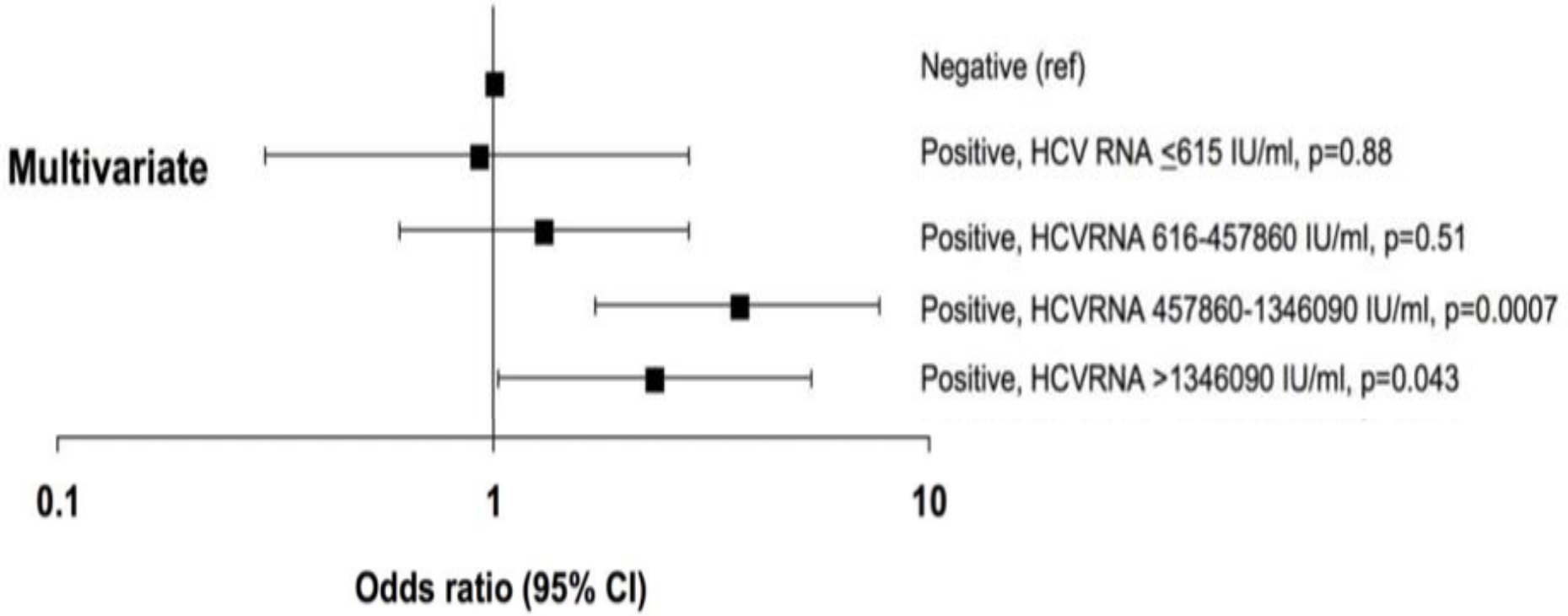
COINFEZIONE HIV/HCV E CKD

- The mechanisms by which HCV may affect renal function are unclear and warrant further study
  - Direct effect of the virus?
  - Marker of severe liver disease?
- Should HIV/HCV coinfected patients avoid ARVs associated with risk of CKD?
- Does anti-HCV treatment reverse the decline in renal function in HCV patients with CKD?

OPEN ACCESS Freely available online PLoS one

Hepatitis B and C Co-Infection Are Independent Predictors of Progressive Kidney Disease in HIV-Positive, Antiretroviral-Treated Adults

Participants with undetectable or low HCV-RNA had similar odds of progressive CKD as HCV seronegative, while participants with HCV-RNA .800,000 IU/ml had increased odds (OR 3.07; 95% CI 1.60–5.90).



Mocroft A et al., PLoSOne 2012; 7(7):e40245

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NRTI			X					X	X
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X
ddI		X	X	X			X		X
3TC									
FTC									
ABC	X			X			X		
TDF					X	X			
NNRTI	X								
EFV	X		X				X		X
NVP	X		X						
ETV	X								
RPV*	X						X		
IP		X		X	X			X	X
IDV		X	X	X		X		X	X
SQV		X							
LPV		X		X					X
FPV	X	X		X					X
ATV			X			X			
DRV		X							
TPV			X				X		X
Inibitori della fusione									
ENF	X								
Inibitori integrasi									
RAL					X		X		
Inibitori CCR5									
MVC			X						

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  metabolica

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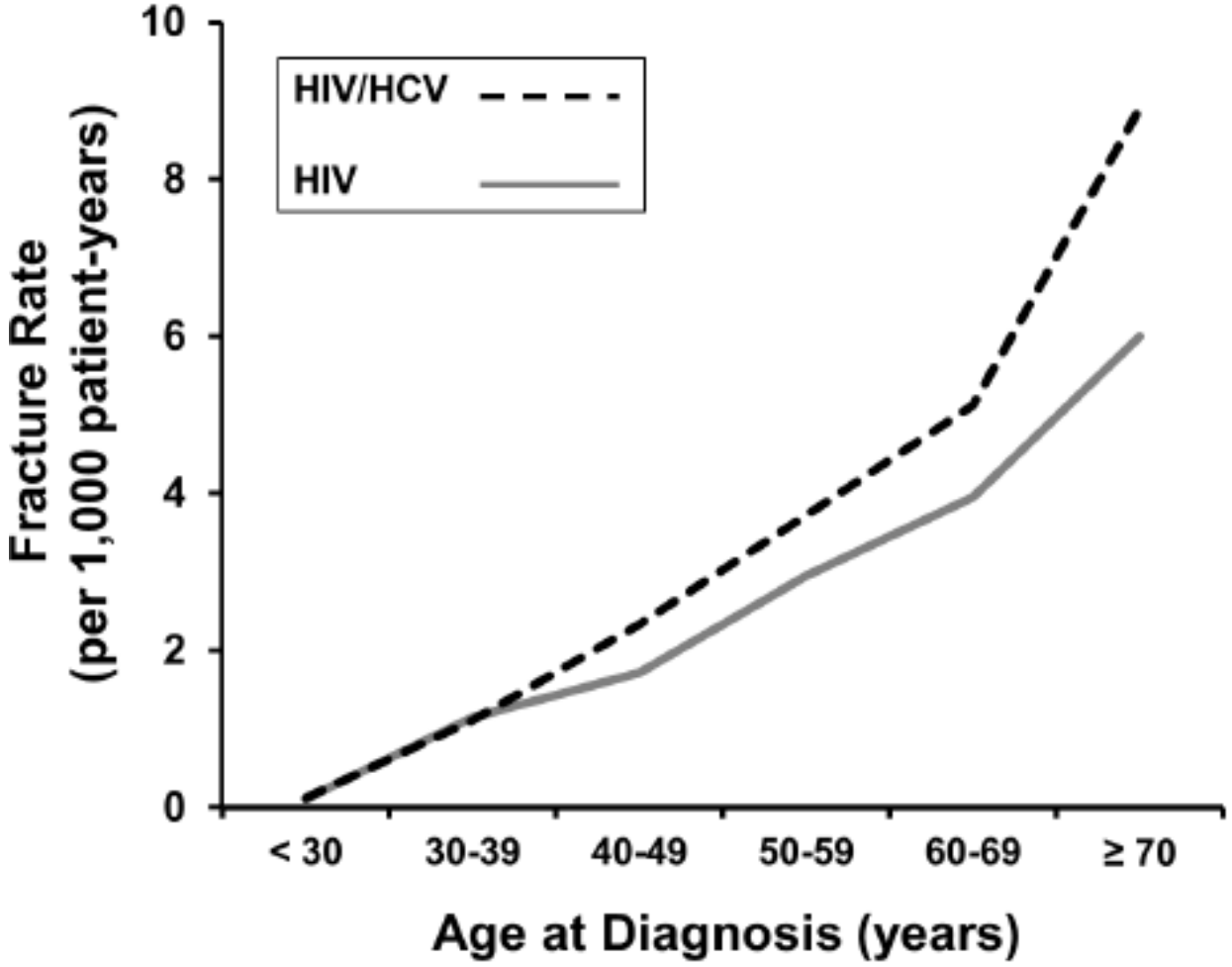
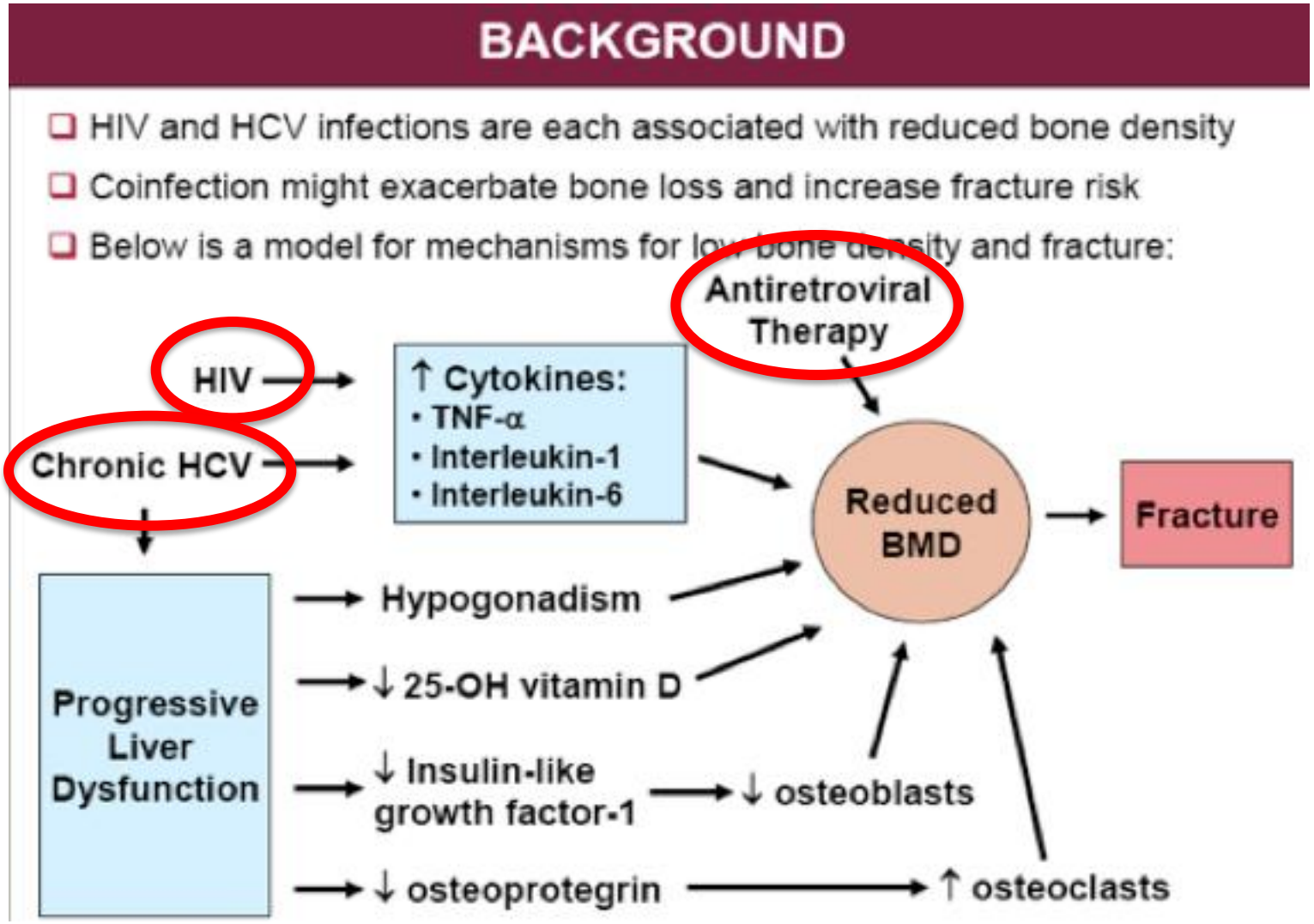
Hepatitis C co-infection and severity of liver disease as risk factors for osteoporotic fractures among HIV-infected patients



Fracture rates were significantly higher among HIV/HCV patients than HIV-only patients (2.57 versus 2.07/1000 patient-years, relative risk = 1.24, $p < 0.0001$).

Maaoluf NM et al., J Bone Miner Res. 2013 Dec;28(12):2577-83

Risk of Fractures Associated with HIV/HCV Coinfection



Volk J et al., 20 CROI 2013

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NRTI			X					X	X
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X
ddI		X	X	X			X		X
3TC									
FTC									
ABC	X			X			X		
TDF					X	X			
NNRTI	X								
EFV	X		X				X		X
NVP	X		X						
ETV	X								
RPV*	X						X		
IP		X		X	X			X	X
IDV		X	X	X		X		X	X
SQV		X							
LPV		X		X					X
FPV	X	X		X					X
ATV			X			X			
DRV		X							
TPV			X				X		X
Inibitori della fusione									
ENF	X								
Inibitori integrasi									
RAL					X		X		
Inibitori CCR5									
MVC			X						

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- **RIDOTTE DDI CON I NUOVI DAAs**

COINFEZIONE HIV/HCV E HAND

Linee Guida Italiane

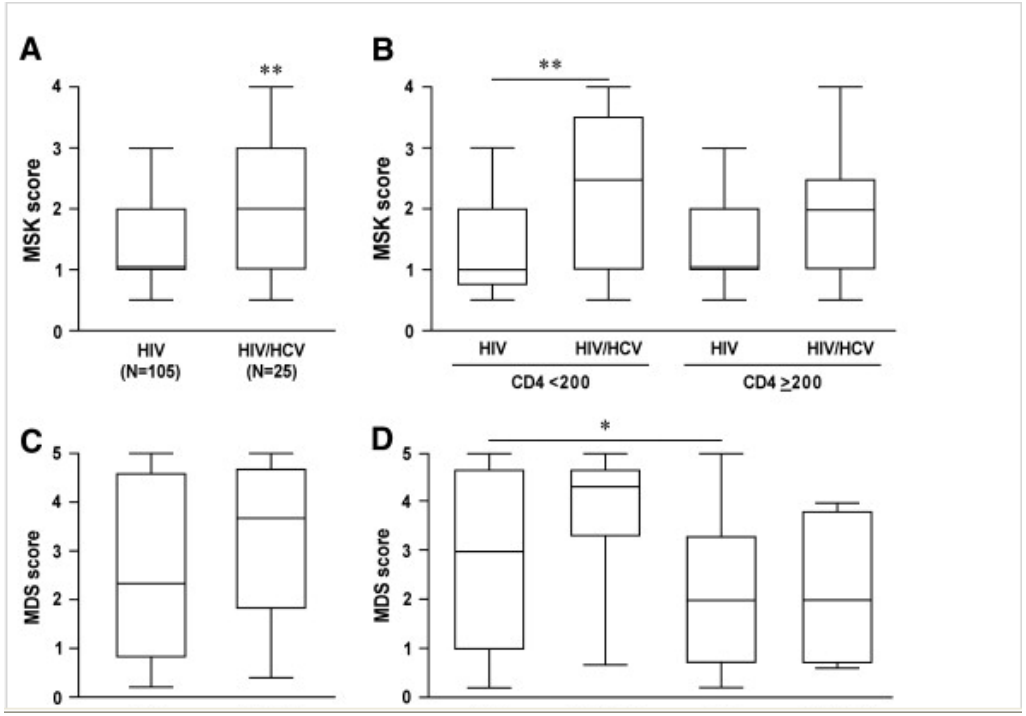
	ALTERAZIONE ACQUISITA IN ≥2 AREE COGNITIVE DOCUMENTATA DA ESAME NP	INTERFERENZA CON LA VITA QUOTIDIANA
Deficit Neurocognitivo Asintomatico (ANI)	Presente	No
Disturbo Neurocognitivo Lieve (MND)	Presente	Lieve
Demenza HIV-associata (HAD)	Presente	Grave

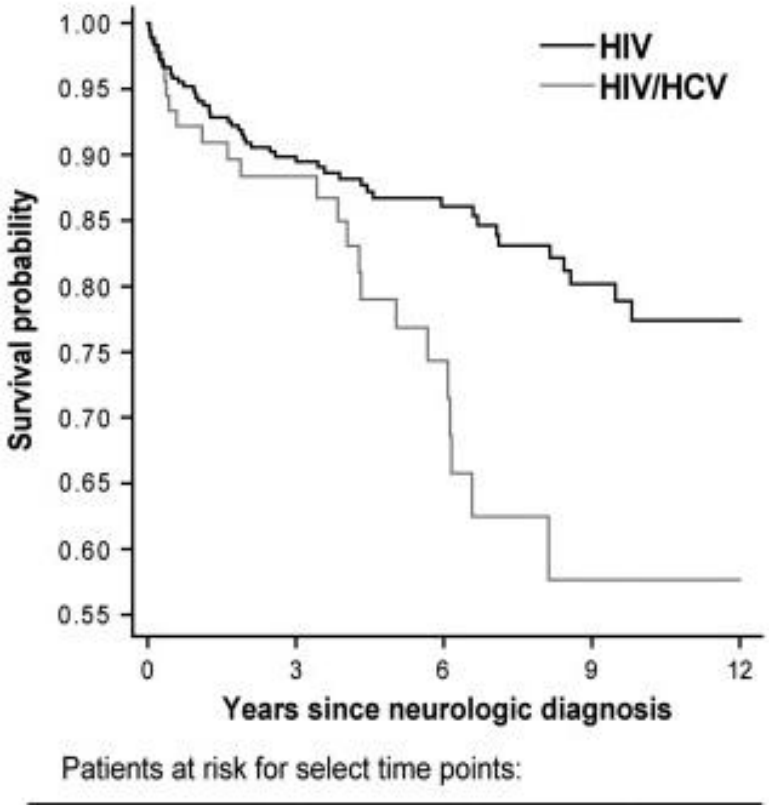
HAND: *HIV-associated Neurocognitive Disorders*; ANI: *Asymptomatic Neurocognitive Impairment*; MND: *Mild Neurocognitive Disorder*; HAD: *HIV-Associated Dementia*; Esame NP: Esame Neuropsicologico

Fattori di rischio:

- Nadir di CD4 < 200 cellule/uL
- Età superiore a 50 anni
- Coinfezione con HCV, diabete, insulino-resistenza

Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS





Vivithanaporn P et al., J Neurol Sci. 2012 Jan 15;312(1-2):45-51

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NRTI			X					X	X
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X
ddI		X	X	X			X		X
3TC									
FTC									
ABC	X			X			X		
TDF					X	X			
NNRTI	X								
EFV	X		X				X		X
NVP	X		X						
ETV	X								
RPV*	X						X		
IP		X		X	X			X	X
IDV		X	X	X		X		X	X
SQV		X							
LPV		X		X					X
FPV	X	X		X					X
ATV			X			X			
DRV		X							
TPV			X				X		X
Inibitori della fusione									
ENF	X								
Inibitori integrasi									
RAL					X		X		
Inibitori CCR5									
MVC			X						

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HAART IN HIV/HCV

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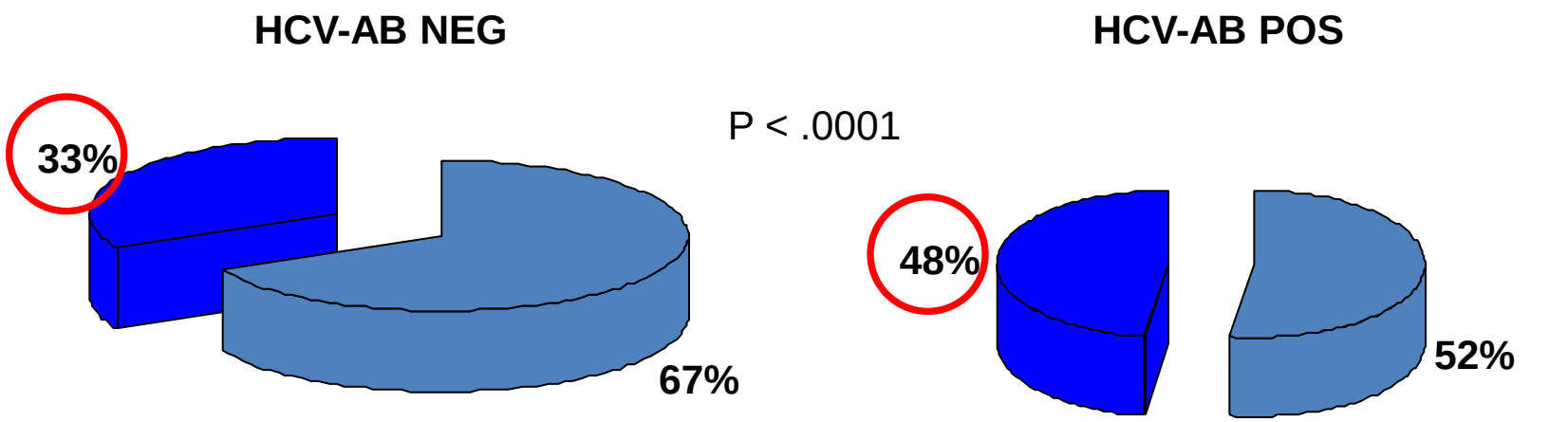
Prevalence of Insulin Resistance in Coinfected and Monoinfected Patients

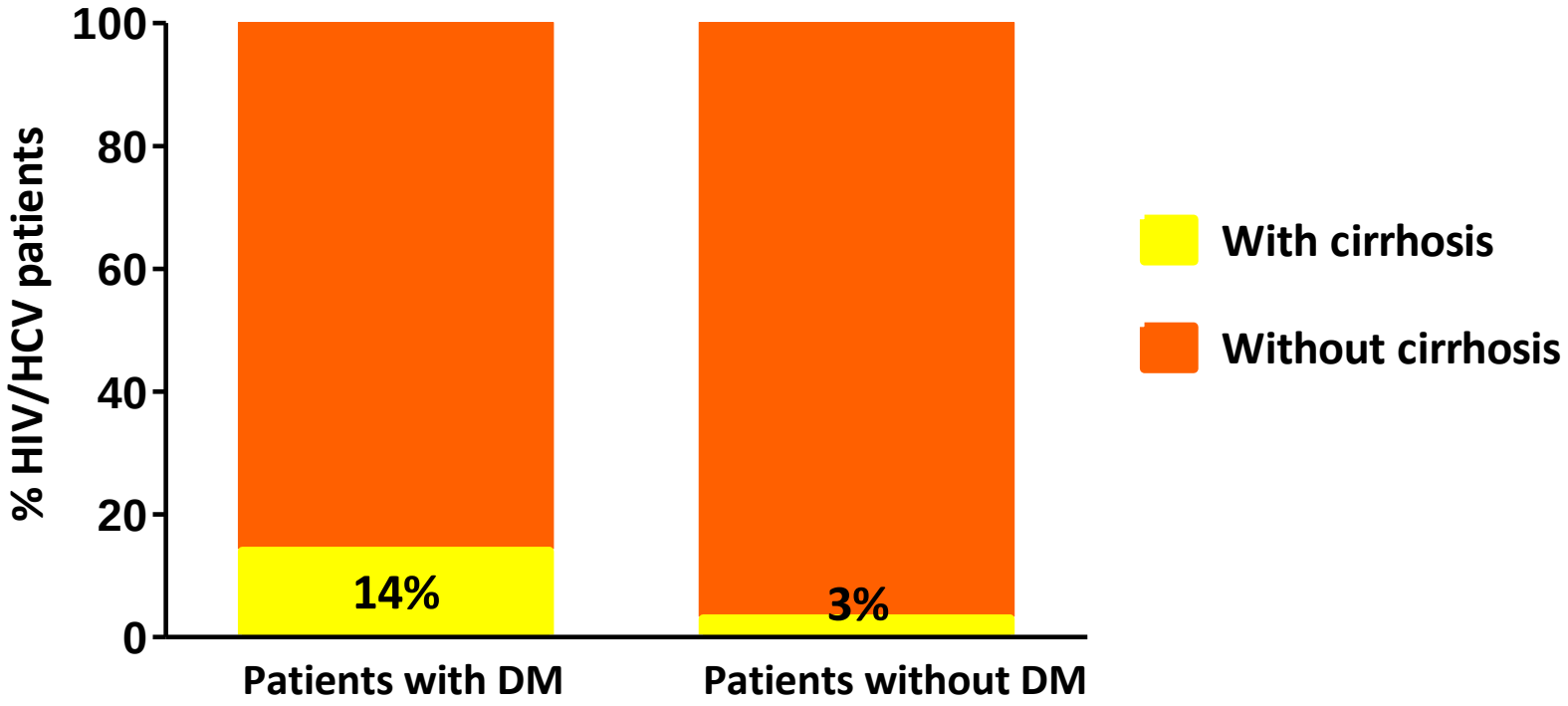
- 1041 nondiabetic HIV patients
- **373 coinfected by HCV**
- **502 HIV monoinfected**
- 166 with unknown HCV-Ab status



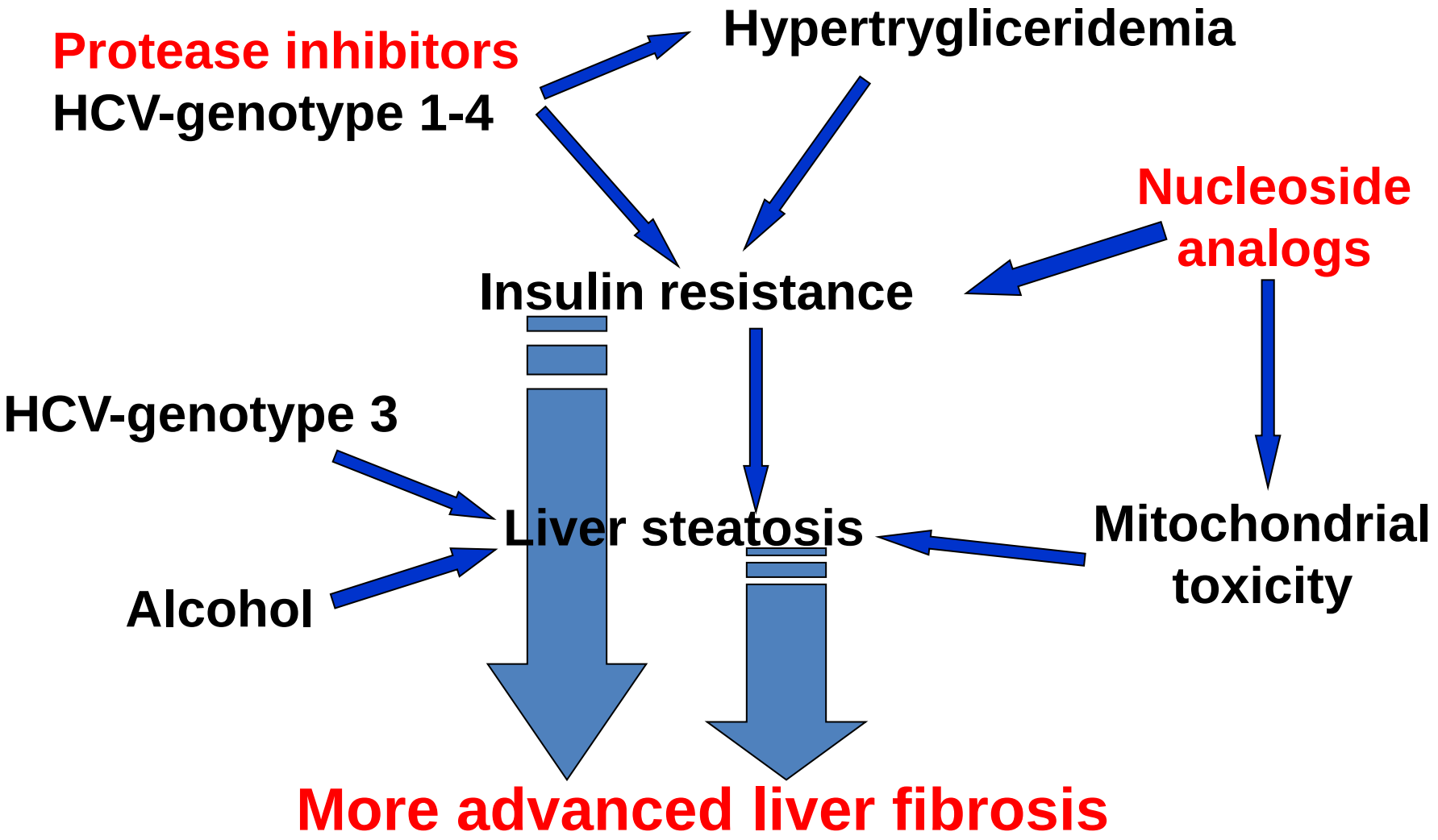
*HOMA (IR) model: (fasting plasma Insulin mU/l x fasting plasma glucose nM/l)/22.5. The cut off of 3.8 was used to define the percentage of insulin-resistant patients.

Squillace N. 2006 Conf ADR and Lipo. Abstract

Diabetes and cirrhosis in HIV/HCV infected patients (IDD-OSR)



Metabolic syndrome as key factor for liver damage in HIV/HCV coinfected individuals



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NRTI			X					X	X
AZT		X	X		X		X	X	X
d4T		X	X				X	X	X
ddI		X	X	X			X		X
3TC									
FTC									
ABC	X			X			X		
TDF					X	X			
NNRTI	X								
EFV	X		X				X		X
NVP	X		X						
ETV	X								
RPV*	X						X		
IP		X		X	X			X	X
IDV		X	X	X		X		X	X
SQV		X							
LPV		X		X					X
FPV	X	X		X					X
ATV			X			X			
DRV		X							
TPV			X				X		X
Inibitori della fusione									
ENF	X								
Inibitori integrasi									
RAL					X		X		
Inibitori CCR5									
MVC			X						

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FRAILTY NEI COINFETTI HIV/HCV

Patients with HIV/HCV co-infection are more frail for viral and behavioral factors and possible strategies could be:

- **Treat them with less toxic antiretroviral drugs in order not to have an additional effect**

- **Treat them for HCV as soon as we will have the drugs**

HAART IN HIV/HCV

VANNO VALUTATI 3 TARGET DELLA HAART IN HCV:

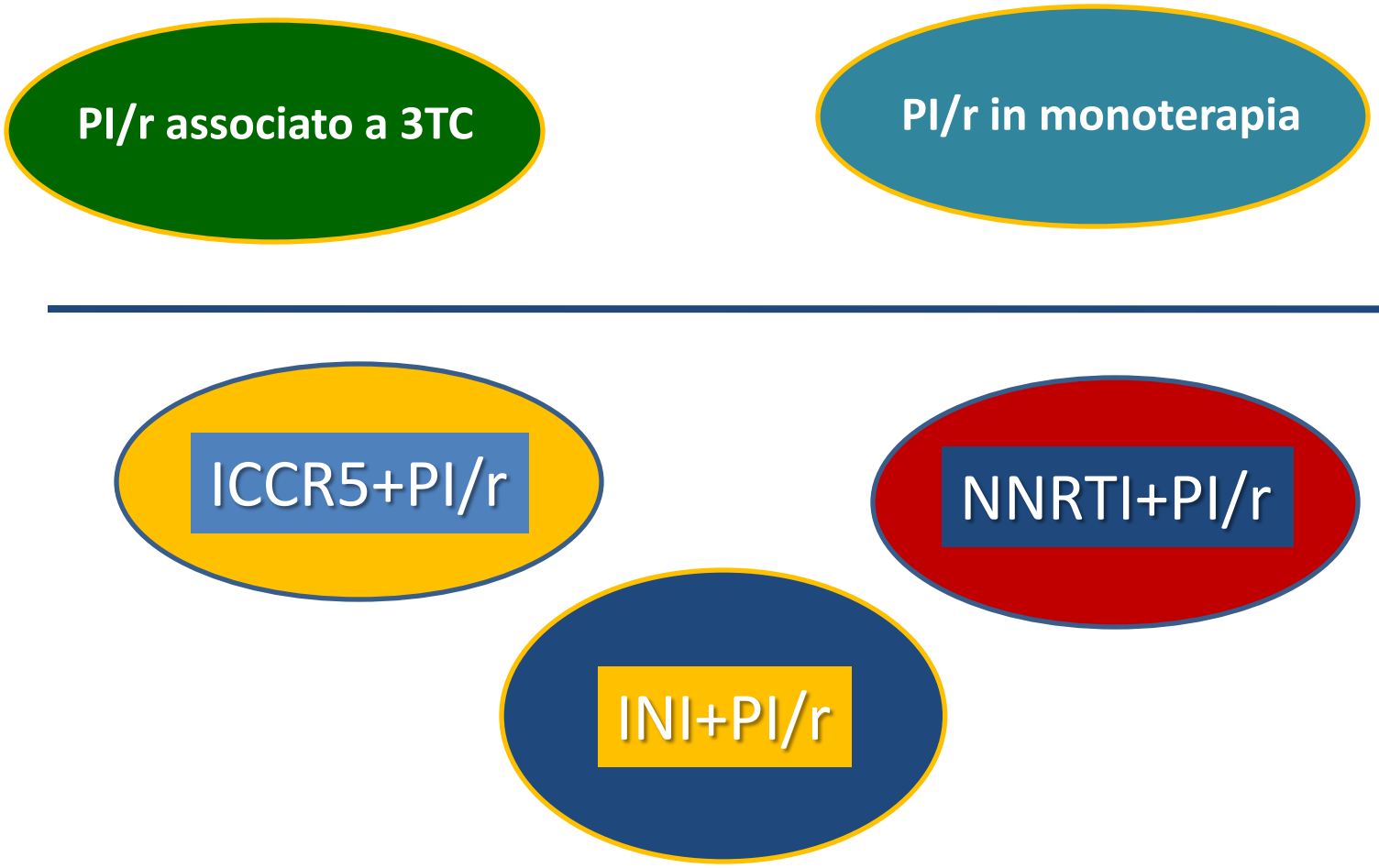
- **EFFICACIA**
- **TOLLERABILITA'**
- **RIDOTTE DDI CON I NUOVI DAAs**

DDI, the very last issue?

		Simeprevir	Sofosbuvir	Daclatasvir
INTI	TDF	SIM ↔; TFV ↔	SOF ↔; TFV ↔	DCV ↔; TFV ↔
	FTC	No data, no predictable interaction	SOF ↔; FTC ↔	No data, no predictable interaction
	3TC	No data, no predictable interaction	No data, no predictable interaction	No data, no predictable interaction
	ABC	No data, no predictable interaction	No data, no predictable interaction	No data, no predictable interaction
Protease Inhibitor	ATV/r	CI; No data, Expected SIM ↑	No data, no predictable interaction	DCV ↑* →Lower Dacla to 30mg
	DRV/r	CI; SIM ↑; DRV ↔	SOF ↑; DRV ↔	CI; No data
	LPV/r	CI; No data, Expected SIM ↑	No data, no predictable interaction	CI; No data
NNRTIs	EFV	CI; SIM ↓; EFV ↔	SOF ↔; EFV ↔	DCV ↓* →Upper Dacla to 90mg
	NVP	CI; No data, Expected SIM ↓	No data, no predictable interaction	No data, Expected DCV ↓
	RPV	SIM ↔; RPV ↔	SOF ↔; RPV ↔	No data, no predictable interaction
	ETV	CI; No data, Expected SIM ↓	No data, no predictable interaction	No data, DCV ↓* →Upper Dacla to 90mg
Integrase Inhibitor	RAL	SIM ↔; RAL ↔	SOF ↔; RAL ↔	No data, no predictable interaction
	ELV/cobi	CI; No data, Expected SIM ↑	No data, no predictable interaction	No data, Expected DCV ↑
	DLG	No data, no predictable interaction	No data, no predictable interaction	No data, no predictable interaction
	MVC	No data, no predictable interaction	No data, no predictable interaction	No data, no predictable interaction

[1]Karageorgopoulos, Curr Opin HIV/AIDS 2014. [2]EACS Guidelines

NEW SWITCH STRATEGY
NEI COINFETTI HIV/HCV



Regimi di semplificazione

PI/r in monoterapia

Razionale

- Riduzione degli effetti collaterali
- Risparmio di classi terapeutiche
- Riduzione dei costi

Target

- Pazienti virosoppressi da almeno 6 mesi
- Assenza di pregresse resistenze per il PI/r da usare
- Nadir > 200 CD4
- Ottimale aderenza

Ricette con LPV/r nei coinfetti HIV/HCV..

LPV/r in monotherapy: Trial KAMON 2

IAS 2011

Abstract no. CDB358

HAART simplification with lopinavir/ritonavir monotherapy in HIV/HCV coinfected patients starting anti-HCV treatment: final results of a randomised, proof-of-principle clinical trial (KAMON 2 Study)

H. Hasson[1], L. Galli[1], G. Gallotta[1], V. Neri[2], P. Blanc[3], M. D'Annunzio[4], G. Morsica[1], S. Bagaglio[1], S. Sollima[5], A. Lazzarin[1], C. Uberti Foppa[1]

1Vita & Salute University Milano, Infectious Diseases, Milano, Italy, 2National Institute of Infectious Diseases, Spallanzani, Infectious Diseases, Roma, Italy, 3Infectious Diseases Section,Hospital SS Annunziata, Firenze, Italy, 4Institute of Infectious Diseases,University of Bari, Bari, Italy, 5Ospedale Luigi Sacco, Malattie Infettive e Tropicali, Milano, Italy

Ricette con LPV/r nei coinfetti HIV/HCV..

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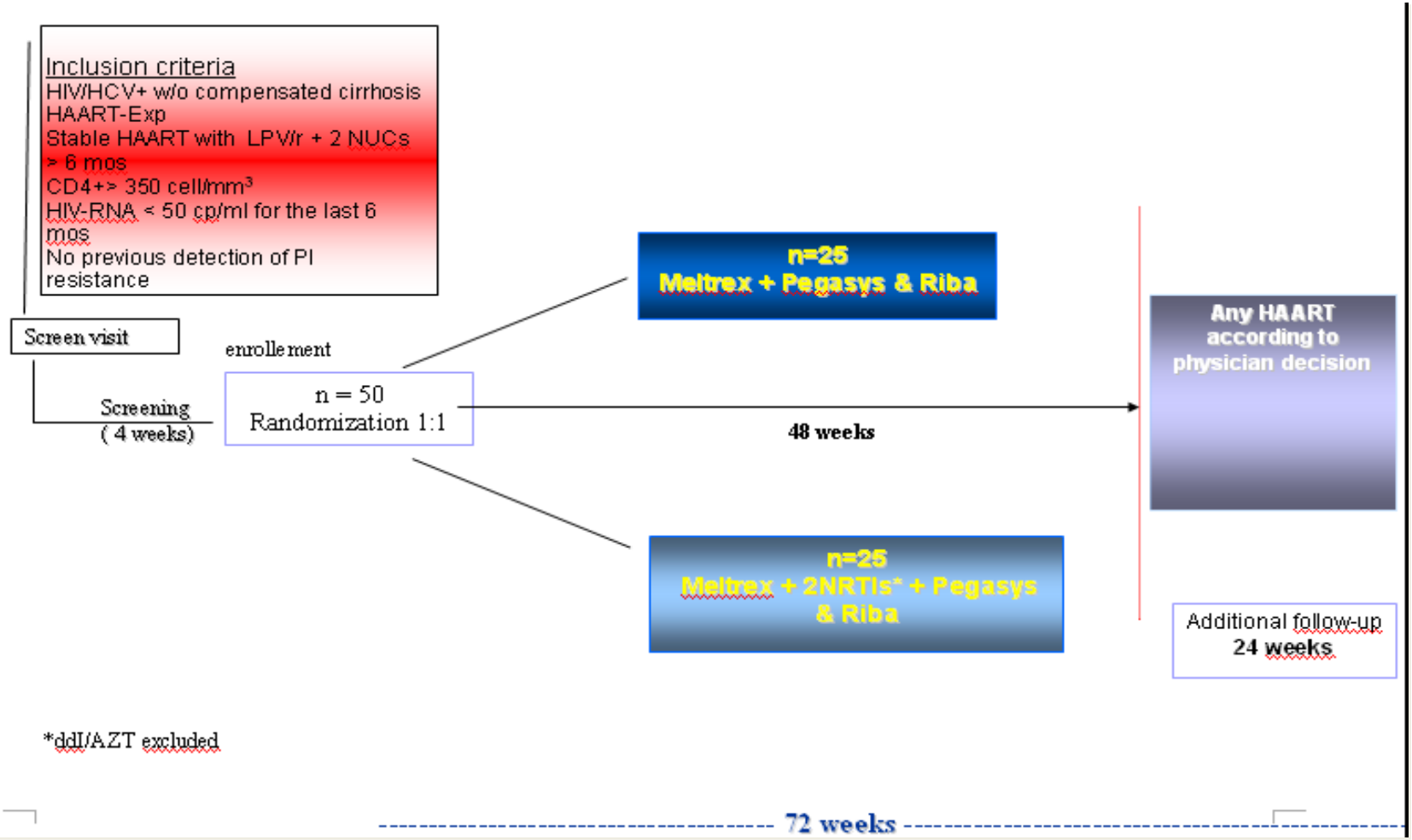

Ricette con LPV/r nei coinfetti HIV/HCV..

LPV/r in monotherapy: Trial KAMON 2

IAS 2011

Abstract no. CDB358

Conclusion

- In this proof-of-principle clinical trial, PI monotherapy + anti-HCV drugs was safe and effective as HAART + anti-HCV drugs . This results might encourage the evaluation of HAART simplification strategy in patients receiving anti-HCV treatment

- Simplified PI-based regimen may be equally tolerated and effective as full HAART also in HIV-HCV coinfected patients on anti-HCV therapy

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1-Bierman WF, van Agtmael MA, Nijhuis M, Danner SA, Boucher CA. HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review. *AIDS* 2009,23:279-291

2-Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, *et al*. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 2008,9:82-88.

3-DHHS Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. . In; 2011. pp. 1-166.

4-Perez-Valero I, Arribas JR. Protease inhibitor monotherapy. *Curr Opin Infect Dis* 2011,24:7-11.

Regimi di semplificazione

PI/r associato a 3TC

Razionale

- Riduzione degli effetti collaterali
- Risparmio di classi terapeutiche
- Riduzione dei costi

Target

- Pazienti virosoppressi da almeno 6 mesi
- Assenza di pregresse resistenze per il PI/r da usare
- Nadir > 200 CD4
- Ottimale aderenza

Studi di semplificazione con PI/r associato a 3TC per i coinfetti HIV/HCV?

Name of Study	Description of Study	Study Population	N
LOREDA	Single-Arm, Pilot Study of LPV/r BID/QD + 3TC QD	ARV-Naive	N=40
GARDEL	LPV/r BID + 3TC vs LPV/r BID + 3TC/FTC + N(t)RTI	ARV-Naive	N=410
OLE	Simplification to LPV/r BID + 3TC QD	ARV-Experienced, VL<50 c/mL for at least 6 months	N=336
ATLAS	Simplification to ATV+rtv + 3TC QD	ARV-Experienced, VL<50 c/mL x 2, 3 months apart	N=40

Studi sulla dual therapy con RAL

RAL+PI/r nei coinfetti HIV/HCV?

ARV Combination	Name of Study	Experimental Arm	Reference Arm	Study Population	N
RAL + LPV/r	PROGRESS	RAL BID + LPV/r BID	LPV/r BID + TDF/FTC QD	ARV-Naive	N= 206
RAL + ATV 300	SPARTAN	RAL BID + ATV 300 BID	ATV+rtv QD + TDF/FTC QD	ARV-Experienced	N=94
RAL + DRV+rtv	ACTG 5262	RAL BID + DRV+rtv QD	Single Arm	ARV-Naive	N=112
RAL + DRV+rtv	NEAT	RAL BID + DRV+rtv QD	DRV+rtv QD + TDF/FTC QD	ARV-Naive	N=800

Percent of Patients with Grade 3 or Grade 4 Laboratory Abnormalities in BENCHMRK-2 (cont.)

Laboratory Test (Unit)	Toxicity Criteria*		Raltegravir (N=230)	Placebo (N=119)
Total bilirubin (mg/dL)	Grade 3	2.6 – 5.0 x ULN	3.0	4.2
	Grade 4	>5.0 x ULN	0	0
AST (IU/L)	Grade 3	5.1 – 10.0 x ULN	3.5	3.4
	Grade 4	>10.0 x ULN	0.4	1.7
ALT (IU/L)	Grade 3	5.1 – 10.0 x ULN	1.7	0.8
	Grade 4	>10.0 x ULN	0.4	1.7
Alkaline phosphatase (IU/L)	Grade 3	5.1 – 10.0 x ULN	0.4	0.8
	Grade 4	>10.0 x ULN	0	0
Pancreatic amylase (IU/L)§	Grade 3	2.1 – 5.0 x ULN	4.3	2.5
	Grade 4	>5.0 x ULN	0.4	0
Lipase (IU/L)	Grade 3	3.1 – 5.0 x ULN	0.4	0.8
	Grade 4	>5.0 x ULN	0	0
Creatine kinase (IU/L)	Grade 3	10.0 – 19.9 x ULN	3.0	2.5
	Grade 4	≥20.0 x ULN	3.0	1.7

* Grades 3 and 4 per DAIDS toxicity criteria.
Defined as (number of patients meeting the specific serum pancreatic amylase criteria) / (number of patients with serum amylase test result).

Dual therapy with Raltegravir associated to different Protease Inhibitors in HIV+ experienced patients: data of long-term longitudinal follow-up of 192 weeks

Martini S.[1], Coppola N.[1], Bonora S.[2], D'Avolio A.[2], Macera M.[1], Iodice V.[1], Cascone A.[1], Di Perri G.[2], Filippini P.[1]

[1] UOC Diagnosi e Terapia AIDS e Patologie Infettive Correlate della Seconda Università degli studi di Napoli; [2] Clinica di Malattie Infettive dell'Università di Torino

Introduction

- In last years many data in literature about HIV treatment have evidenced the efficacy and tolerability of integrase inhibitors, remarking the opportunity of avoiding NRTI backbone, to improve long-term management of treatment.
- NRTI-sparing regimen, based on association of Raltegravir (RAL) with a boosted Protease Inhibitor (PI), may combine these two aspects.
- Our aim is to evaluate efficacy and tolerability of an NRTI-sparing regimen, based on RAL+PI, in switch strategy, observed in a long-term follow-up of 192 weeks.

Study Design

- We have retrospectively analyzed a cohort of 72 HIV+ experienced patients, treated by a standard regimen of 2 NRTI+ PI/r, since October 2009.
- Among these patients, 23 have switched to an NRTI-sparing regimen, based on association of Ral+PI (Cases) and 49 patients have continued standard regimen (Controls).
- In Cases group, 16 patients showed, before switch, uncontrolled HIV plasmatic replication. Mean follow-up for two groups has been of 192 weeks.

Figure 1 STUDY DESIGN

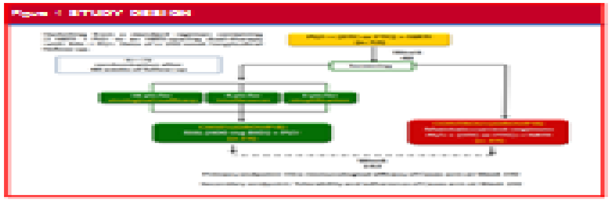
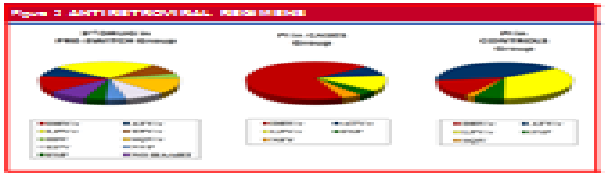


Figure 2 ANTIRETROVIRAL REGIMENS



Methods

- Laboratory tests have been performed (CD4, HIV-RNA, Triglycerides, Cholesterol, ALT, AST, Creatinine, Haemogram) to assess efficacy and tolerability. CKD-EPI equation has been used to estimate glomerular filtration rate (GFR).
- Adherence has been assessed by counseling and SERAD questionnaire (Self-Reported Adherence).
- C-trough of drugs in Cases Group has been evaluated by a validated HPLC method to confirm the propriety of RAL in combination to different PI.

Figure 3 BASELINE DATA

Baseline Data	CASES GROUP (RAL + PI)	CONTROL GROUP (2 NRTI + PI/r)
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

Results

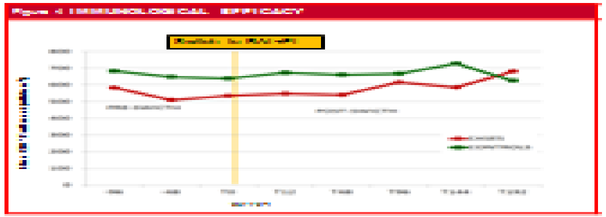
- Data of Cases have been compared to Pre-switch (PS) data and to Controls.
- In Cases Group there has been a progressive CD4 recovery of 100 cells at the end of follow-up with a virological success (< 20 copies/ml) in about 75% of patients versus 88% of Control Group.
- About hepatic parameters and lipid profile, no pathological values have been observed in both groups.
- About CKD-EPI, no alteration has been observed in two groups, except two cases with lower GFR in Cases group, not related to antiretroviral treatment.
- About pharmacokinetic (PK) data, C-trough of RAL has appeared lower than range of studies in literature in 2 patients and higher in 11 cases, but no virological failures and no collateral effects have been reported.
- All data have been summarized in attached table

Viro-Immunological Data

Mean CD4+ count after switch from ST to Raltegravir + PI

- [illegible]
- [illegible]

Figure 4 IMMUNOLOGICAL EFFICACY



Proportion of Patients with Virological Suppression at Week 48

- [illegible]
- [illegible]

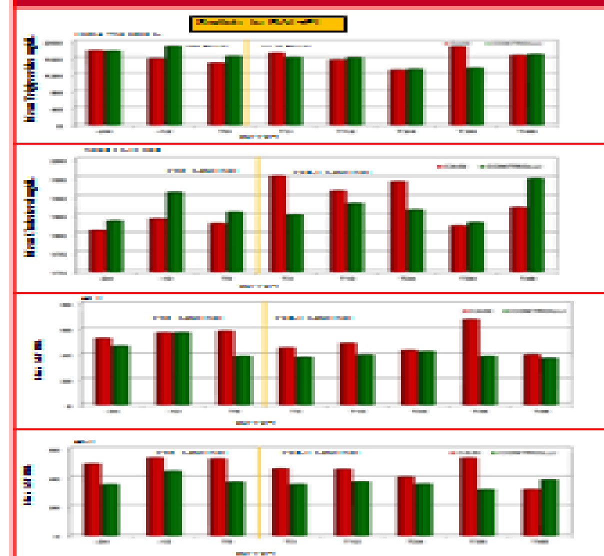
Figure 5 VIROLOGICAL EFFICACY

Metabolic Data

Metabolic results after switch from ST to Raltegravir + PI

- [illegible]
- [illegible]

Figure 6 METABOLIC RESULTS



Analysis of Statistical Significance

Table 1 Statistical significance of data

	CASES GROUP RAL + PI	PRE-SWITCH GROUP 2 NRTI + PI/r	P	CASES GROUP RAL + PI	CONTROL GROUP 2 NRTI + PI/r	P
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]			[illegible]		

Conclusion

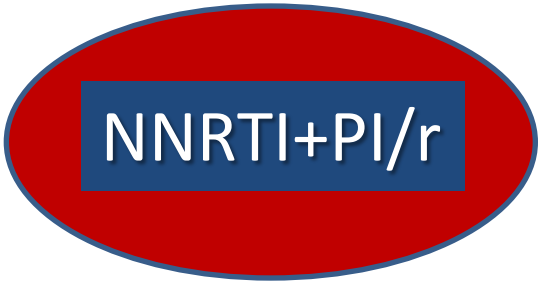
There are few data in literature about dual therapy based on association of RAL to PI. Two trials, in particular, have associated RAL to Lopinavir (Progress Trial) or to Darunavir (Neat Trial) in HIV+ naive patients with good results. In our study Raltegravir has been associated to 5 different PI in switch strategy for experienced patients in a long-term follow-up of 192 weeks. PK parameters have resulted in range of studies in literature. According to literature, RAL, associated to PI, resulted in non-inferior efficacy and similar safety, tolerability and adherence, when is compared with a traditional antiretroviral regimen (2NRTI+PI) through 192 weeks of treatment. Rapid HIV-RNA decay induced by RAL, associated to high genetic barrier of PI, may let to optimize long-term efficacy and tolerability.

Reference

[illegible]

Studi sulla dual therapy con ETV

ETV+PI/r nei coinfetti HIV/HCV?



ARV Combination	Name of Study	Experimental Arm	Reference Arm	Study Population	N
LPV/r + NNRTI	KAL Y INTE	LPV/r BID + ETR BID	Single Arm	ARV-Naive	N=30
DRV+rtv + NNRTI	CID 0821	DRV+rtv QD + ETR BID or QD	Single Arm	Acute HIV	N=20

284

Hepatic safety and tolerability of etravirine: pooled 96-week analysis of DUET-1 and DUET-2

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Abstract

Background

DUET-1 and DUET-2 are identically designed, randomized, double-blind, Phase III trials that assessed the efficacy and safety of etravirine (ETR; TMC125) in HIV-1-infected, treatment-experienced patients. We report pooled 96-week hepatic safety data.

Methods

Patients with HIV-1 RNA ≥5000 copies/mL, documented genotypic NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations were randomized to ETR 200mg bid or placebo, both with a background regimen (BR) of darunavir/ritonavir (DRV/r) + NRTI(s) ± enfuvirtide (ENF). Patients co-infected with chronic hepatitis B and/or C were allowed to enroll if clinically stable, not expected to require hepatitis treatment during the trial, and had baseline aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels <5x upper limit of normal (ULN). Hepatic adverse events (AEs) and laboratory parameters were assessed.

Results

One thousand, two hundred and three patients (12.4% co-infected with hepatitis B and/or C) were evaluated. Median treatment duration was 26 weeks longer in the ETR group (96 vs 69.6 weeks for placebo). Total patient-years exposure (PYE) was higher in the ETR group (895.4 vs 766.7 for placebo). Incidence of hepatic AEs was comparable between the two groups (see table below). Incidence of serious hepatic AEs and treatment-emergent grade 3/4 ALT/AST elevations was low in both groups. No hepatic AE-related deaths occurred.

	Overall incidence, n (%)		Incidence adjusted for difference in exposure time, number of patients/100 PYE	
	ETR + BR (n=599)	Placebo + BR (n=604)	ETR + BR (n=599)	Placebo + BR (n=604)
AE				
Any hepatic AE	52 (9)[a]	43 (7)	5.8	5.6
Grade 3 or 4 hepatic AEs	25 (4)	18 (3)	2.8	2.3
Serious hepatic AEs	10 (2)	9 (1)	1.1	1.2
Any hepatic AE leading to discontinuation	8 (1)	4 (1)	0.9	0.5
Treatment-emergent grade 3 or 4 hepatic laboratory abnormalities				
ALT increase (>5.1x ULN)	26 (4)	14 (2)	2.9	1.8
AST increase (>5.1x ULN)	23 (4)	15 (2)	2.6	2.0

[a]p value vs placebo = 0.3370 (Fisher's exact test)

Conclusions

In treatment-experienced patients, the frequency of hepatic events with ETR was generally comparable to placebo through 96 weeks in DUET-1 and DUET-2. Discontinuation due to hepatic AEs with ETR was low and comparable with placebo.

DUET study design and major inclusion criteria

Baseline characteristics and background ARVs

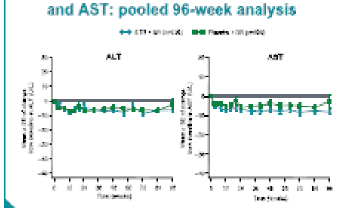
Overview of AEs (regardless of causality): pooled 96-week analysis

Summary of hepatic AEs: pooled 96-week analysis

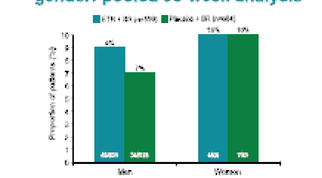
Incidence of any hepatic AE adjusted for difference in treatment exposure: pooled 96-week analysis

Most common hepatobiliary AEs:* pooled 96-week analysis

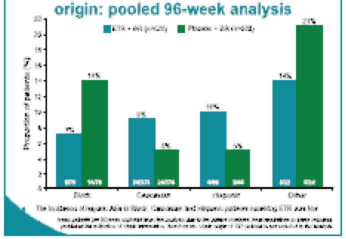
Mean change from baseline in ALT and AST: pooled 96-week analysis



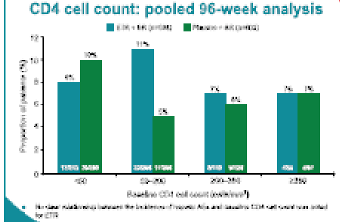
Incidence of any hepatic AE by gender: pooled 96-week analysis



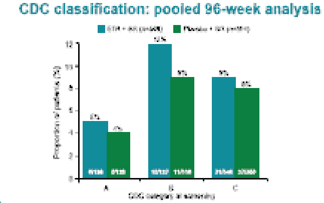
Incidence of any hepatic AE by ethnic origin: pooled 96-week analysis



Incidence of any hepatic AE by baseline CD4 cell count: pooled 96-week analysis



Incidence of any hepatic AE by CDC classification: pooled 96-week analysis



Incidence of hepatic AEs by hepatitis B and/or C co-infection status: pooled 96-week analysis

Conclusions

- In treatment-experienced patients, the incidence of hepatic AEs with ETR + BR was generally low and comparable with placebo + BR through 96 weeks
  - when adjusted for the difference in treatment exposure, the incidence of hepatic AEs was similar in both treatment groups
- Discontinuation due to hepatic AEs was low and comparable in both groups
  - there were no hepatic-related deaths
- The incidence of hepatic AEs was generally low and comparable between ETR + BR and placebo + BR regardless of
  - gender
  - ethnic origin
  - baseline CD4 cell count
  - screening CDC category
- The incidences of hepatic AEs were higher in patients with hepatitis B and/or C co-infection in both the ETR and placebo groups; however, ETR + BR did not appear to increase hepatic risk in these patients

Acknowledgments

- We express our gratitude to the patients who participated in the studies, as well as the study center staff, the data safety and monitoring board, clinical event adjudication panels, Virco, Tibotec personnel and the following principal investigators.

DUET-1

Argentina: HA Ariza, J Benetucci, P Cahn, LM Calanni, LI Cassetti, J Corral, DO David, A Krolewiecki, MH Losso, P Patterson, RA Teijeiro; **Brazil:** CA da Cunha, B Grinsztejn, EG Kallas, JV Madruga, EM Netto, JH Pilotto, M Schechter, J Suleiman, A Timerman; **Chile:** J Ballesteros, R Northland; **Costa Rica:** AA Avilés Montoya, G Herrera Martinez, A Solano Chinchilla; **France:** M Dupon, C Katlama, JM Livrozet, P Morlat, G Pialoux, C Piketty, I Poizot-Martin; **Mexico:** J Andrade-Villanueva, G Reyes-Terán, J Sierra-Madero; **Panama:** A Canton, A Rodriguez, N Sosa; **Puerto Rico:** JO Morales Ramirez, JL Santana Bagur, R Soto-Malave; **Thailand:** T Anekthananon, P Mootsikapun, K Ruxrungtham; **USA:** M Albrecht, N Bellos, R Bolan, P Brachman, C Brinson, F Cruickshank, R Elion, WJ Fessel, R Haubrich, T Hawkins, S Hodder, P Hutcherson, T Jefferson, H Katner, C Kinder, M Kozal, J Lalezari, J Leider, D McDonough, A Mills, K Mounzer, J Nadler, D Norris, W O'Brien, G Pierone, K Raben, B Rashbaum, M Rawlings, B Rodwick, P Ruane, J Sampson, S Schrader, A Scribner, M Sension, D Sweet, B Wade, D Wheeler, A Wilkin, T Wilkin, T Wills, M Wohlfeiler, K Workowski

DUET-2

Australia: J Chuah, D Cooper, B Eu, J Hoy, C Workman; **Belgium:** N Clumeck, R Colebunders, M Moutschen; **Canada:** J Gill, K Gough, P Junod, D Kilby, J Montaner, A Rachlis, B Trottier, CM Tsoukas, S Walmsley; **France:** C Arvieux, L Cotte, JF Delfraissy, C Katlama, PM Girard, B Marchou, JM Molina, D Vittecoq, Y Yazdanpanah, P Yeni; **Germany:** K Arasteh, S Esser, G Fätkenheuer, H Gellermann, K Göbels, FD Goebel, H Jäger, JK Rockstroh, D Schuster, S Staszewski, A Stoehr; **Italy:** A Antinori, G Carosi, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, S Rusconi, L Sighinolfi, F Suter; **The Netherlands:** PHJ Frissen, JM Prins, BJA Rijnders; **Poland:** A Horban; **Portugal:** F Antunes, M Miranda, J Vera; **Spain:** P Domingo, B Clotet, G Garcia, JM Gatell, J González-Lahoz, J López-Aldeguer, D Podzamczer; **UK:** P Easterbrook, M Fisher, M Johnson, C Orkin, E Wilkins; **USA:** B Barnett, J Baxter, G Beatty, D Berger, C Borkert, T Campbell, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, JE Gallant, RN Greenberg, C Hicks, DT Jayaweera, S Kerkar, N Markowitz, C Martorell, C McDonald, D McMahon, M Mogyoros, RA Myers Jr, G Richmond, S Schneider, H Schrager, P Shalit, FP Siegal, L Sloan, K Smith, S Smith, P Tebas, LS Tkatch, W Towner

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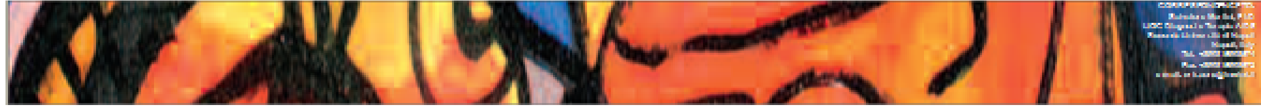
Presented at the 47th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, Pennsylvania, USA, October 29–November 1 2009.

This poster is available on-line at www.tibotec.com

HIVee experience exchange
7-8 February 2013
Hotel Barceló Renacimiento
Seville, Spain
Co-Chairs: Jade Ghosn, France; Christoph Stephan, Germany; and Alan Winston, UK



Dual Therapy with Etravirine, 400 mg, Darunavir, 800 mg and Ritonavir, 100 mg in once daily regimen for switch strategy: Results of 48 weeks of follow-up.

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Introduction/Summary

- The prognostic improvement in HIV patients, induced by HAART, may involve more difficulties in the management of antiviral therapy for the growing clinical complications related to the aging[1].
- The advent of new drugs allows to evaluate new simplified NRTI-Sparing regimens, based on just 2 drugs ("dual therapy")[2] that may represent a valid option either in pro-active switches than in viro-immunological failures.

Study Design

- Our aim is assessing if a "dual therapy", based on association of Etravirine (ETV), 400 mg qd (4 tablets dissolved in water to optimize compliance), Darunavir (DRV),800 mg qd and Ritonavir (RTV),100 mg qd, may be a good therapeutic option about efficacy, tolerability and adherence compared to standard regimen (ST) with 2 NRTI+ 1 PI/r in switches for toxicity, simplification or failure.
- This regimen would let to obtain, at the same time, high efficacy, high genetic barrier, good tolerability and low pill burden[3].

Methods

- We have enrolled 42 consecutive patients, treated for HIV infection from at least 48 weeks, observed from January 2010 to March 2012.
- Among these patients, 9 have switched (2 for failure,1 for intolerance, 6 for simplification) to a once daily (OD) regimen with ETV+DRV/r (Cases); 33 were in ST (Controls). HIV/HCV coinfection was in 44% of Cases and 45% of Controls. Mean follow-up for Cases has been of 48 weeks.
- At the end of follow-up, 2 patients have been lost in Controls group (1 for virological failure,1 for non adherence) and 1 in Cases, died of a heart attack.
- Laboratory tests have been performed (CD4, HIV-RNA, Triglycerides, Cholesterol, ALT, AST, Creatinine, Haemogram) to assess efficacy and tolerability.
- Adherence has been assessed by counseling and SERAD questionnaire (Self-Reported Adherence).
- C-trough of drugs in Cases have been evaluated by a validated HPLC method, required to confirm the propriety of the uncommon dosage of ETV, administered QD and with all tablets dissolved in water.

Results

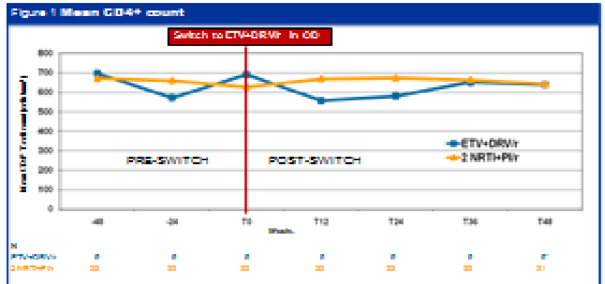
- Data of Cases have been compared to pre-switch (PS) and to Controls. Mean CD4 count during follow-up has been 607 in Cases, 653 in PS,661 in Controls, without statistical significance.
- After switch, 2 patients have suppressed their previous HIV viremia,1 has reduced it, 6 have confirmed previous negativity.
- About metabolic parameters, it seemed to be a trend in increasing cholesterol levels in Cases, with statistical significance compared to PS and to Controls.
- C-trough, although variable, appeared consistent with the data of literature. Pharmacokinetic (PK) and metabolic data are summarized in attached table.

Viro-Immunological Data

Mean CD4+ count after switch from ST to Darunavir/r + Etravirine

- Mean CD4+ count evaluated in Cases for 48 weeks before switch to dual therapy with Etravirine and Darunavir/r in OD regimen and for 48 weeks after switch.
- Cases data have been compared with patients (Controls) in standard regimen of 2 NRTI + PI/r, followed for 96 weeks.

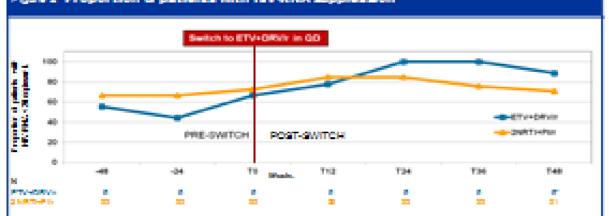
Figure 1 Mean CD4+ count



Proportion of Patients with Virological Suppression at Week 48

- Proportion of HIV-RNA undetectability in Cases analyzed for 48 weeks before switch to dual therapy with Etravirine and Darunavir/r in OD regimen and for 48 weeks after switch.
- Cases data have been compared with patients (Controls) in standard regimen of 2 NRTI + PI/r, followed for 96 weeks.

Figure 2 Proportion of patients with HIV-RNA suppression

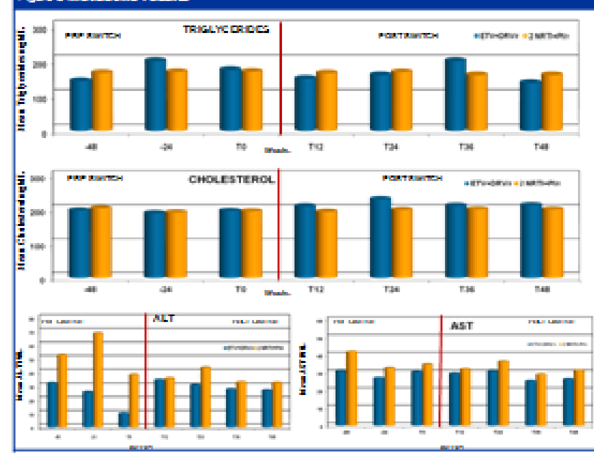


Metabolic Data

Metabolic results after switch from ST to Darunavir/r + Etravirine

- Mean Triglycerides, Cholesterol, ALT and AST levels evaluated in Cases for 48 weeks before switch to dual therapy with Etravirine and Darunavir/r in OD regimen and for 48 weeks after switch.
- Cases data have been compared with patients (Controls) in standard regimen of 2 NRTI + PI/r, followed for 96 weeks.

Figure 3 Metabolic results



Analysis of Statistical Significance

Table 1 Statistical significance of data

	CASES	CONTROLS	P CASES vs CONTROLS
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]		
[illegible]	[illegible]		
[illegible]	[illegible]		

Conclusion

- There are few data in literature about dual therapy with NNRTI+PI/r[4].
- Our preliminary data show that HIV treatment regimen of ETV and DRV/r in QD resulted in non-inferior efficacy and tolerability compared with a standard regimen of 2 NRTI+1PI/r through 48 weeks of treatment.
- This regimen shows great adherence through favorable dosage, validated by PK data, allowing to preserve other drug classes for future HAART sequencing.

Reference

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2. Reynes J, Lawal A, Pulido F et al. Examination of non inferiority, safety, and tolerability of lopinavir/ritonavir and raltegravir compared with lopinavir/ritonavir and tenofovir/ emtricitabine in antiretroviral-naive subjects: the progress study, 48-week results. HIV Clin Trials. 2011 Sep-Oct;12(5):255-67.
3. Katlama C, Clotet B, Mills A et al. Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials. Antivir Ther. 2010;15(7):1045-52.
4. Zager A. Report from the XVI International AIDS Conference. ACTG 5142 compares class-sparing regimens in treatment-naive patients. AIDS Clin Care. 2006 Nov;18(11):90.

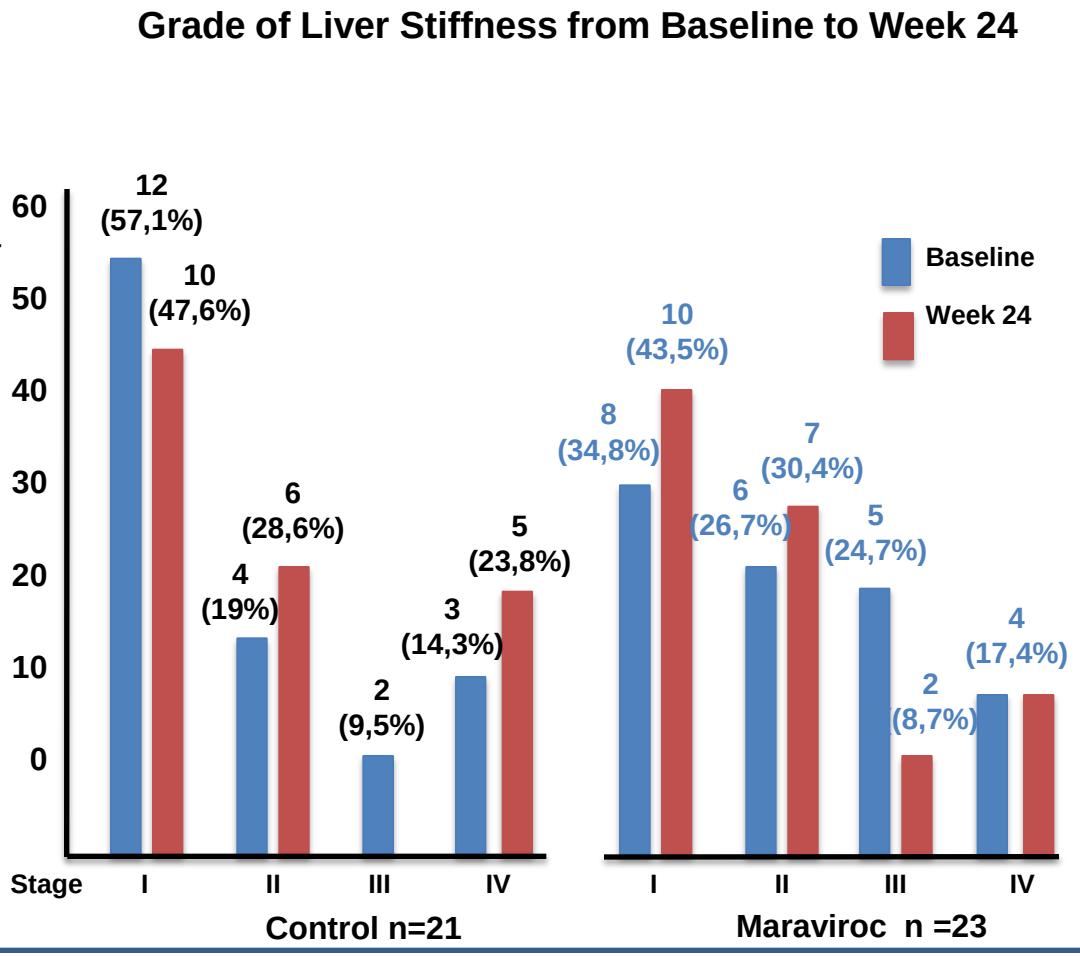
Studi sulla dual therapy con MVC

MVC+PI/r nei coinfetti HIV/HCV?

ARV Combination	Name of Study	Experimental Arm	Reference Arm	Study Population	N
LPV/r + CCR5 RA	VEMAN	LPV/r QD + MVC QD	LPV/r QD + TVD	ARV-Naive	N= 60
ATV+rtv + CCR5 RA	A4001078	ATV+rtv + MVC QD	ATV+rtv + TVD	ARV-Naive	N=121
DRV+rtv + CCR5 RA	MIDAS	DRV+rtv QD + MVC QD	Single Arm	ARV-Naive	N=25

Maraviroc to Prevent HCV-Related Liver Fibrosis in HIV Coinfection

- Proof of concept, open-label trial of maraviroc to prevent acceleration of liver fibrosis
- HIV/HCV coinfection with undetectable VL on TDF/FTC + ATV/r
- Addition of maraviroc 150 mg BID vs. maintenance therapy x 96 wk
- Liver stiffness measured by elastography
- Results of safety on first 60 patients prior to continued enrollment
- Possible delay in fibrosis as evidenced by shift towards Stage I and II fibrosis after 24 weeks of therapy



Hepatic Safety of maraviroc

Table 3. Adverse Events (MOTIVATE 1 and MOTIVATE 2 Study Populations Combined).*

	Placebo (N=209)	Maraviroc Once Daily (N=414)	Maraviroc Twice Daily (N=426)
Duration of treatment — patient-yr	111	300	309
Aspartate aminotransferase elevation (maximum, all causes, without regard to baseline) — no. of patients/total no. of patients (%)††			
Grade 3 (>5 to 10 × upper limit of normal)	6/207 (3)	12/408 (3)	14/421 (3)
Grade 4 (>10 × upper limit of normal)	0/207	4/408 (1)	6/421 (1)
Alanine aminotransferase elevation (maximum, all causes, without regard to baseline) — no. of patients/total no. of patients (%)††			
Grade 3 (>5 to 10 × upper limit of normal)	6/207 (3)	16/408 (4)	7/421 (2)
Grade 4 (>10 × upper limit of normal)	1/207 (<1)	2/408 (<1)	4/421 (1)

Gulick RM et al., NEJM 2008;359:1429-41

Once daily maraviroc 300 mg or 150 mg in combination with ritonavir-boosted darunavir 800/100 mg

Chinyere Okoli[1]*, Marco Siccardi[2], Sathish Thomas-William[3], Ngozi Dufty[3,4], Kirstin Khonyongwa[1], Jonathan Ainsworth[1], John Watson[3,4], Roseanne Cook[3], Kate Gandhi[3], Geraldine Hickinbottom[3], Andrew Owen[2] and Stephen Taylor[3–5]

[1]North Middlesex University Hospital, London, UK; [2]Department of Therapeutics and Pharmacology, University of Liverpool, Liverpool, UK; [3]Birmingham Heartlands HIV Service, Birmingham, UK; [4]Department of Military Medicine, Royal Centre for Defence Medicine, Birmingham, UK; [5]University of Birmingham, Birmingham, UK

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Objectives: To describe the pharmacokinetics of maraviroc when dosed at 150 or 300 mg once daily with 800/100 mg of darunavir/ritonavir.

Methods: A retrospective case-note review of HIV-infected adults taking maraviroc was conducted. Patients on a maraviroc-based regimen for a minimum of 5 weeks were grouped as receiving: (i) 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine; (ii) 300 mg of maraviroc once daily with 800/100 mg of darunavir/ritonavir once daily; and (iii) 150 mg of maraviroc once daily with 800/100 mg of darunavir/ritonavir once daily. C_{trough} and C_{peak} data were collected at 2, 12 or 24 h post-dose.

Results: Sixty-six patients were included, providing 115 samples. The median (IQR) C_{peak} was 378 (350–640) ng/mL for 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine ($n=9$), 728 (378–935) ng/mL for 300 mg of maraviroc once daily with darunavir/ritonavir ($n=29$) and 364 (104–624) ng/mL for 150 mg of maraviroc once daily with darunavir/ritonavir ($n=2$; $P=0.24$). The median (IQR) C_{trough} was 46 (33–61) ng/mL for 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine ($n=12$), 70 (49–97) ng/mL for 300 mg of maraviroc once daily with darunavir/ritonavir ($n=34$) and 43 (35–55) ng/mL for 150 mg of maraviroc once daily with darunavir/ritonavir ($n=17$; $P=0.001$). The maraviroc C_{trough} in black patients ($n=34$) was 61 (45–110) ng/mL and in white patients ($n=29$) it was 49 (42–70) ng/mL ($P=0.04$). The C_{peak} in black patients ($n=20$) was 800 (397–1060) ng/mL versus 387 (336–723) ng/mL in white patients ($n=20$; $P=0.02$).

Conclusions: Once daily coadministration of 300 mg of maraviroc with 800/100 mg of darunavir/ritonavir was well tolerated and had favourable pharmacokinetics when compared with 300 mg of maraviroc twice daily with 245 mg of tenofovir/200 mg of emtricitabine. A 24% higher C_{trough} and 107% higher C_{peak} was seen in black patients compared with white patients.

XIII CONGRESSO NAZIONALE SIMIT

Analisi multicentrica di un regime NRTI-sparing con Maraviroc, associato in dual therapy, ad un PI boosterato con ritonavir, in pazienti experienced con coinfezione HIV/HCV, R5 tropici.

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PREMESSA

- Il miglioramento prognostico dei pazienti (pz) HIV+, ottenuto grazie a farmaci sempre più efficaci, ha modificato il target della terapia, inducendo a sperimentare nuovi regimi antiretrovirali capaci di garantire una migliore tollerabilità, aderenza, ottimizzando la gestione delle comorbidità che spesso compaiono con l'invecchiamento.
- Tale aspetto appare importante nei coinfetti HIV/HCV per la maggiore fragilità di questi pz, che, accanto al più rapido sviluppo di cirrosi, presentano maggior rischio di danno renale,cardiaco e neurologico.
- In tale contesto un ruolo importante potrebbe averlo il Maraviroc (MVC) che è un antagonista del recettore cellulare CCR5.Tale farmaco, oltre a svolgere azione antivirale, potrebbe determinare una riduzione delle citochine infiammatorie coinvolte nella fibrogenesi epatica, rallentando di fatto lo sviluppo di cirrosi epatica.

OBIETTIVO

Valutare se una "dual therapy" con MVC associato ad un PI boosterato (PI/r), possa rappresentare una valida alternativa alla terapia standard (OBT) nei pz experienced con coinfezione HIV/HCV in termini di efficacia, tollerabilità ed aderenza, contribuendo a stabilizzare la fibrosi epatica.

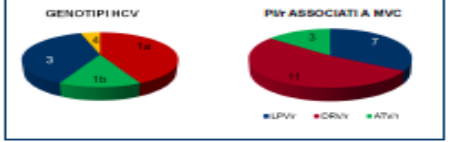
Figura 1

Dati al Baseline	
Numero di pazienti	21
Età media ± DS	47,57 ± 8,85
Sesso M/F	17/4
% HIV-RNA < 50 copie/ml	100 %
Media dei CD4 ± DS	574 ± 265,67
Genotipo 1-4 HCV	13 (62%)
Genotipo 2-3 HCV	8 (38 %)
Fibrosi F0-F1	8(38%)
Fibrosi F2-F3	5 (23.8%)
Fibrosi F4	8 (38%)

METODI

- Abbiamo arruolato 21 pz HIV/HCV (Casi) in terapia antiretrovirale stabile, virologicamente soppressi.Tutti i pz risultavano R5 tropici e venivano switchati ad un regime con MVC associato ad un PI/r. Prima dello switch veniva eseguito un fibroscan per valutare la fibrosi epatica. I pz sono stati monitorati con un follow-up medio di 12 mesi eseguendo periodicamente tests di laboratorio di routine per valutare efficacia e tollerabilità, ripetendo il fibroscan dopo 12 mesi dallo switch. L'aderenza è stata valutata con il counseling ed il questionario SERAD (Self Reported Adherence). Il MVC è stato associato in terapia a Darunavir/r in 11 pz, Lopinavir/r in 7, Atazanavir/r in 3; il dosaggio del MVC adottato è stato di 150 mg BID in 10 pz e 300 mg QD in 11 pz. La fibrosi pre-switch (PS) è risultata F0 in 7 pz,F1 in 2 pz,F2 in 4 pz ed F4 in 8 pz.

Figura 2 : Genotipi di HCV nei CASI E PI/r usati in associazione a MVC

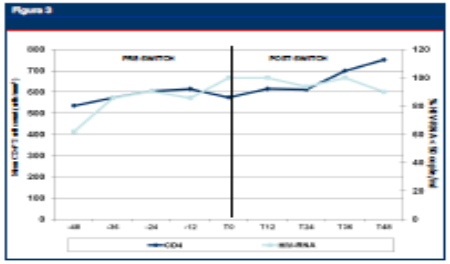


RISULTATI

- I dati dei Casi sono stati paragonati a quelli PS. La media di CD4 è stata nei Casi di 669,25 e 579,95 nei PS, mostrando un maggior recupero immunologico nel braccio MVC, statisticamente significativo. Tutti i pz sono rimasti virosoppressi, tranne uno che ha presentato,dopo 17 mesi di efficacia virologica,un rebound viremico di 6310 copie/ml. La media delle ALT nei Casi è stata di 82,79, mentre era 67,21 nei PS, anche in tal caso la differenza è apparsa statisticamentet significativa, stavolta a svantaggio del braccio in MVC. Le AST sono risultate in media 68,49 nei Casi, sovrapponibili al 67,84 dei PS. La media dei trigliceridi nei Casi è stata di 160,97,nei PS 155,56,differenza statisticamente non significativa;per il colesterolo 166,59 nei Casi,167,42 nei PS. La fibrosi nei Casi è risultata stabile rispetto ai relativi valori PS.

DATI VIRO-IMMUNOLOGICI

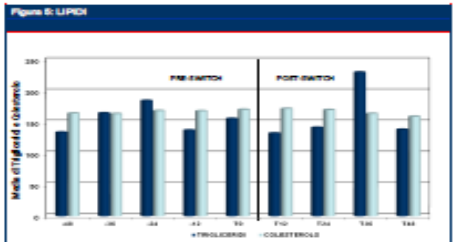
Figura 3



DATI METABOLICI

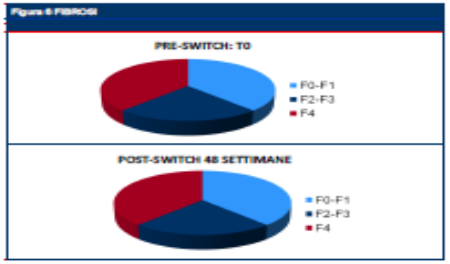
Figura 4: TRANSAMINASI

Figura 5: LIPIDI



DATI DI FIBROSI

Figura 6 FIBROSI



Significatività statistica

	CASI	PRE-SWITCH	p
Media dei CD4 ± DS	**669,25 ± 67,87**	**579,95 ± 31,28**	**0,03**
% HIV-RNA < 50 copie/ml	90%	100%	0,69
Media delle ALT ± DS	**82,79 ± 12**	**67,21 ± 4,29**	**0,02**
Media delle AST ± DS	68,49 ± 8,2	67,84 ± 7,4	0,90
Media dei Trigliceridi ± DS	160,97 ± 46,42	155,56 ± 20,76	0,82
Media del Colesterolo ± DS	166,59 ± 5,76	167,42 ± 2,93	0,78
Fibrosi F0-F1	8(38%)	8/21 (38%)	
Fibrosi F2-F3	5 (23.8%)	5/21 (23,8%)	
Fibrosi F4	8 (38%)	8/21 (38%)	

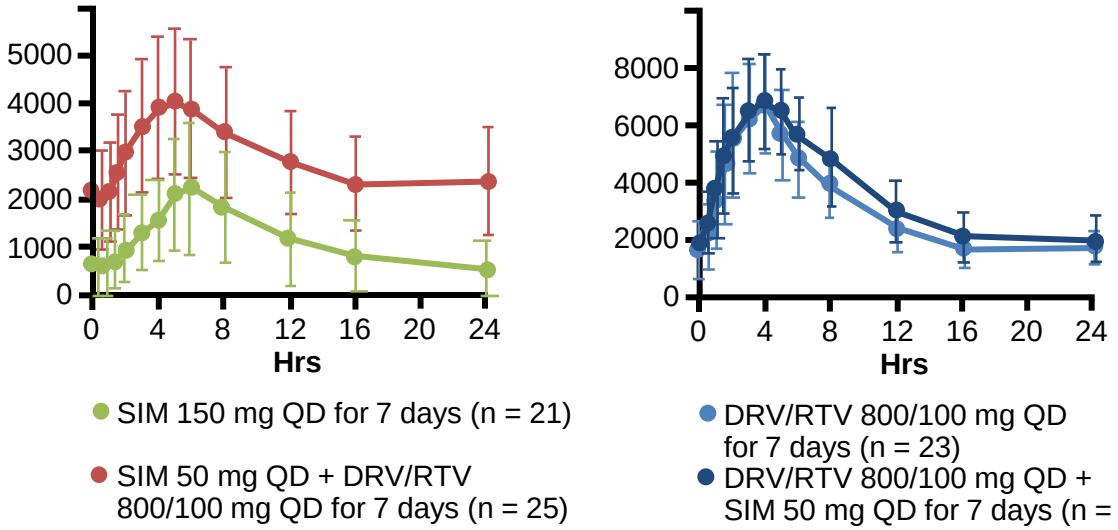
CONCLUSIONI

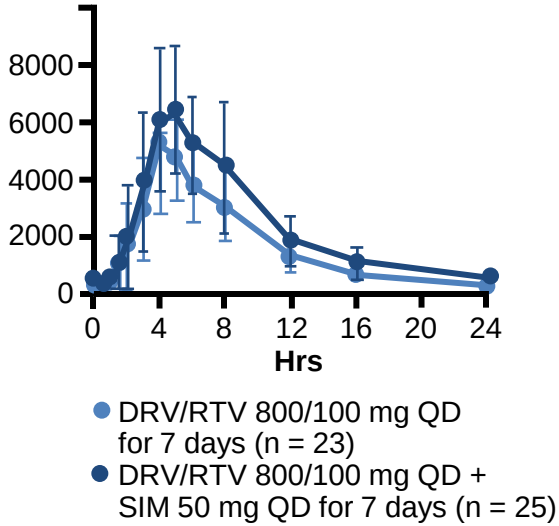
- Sono pochi i trials relativi a nuovi regimi antiretrovirali nei coinfetti HIV/HCV.
- I nostri dati preliminari evidenziano che un regime con MVC associato ad un PI/r, in switch proattivo, garantisce efficacia e tollerabilità, con apparente stabilizzazione della fibrosi epatica, da rivalutare in un follow-up più lungo.

COINFEZIONI HIV/VIRUS EPATITICI

- EPIDEMIOLOGIA DELLE COINFEZIONE HIV/HBV
- HAART IN PZ CON COINFEZIONE HIV/HBV
- EPIDEMIOLOGIA DELLE COINFEZIONE HIV/HCV
- HAART IN PZ CON COINFEZIONE HIV/HCV
- HAART E NUOVI DAA ANTI-HCV
- OPZIONI FUTURE

Simeprevir and Darunavir/Ritonavir: Day 7 PK Alone and in Combination

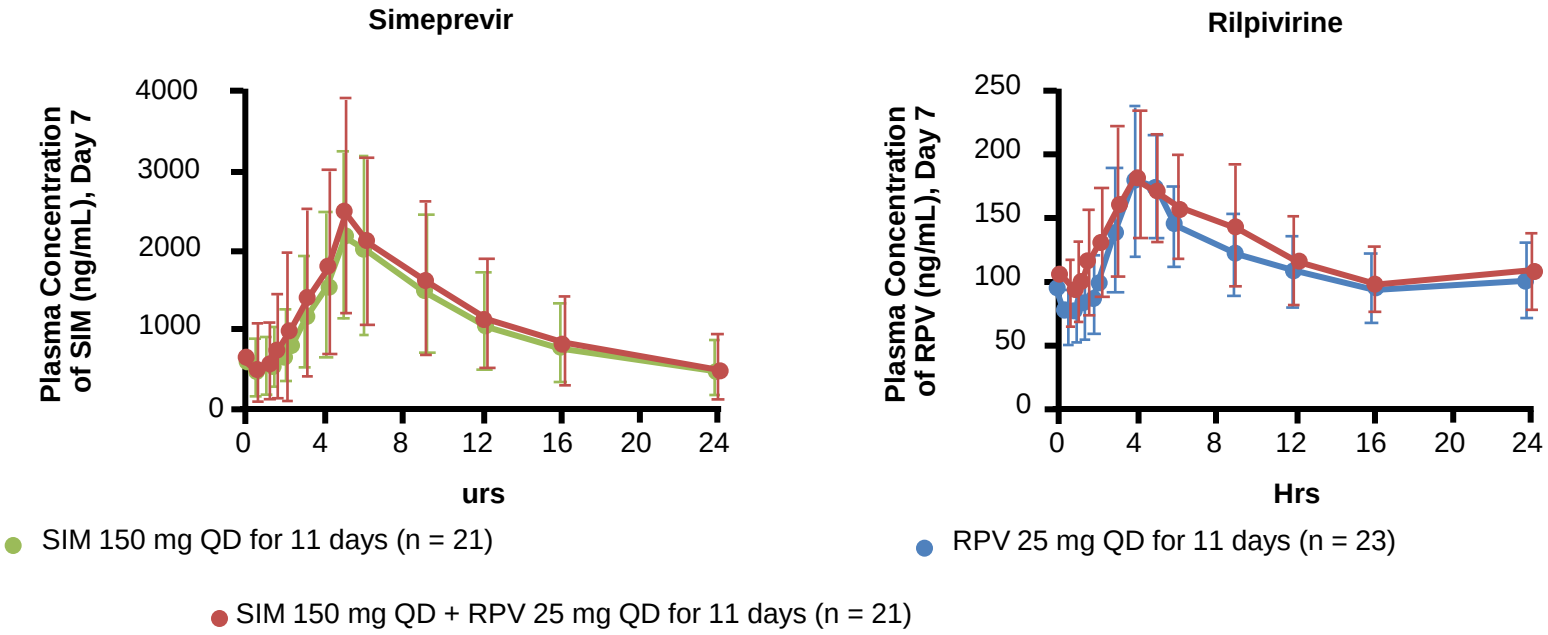




- SIM exposure 2.6-fold higher when coadministered with DRV/RTV vs SIM alone
- **When coadministered with SIM, DRV exposure increased 18% and RTV exposure increased 32%**

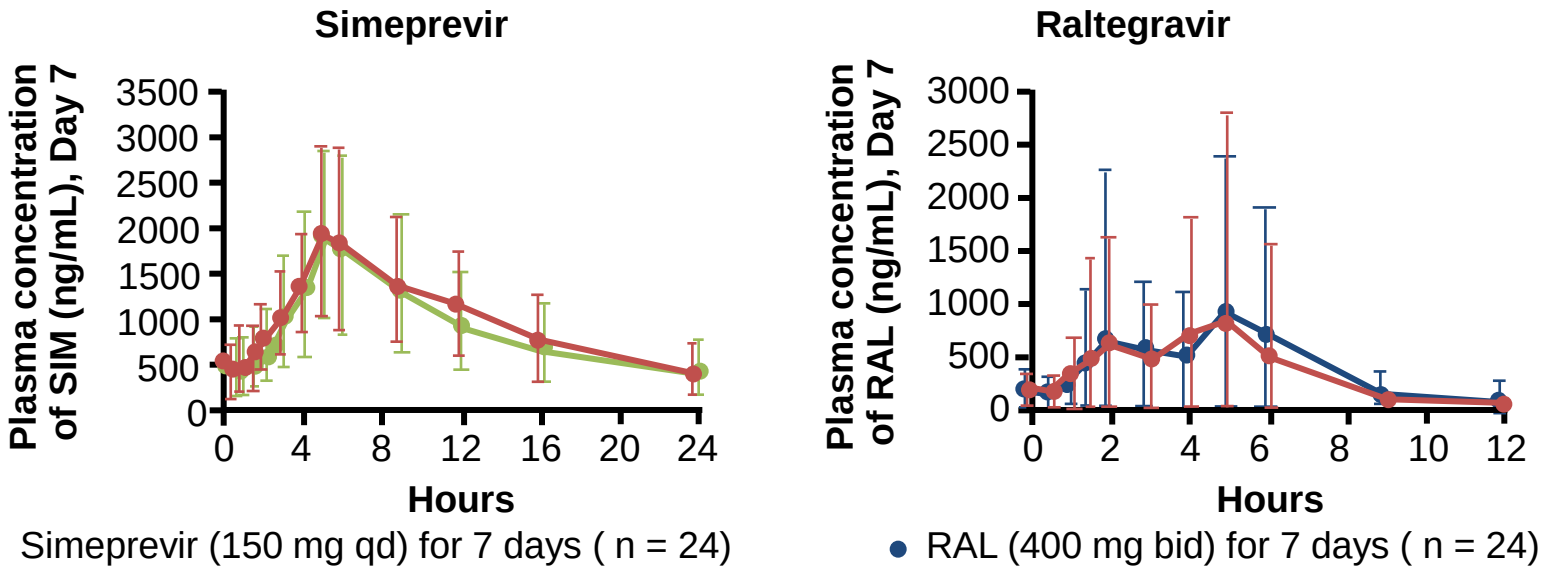
Ouwerkerk-Mahadevan S, et al. IDWeek 2012. Abstract 36620.

Simeprevir and Rilpivirine: Day 7 PK Alone and in Combination



- **No clinically relevant interactions observed between RPV and SIM**
- No relevant differences in incidence of AEs observed with SIM alone vs coadministration of SIM and RPV

Simeprevir and Raltegravir: Day 7 PK Alone and in Combination



- **No clinically relevant interactions were observed between RAL and SIM**
- No relevant differences in incidence of AEs observed with SIM alone vs coadministration of SIM and RAL

Ouwerkerk-Mahadevan S, et al. IDWeek 2012. Abstract 36620.

Effect of ARVs on Sofosbuvir

Drug	Effect on Sofosbuvir and GS-331007 AUC (exposure)	Recommendation
Darunavir/r	SOF increased 34%; GS-331007 – no effect	No dose adjustment
Rilpivirine	No effect on SOF or GS-331007	No dose adjustment
Efavirenz	No effect on SOF or GS-331007	No dose adjustment
Raltegravir	No effect on SOF or GS-331007: RAL decreased 27%	No dose adjustment
Tenofovir	No effect on SOF or GS-331007	No dose adjustment

Mathias A 14th Int Workshop on Clin Pharm of HIV Ther Session 5; Kirby B et al 63rd AASLD 2012; Abs 1877. ; Sofosbuvir USPI 2013

COINFEZIONI HIV/VIRUS EPATITICI

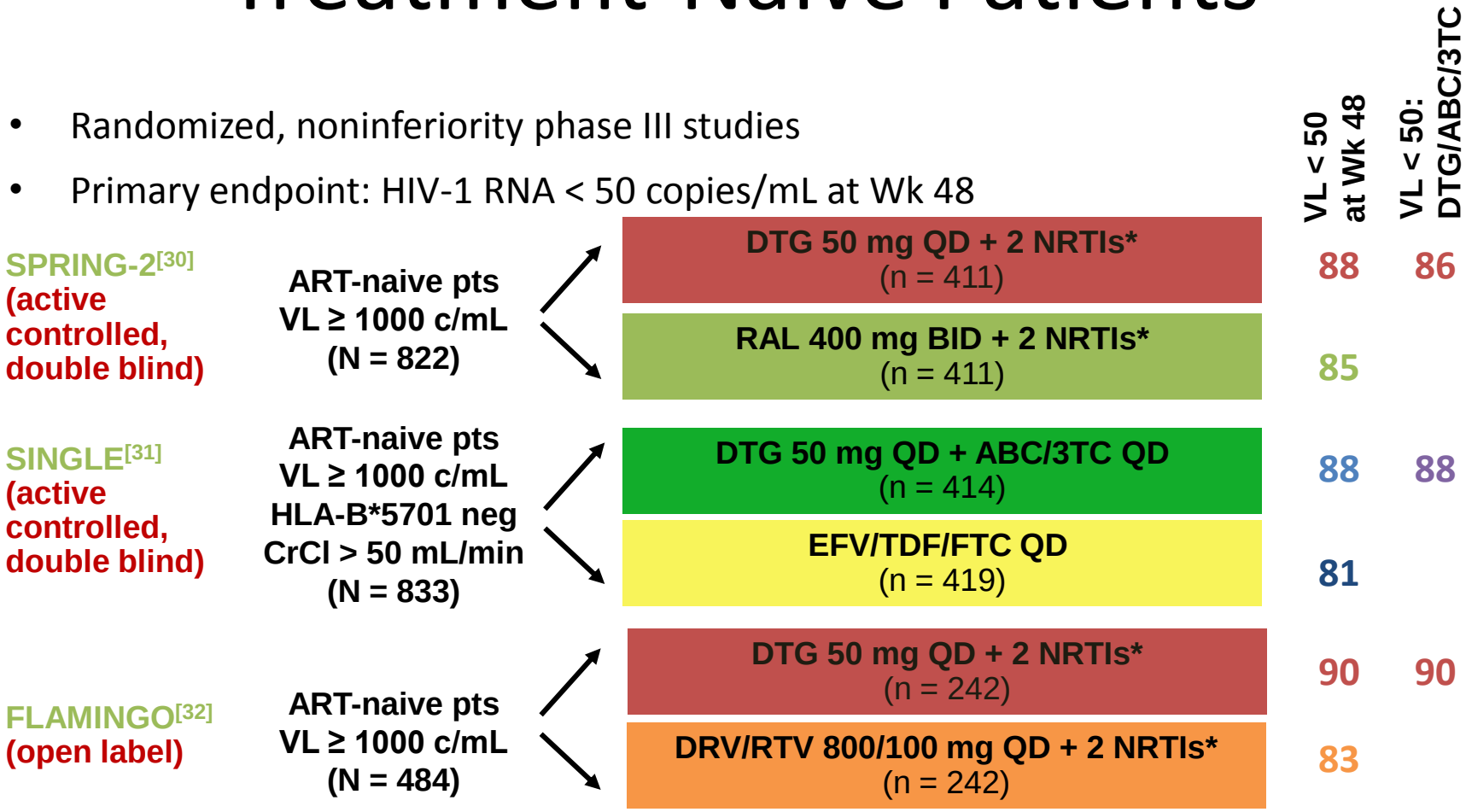
- EPIDEMIOLOGIA DELLE COINFEZIONE HIV/HBV
- HAART IN PZ CON COINFEZIONE HIV/HBV
- EPIDEMIOLOGIA DELLE COINFEZIONE HIV/HCV
- HAART IN PZ CON COINFEZIONE HIV/HCV
- HAART E NUOVI DAA ANTI-HCV
- OPZIONI FUTURE

What's New in Coformulated Agents and Regimens

- Coformulated regimens including approved agents
  - EVG/COBI/TDF/FTC
  - DTG/ABC/3TC
- PIs coformulated with cobicistat as the pharmacologic booster
  - ATV/COBI
  - DRV/COBI
- Coformulated regimens using investigational agents
  - EVG/COBI/TAF/FTC
  - DRV/COBI/TAF/FTC

Dolutegravir Phase III Trials in Treatment-Naive Patients

- Randomized, noninferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48

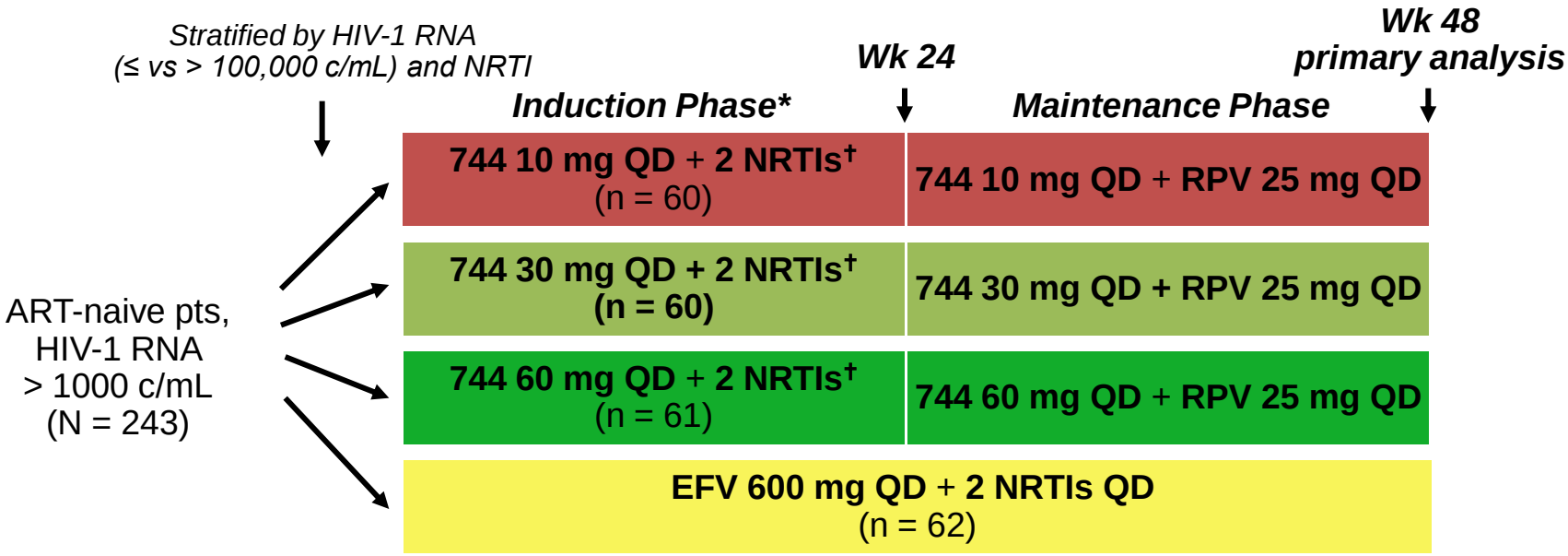


*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

30. Raffi F, et al. Lancet. 2013;381:735-743. 31. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818. 32. Feinberg J, et al. ICAAC 2013. Abstract H1464a. .

LATTE: GSK1265744 as Part of ART in Naive Pts: Results of 24-Wk Induction

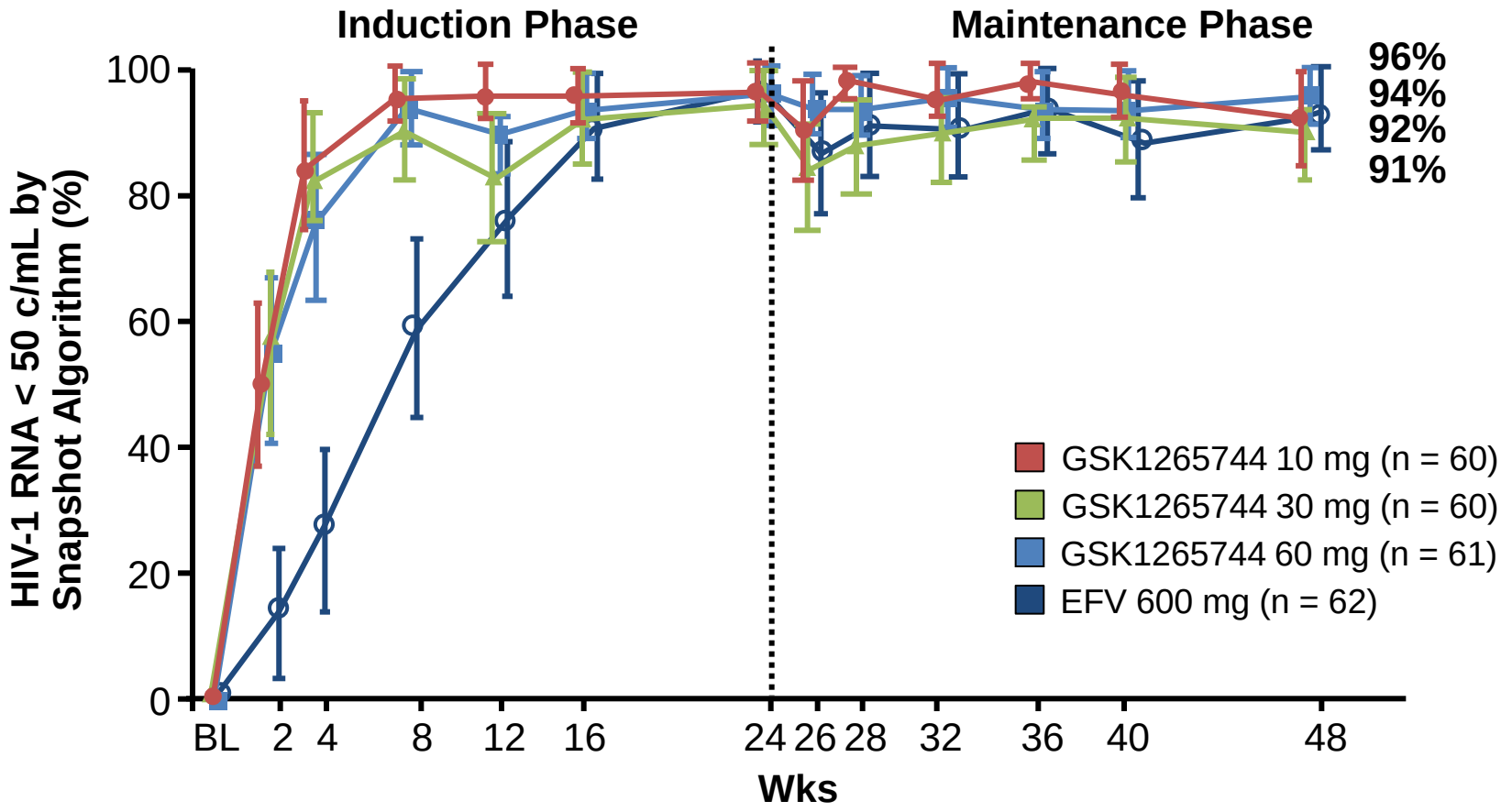
- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†TDF/FTC or ABC/3TC.

Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB.

LATTE: Virologic Success During Induction and Maintenance Phases



- 2 pts with PDVF during maintenance; both with INSTI mutations at BL

Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB

Doravirine (MK-1439): Background

- **Commonly used NNRTIs are associated with suboptimal efficacy and/or safety profiles**
  - Efavirenz is frequently associated with CNS adverse experiences [(1)]
  - Rilpivirine is indicated in treatment naïve patients with RNA ≤100,000 copies/mL [(2)]
- **Doravirine (MK-1439) is a next generation NNRTI with the potential for improved efficacy and safety profiles**
  - High *in vitro* potency against a broad panel of isolates of different HIV subtypes[(3)]
    - <3-fold potency shift *vs.* common NNRTI-resistance mutants K103N, Y181C, G190A, E138K[(4)]
    - Distinct mutations selected *in vitro*: V106A, F227L, and L234I
      - V106A, F227L do not confer cross resistance to rilpivirine or etravirine
  - Low potential for CNS effects, drug-drug interactions; lower protein-binding *vs.* other NNRTIs
  - In Phase 1 studies:
    - Single doses up to 1200 mg and multiple doses up to 750 mg were generally well tolerated[(5)]
    - Minimal food effect observed (after 50-mg single dose)
    - Primary metabolism by CYP3A4, but is not an inducer or an inhibitor[(6)]
    - In a 7-day monotherapy study in treatment-naïve HIV-1 patients, ~1.3 log HIV RNA decline at 25 and 200 mg po QD[(7)]

Perché è importante cercare nuove strade…

Perché non si vive di sola efficacia viro-immunologica!

?

Homa score

DEXA

Test di resistenza

Test di Framingham

Test per tropismo

TDM

Test HLA-B5701

Fibroscan

T-score e Z-score

MELD Risk Score

MMSE

VIAGGIARE RISPARMIANDO…

RISPARMIARE SIGNIFICA:

- **NON PAGARE PEDAGGIO IN TERMINI DI TOSSICITA' A LUNGO TERMINE**
- **RIDURRE I CONSUMI IN TERMINI DI COSTI DEL REGIME TERAPEUTICO**

HIV/HCV COINFECTION: CARE

Il paziente coinfetto per la sua fragilità e per la propensione a presentare altre comorbidità, necessita di una terapia antiretrovirale che risponda a specifici requisiti:

- **Tollerabilità renale, cardiovascolare e metabolica**
- **Con farmaci a basso pill burden per ottimizzare l'aderenza ed evitare di perdere opzioni terapeutiche in un setting già complicato con meno farmaci utilizzabili**
- **Preferendo farmaci che possano consentire di trattare il paziente per epatite da HCV evitando interazioni farmacocinetiche**

GRAZIE PER L'ATTENZIONE