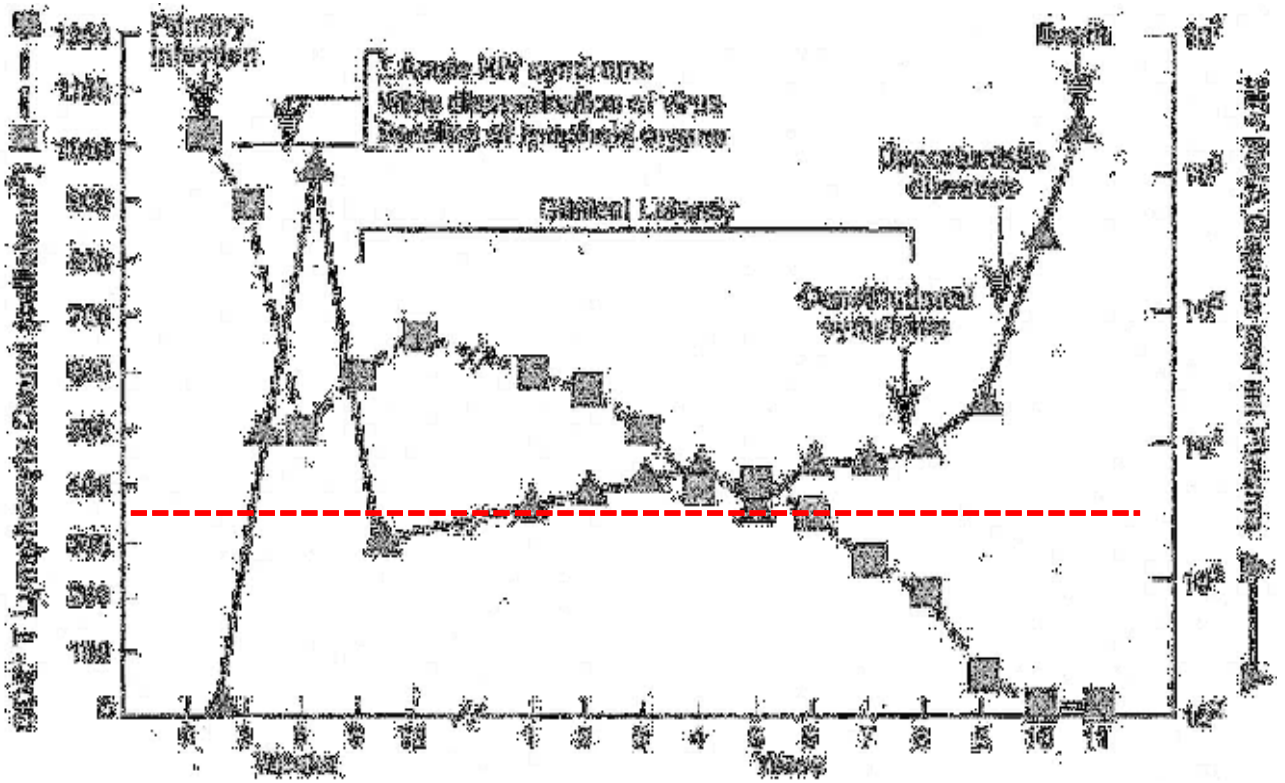
La terapia dell'infezione da HIV,comorbidità ed ageing

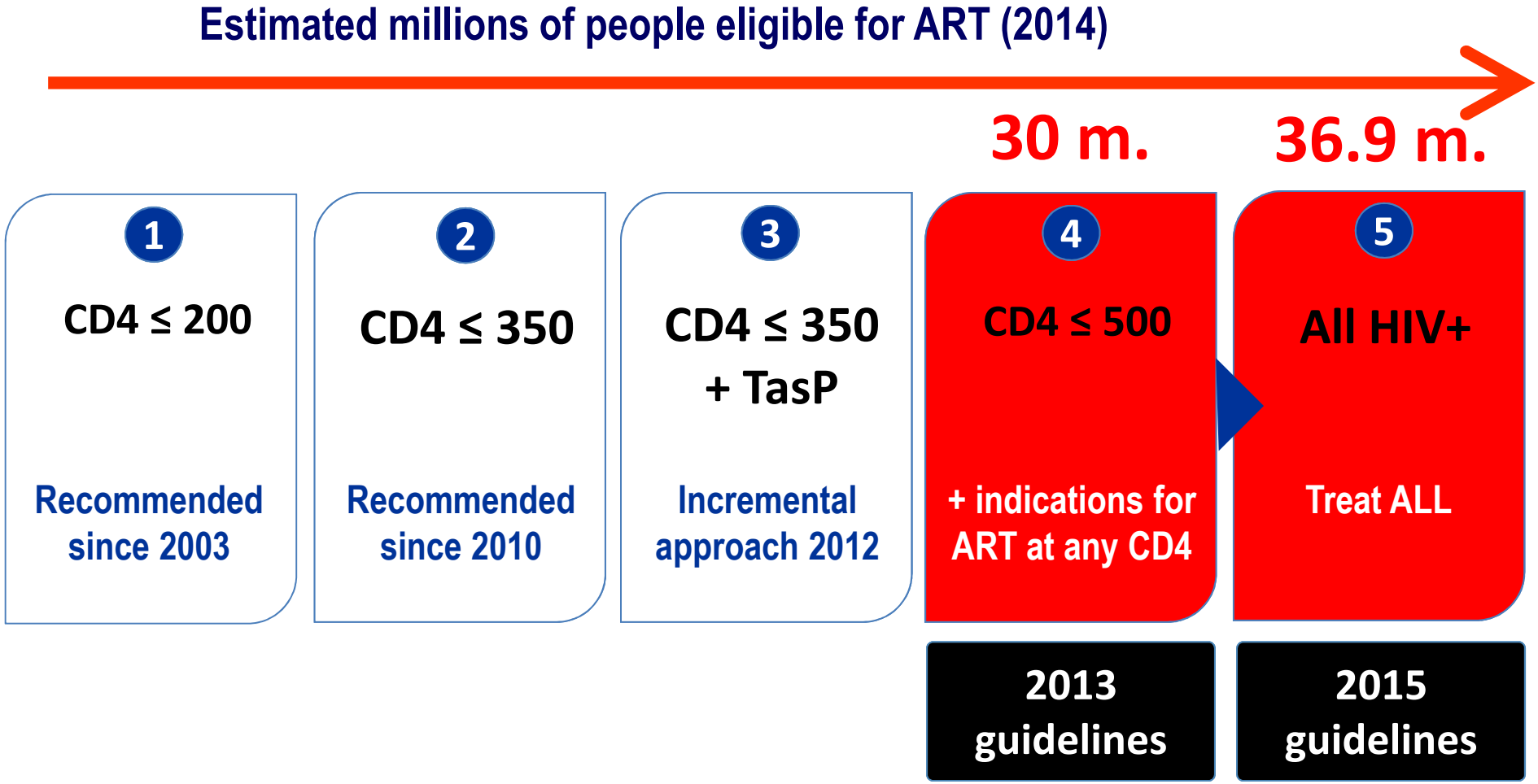
I martedì dell'Ordine dei Medici di Parma 29 novembre 2016

Quando iniziare la terapia?

Natural history of human immunodeficiency virus (HIV) infection.



ART eligibility: 5 policy scenarios



START Study Design

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3

Immediate ART Group	Deferred ART Group
Initiate ART immediately following randomization	Defer ART until CD4+ count drops to <350 cells/mm^3 or AIDS develops
N=2,326	N=2,359

Primary endpoint:

- Serious AIDS
- Serious non-AIDS conditions
  CVD (stroke, MI, revascularization), ESRD, decompensated liver disease, non-AIDS cancer
- All-cause death

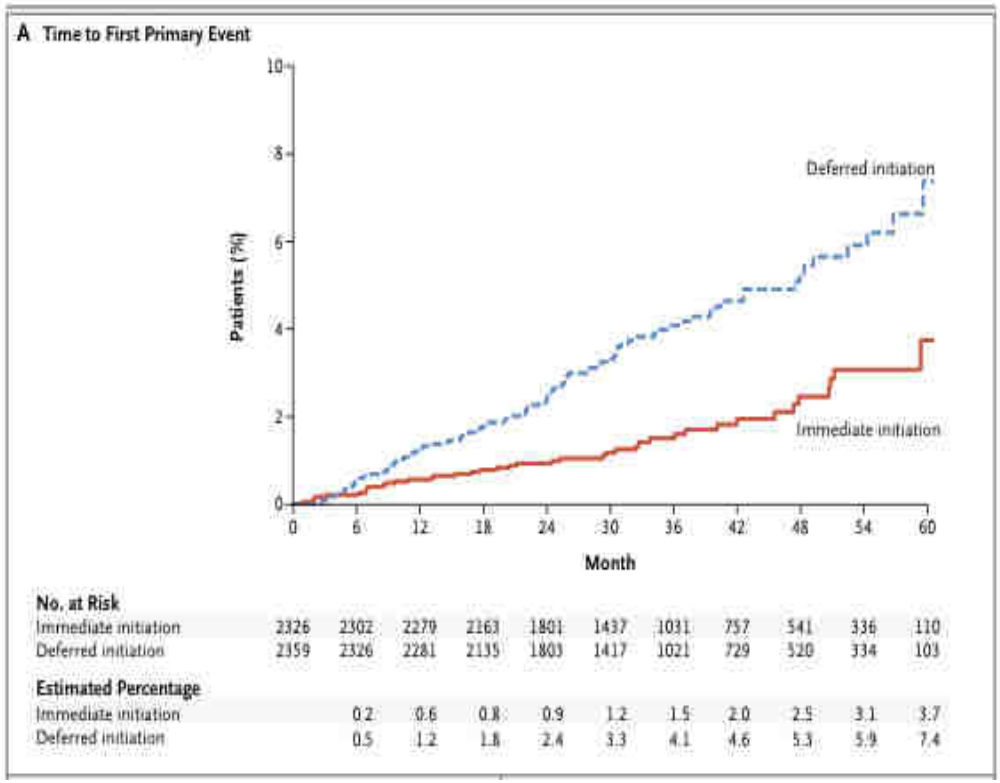
We use data accrued through May 27, 2015, when the START study results were unblinded

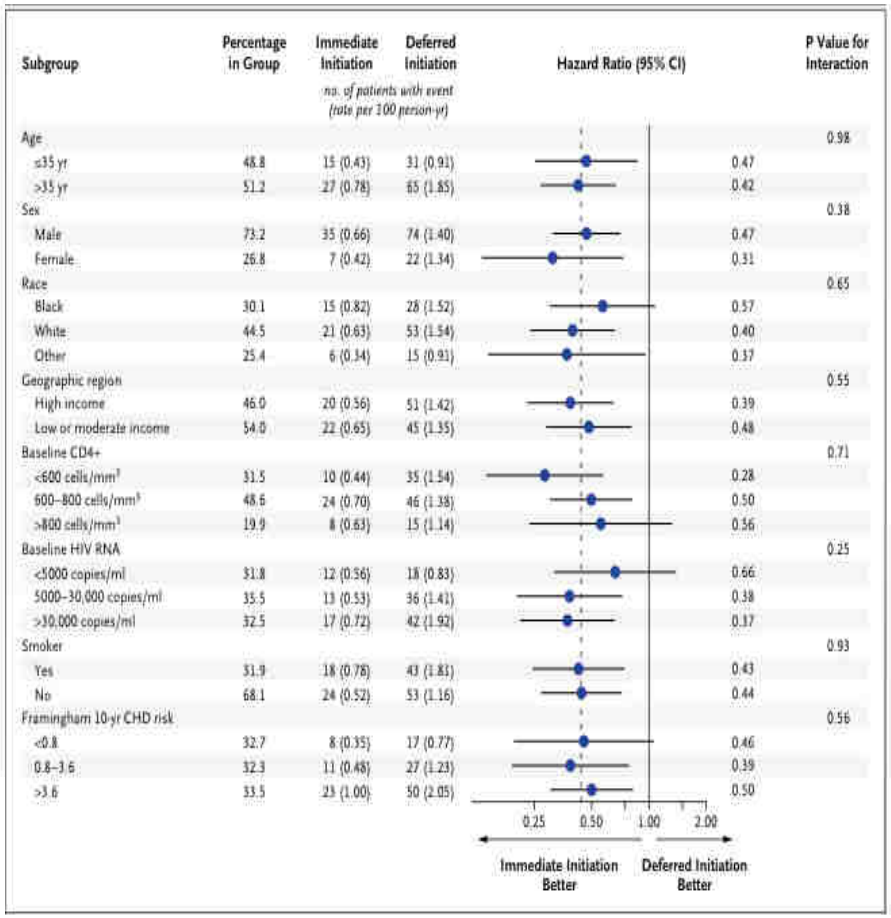
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

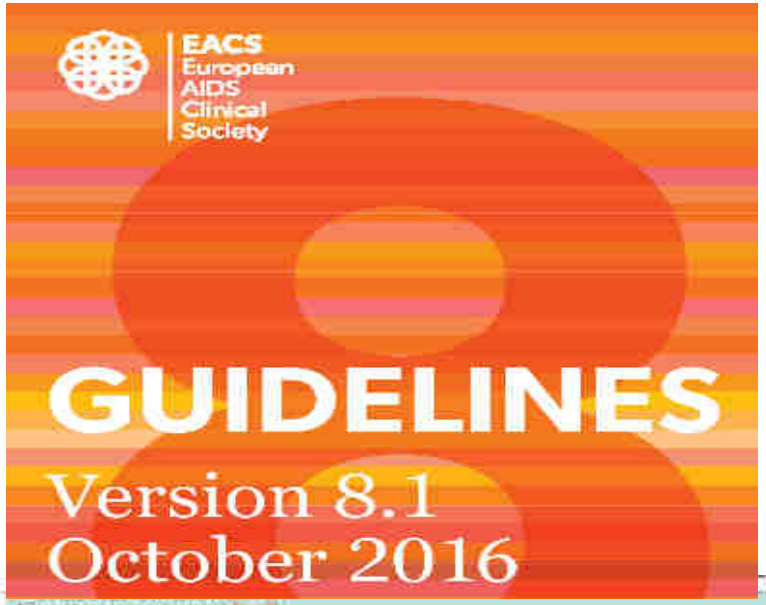
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*





Quando iniziare la terapia?



Starting treatment

Treatment of PHI is recommended for all HIV-positive persons. Several circumstances indicate immediate treatment initiation.

Circumstances where immediate treatment initiation should be advised

Acute infection
Severe or prolonged symptoms
Neurological disease
Age ≥ 50 years
CD4 count < 350 cells/µL

Recommendations for Initiation of ART in HIV-positive Persons with Chronic Infection without prior ART Exposure

Recommendations take into account the level of evidence, the degree of progression of HIV disease and the presence of, or high risk for, developing various types of (co-morbid) conditions.

ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts

ART should always be recommended irrespective of the CD4 count, but the lower the CD4 count, the greater the urgency to start ART immediately.

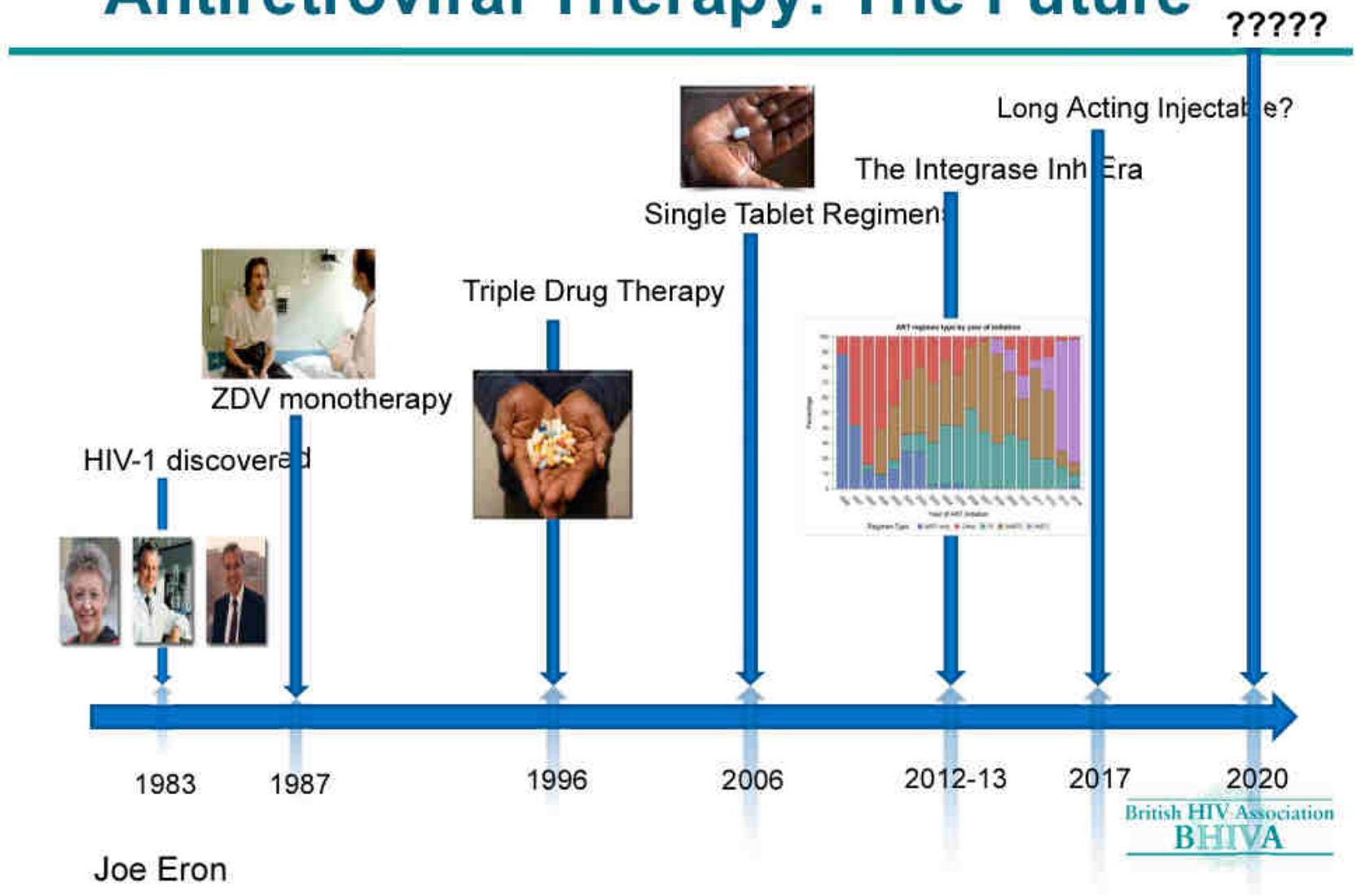
- For best timing for starting ART in persons with tuberculosis and cryptococcal meningitis, see page 14 and page 85.
- A possible exception could be elite controllers with high and stable CD4 count. Time should always be taken to prepare the person, in order to optimise compliance and adherence.
- Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis; otherwise before initiation of ART.
- If ART needs to be initiated before genotypic testing results are available, it is recommended to include a drug with high genetic barrier to resistance in the first-line regimen (e.g. a PI/r, PI/c or DTG). Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to obtain a baseline to assess subsequent response.
- Use of ART should also be recommended with any CD4 count in order to reduce sexual transmission, risk of AIDS event and mother-to-child transmission of HIV (before third trimester of pregnancy).

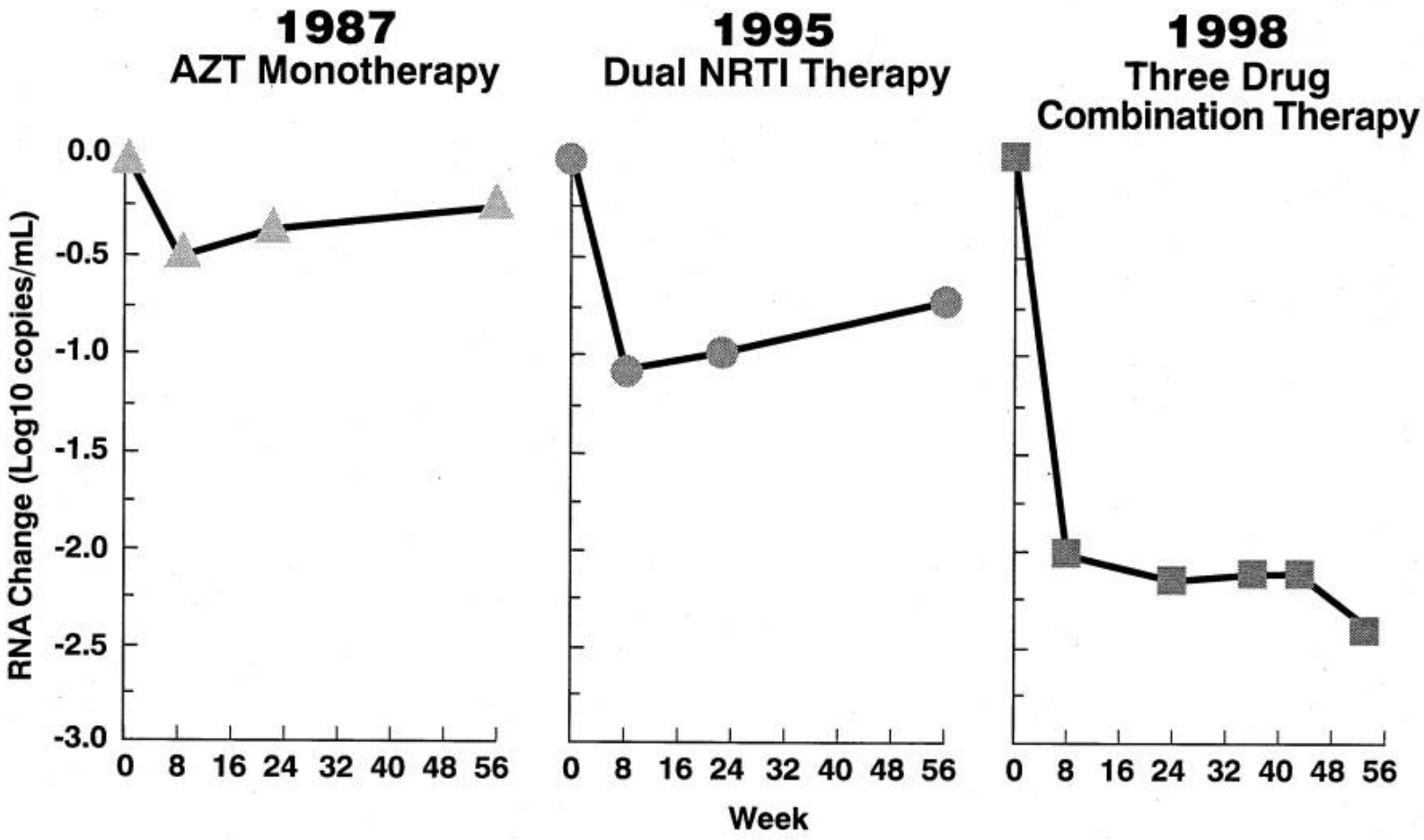
FARMACI ANTIRETROVIRALI

NRTI	NNRTI	PI	inibitori entry/fusione	inibitori integrasi
zidovudina	nevirapina	saquinavir	maraviroc	raltegravir
didanosina	efavirenz	fosamprenavir	enfuvirtide	elvitegravir
lamivudina	etravirina	lopinavir/rit		dolutegravir
~~stavudina~~	rilpivirina	atazanavir*		
abacavir		tipranavir		
tenofovir		darunavir*		
emtricitabina		*ritonavir/cobi		
~~zalcitabina~~		~~nelfinavir~~		
		~~indinavir~~		

in fase 3 un inibitore dell'attachment e uno della maturazione, long acting drugs, etc

Antiretroviral Therapy: The Future




1987
AZT Monotherapy
1995
Dual NRTI Therapy
1998
Three Drug
Combination Therapy
RNA Change (Log10 copies/mL)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
0 8 16 24 32 40 48 56
0 8 16 24 32 40 48 56
0 8 16 24 32 40 48 56
Week

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

17 Dicembre 2015

Tabella 2a - Regimi raccomandati per l'inizio della cART.

REGIME	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Regimi raccomandati		
TDF/FTC+RAL	[AI]	[23-24,26,31-32]
TDF/FTC/EVG/COBI	[AI]	[27-30,66]
TAF/FTC/EVG/COBI	[AI]	[72]
TDF/FTC+DTG	[AI]	[31-32,34]
ABC/3TC+DTG	[AI]	[31-34]
ABC/3TC/DTG	[AI]	[31-35]
TDF/FTC/RPV (in caso di valori di HIV-RNA < 100.000 cp/mL e conta di T CD4+ > 200 cellule/µL)	[AI]	[12,14,18,19]
Regimi raccomandati in particolari condizioni		
TDF/FTC+ATV+r o TDF/FTC+DRV+r (in caso di condizioni non favorenti l'aderenza, di necessità di iniziare il trattamento prima della disponibilità del risultato del test di resistenza, di inizio terapia in gravidanza)	[AII]	[7,11,20-22,26,28-29,34,42,69]
TDF/FTC+ATV/COBI o TDF/FTC+DRV/COBI (in caso di condizioni non favorenti l'aderenza, di necessità di iniziare il trattamento prima della disponibilità del risultato del test di resistenza)	[AII]	[67,68]

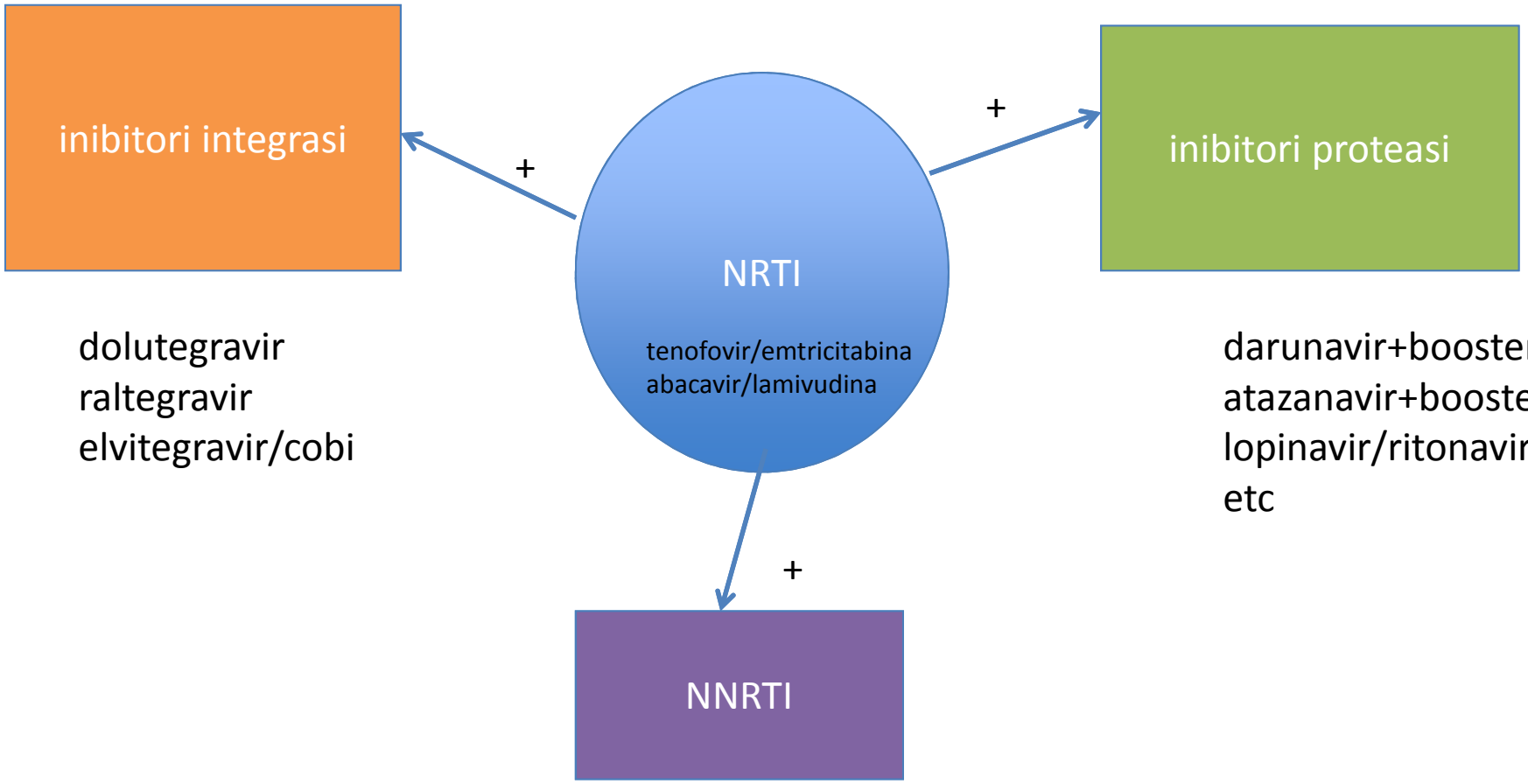
- I regimi basati su NNRTI sono controindicati in caso di presenza di farmacoresistenza trasmessa relativamente agli NRTI ed agli NNRTI.
- ABC, causa HSR, è da utilizzare solo nei soggetti con negatività dell'allele HLA-B*5701.
- COBI da non utilizzare con e-GFR<70 ml/min/1.73m². Dati di follow-up ancora limitati sulla funzione tubulare renale. EVG/COBI/FTC/TAF utilizzabile con eGFR ≥ 50 ml/min
- I regimi contenenti TDF/FTC + ATV+r o ATV/COBI o DRV+r o DRV/COBI sono da considerare raccomandati [AII] solo nelle condizioni specifiche riportate. In tutte le altre condizioni vengono considerati alternativi [BI].
- DRV/r è da utilizzare al dosaggio 800/100 mg QD.
- Nell'utilizzo di ATV/r e ATV/COBI va tenuto conto del rischio di iperbilirubinemia e le potenziali conseguenze di tale effetto collaterale sul paziente.
- Il regime contenente TDF/FTC/RPV non è registrato per il trattamento di pazienti con valori di HIV-RNA > 100.000 copie/mL.
- I regimi contenenti COBI non devono essere utilizzati al momento nella donna in gravidanza.

"/" = co-formulato; "+"= non co-formulato.

FATTORI DA CONSIDERARE NELLA SCELTA INIZIALE DELLA TERAPIA

Correlati a farmaci e combinazioni	efficacia virologica efficacia immunologica compattezza/convenienza tossicità/tollerabilità potenziali interazioni fra farmaci barriera genetica
Clinici/diagnostici	condizione clinica Aids definente o altro valore carica virale plasmatica presenza di resistenza virale trasmessa eventuale presenza allele HLAB5701
Non clinici	valutazione preparazione del paziente alla terapia valutazione contesto di popolazione/condizione

Backbone nucleosidico+terzo farmaco



KIVEXA(abacavir/lamivudina)

-1 cpr die

-utilizzare solo dopo test **HLAB5701** negativo.

L A POSITIVITA' E' ASSOCIATA ALLA REAZIONE DA IPERSENSIBILITA' AD ABACAVIR, CARATTERIZZATADA FEBBRE,MALESSERE, ARTRALGIE, RASH, TURBE RESPIRATORIE, ALTERAZIONE FUNZIONE EPATICA. IL FARMACO VA SOSPESO E **MAI PIU' RIPRESO**

RARAMENTE LA REAZIONE DA IPERSENSIBILITA'
SI PUO' MANIFESTARE ANCHE IN SOGGETTI HLAB5701 NEGATIVI

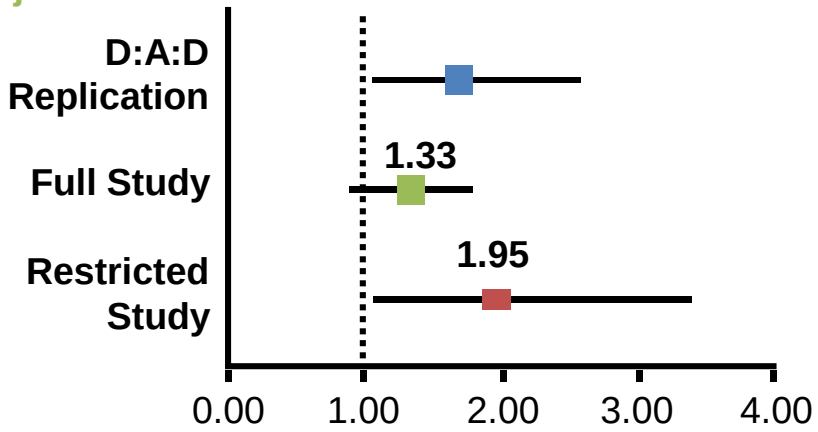
NECESSARIO SOLO CONTROLLO DELLA FUNZIONE EPATICA NEI PRIMI MESI

RIPORTATA ASSOCIAZIONE FRA I PRIMI MESI DI TERAPIA CON ABACAVIR E RISCHIO CARDIO-VASCOLARE(MALATTIA CORONARICA)

NA-ACCORD: Recent Abacavir Use and Risk of MI

- Retrospective analysis of pts in 7 clinical cohorts with recent ABC use from 1/1/1995 to 12/31/2010
- "Recent" ABC initiation: prescribed within previous 6 mos
- ABC initiators (n = 1948) vs non-ABC initiators (n = 14,785):
  - "Full" study population: all ART users excluding persons on ABC at study entry
  - "Restricted" population: ART-naive persons who initiated ART in the cohort
- Endpoint of incident MIs: presence of clinical diagnosis or elevation of cardiac enzymes
  - All MIs independently adjudicated

Adjusted HRs for MI in Those With Recent ABC Use



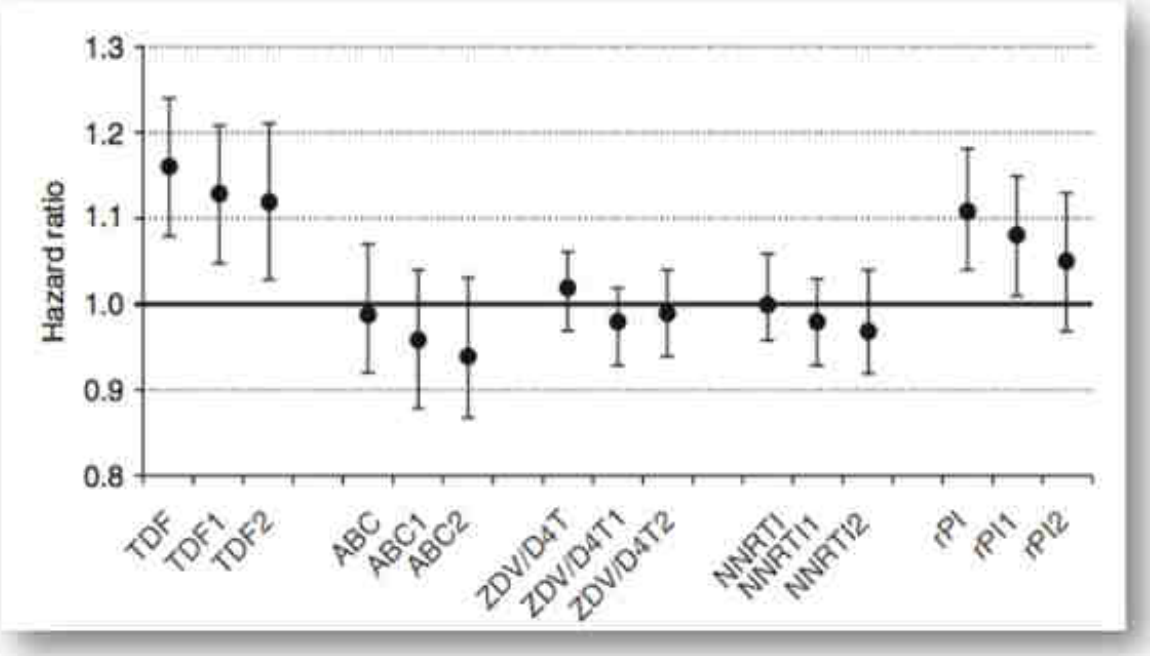
- Recent ABC use significant in restricted population and D:A:D replication
- Association diminished after adjusting for additional CVD risk factors in multivariate analysis
- Significant factors
  - Both: age 60+ yrs, HTN, eGFR < 30, AIDS
  - Full: smoking, DM

Palella F, et al. CROI 2015. Abstract 749LB.
Reproduced with permission.

TRUVADA(tenofovir/emtricitabina)

-FARMACO BEN TOLLERATO, PUO' CAUSARE INSONNIA
-1 CPR DIE
-ASSOCIATO A >PERDITA DI OSSO RISPETTO AGLI ALTRI ANTIRETROVIRALI
-PUO' CAUSARE DANNO RENALE (TUBULOPATIA) CON IPERFOSFATURIA, IPOFOSFOREMIA, PROTEINURIA.
-RICHIEDE CONTROLLO SERIATO DELLA FUNZIONE **RENALE**
-MOLTO UTILIZZATO ANCHE NELLA **PEP** E NELLA **PREP**, ESISTE ANCHE COFORMULATO CON TERZO FARMACO (ES.ATRIPLA, EVIPLERA, STRIBILD)
-ATTIVO CONTRO HBV, VIENE UTILIZZATO NEL COINFETTO B

Cumulative TDF and LPV exposure increase fracture risk



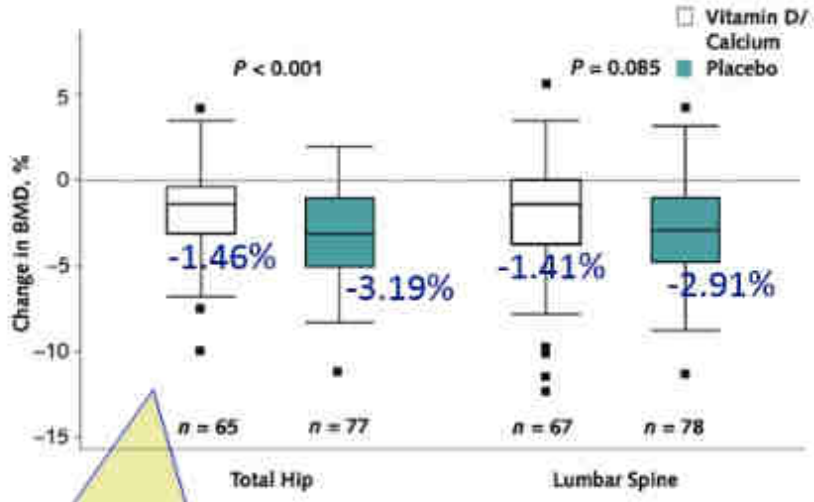
Wrist, Spine, Hip, US Veterans database
n=56600 HIV+, 98% M, 1996-2009; 951 pat with fractures

- Raw data re: ART drugs
- Model 1: + chronic kidney disease, age, ethnicity, smoking, Diabetes, BMI
- Modell 2: same + consideration of other HIV meds

Bedimo AIDS 2012

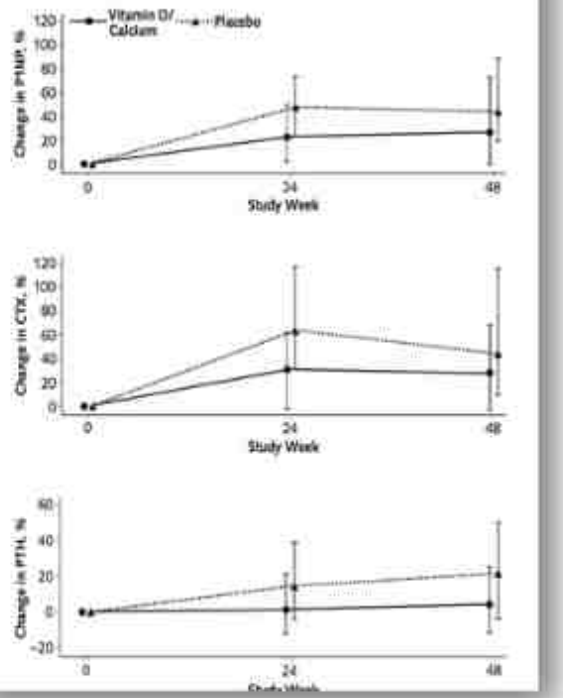
Prevention *of bone mineral density loss after TDF/FTC/EFV start:* **4000 IU Vit D + 1000mg Ca++ daily vs. placebo** (randomized, double blind trial)

Figure 3. Percentage of BMD change from baseline to 48 wk.



With Vit D + Ca++: BMD drop after ART start attenuated approx. 50% ....

Figure 4. Percentage of changes in bone turnover markers and PTH levels at 24 and 48 wk.



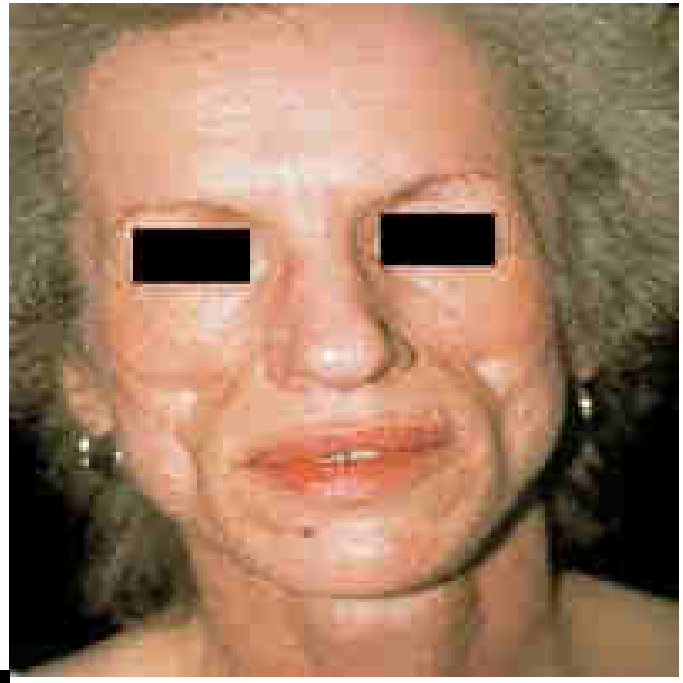
Overton ACTG A5280
Annals Intern Med 2015

INIBITORI della PROTEASI

1995:Saquinavir(Invirase)
1996:Indinavir(Crixivan), Ritonavir(Norvir)

Elevata tossicità:coliche renali, nefropatia(indinavir), tossicità neurologica, metabolica, epatica(ritonavir 1200 mgr die), necessità dietiche(2 litri acqua die con indinavir, digiuno)
Barriera genetica>che le altre classi

1998:scoperto ruolo di ritonavir come booster >potenza,>barriera genetica
1998:indinavir/ritonavir(**Crixivan+Norvir)**,saquinavir/ritonavir(**Invirase+Norvir)**
1999:nelfinavir(unico PI non boosterato)
2000:lopinavir/ritonavir(**Kaletra**)
2000:amprenavir,fosamprenavir/ritonavir(**Telzir+Norvir**)
2002:Atazanavir/ritonavir(**Reyataz+Norvir**)
2005:tipranavir/ritonavir(Aptivus+Norvir)
2007:darunavir/ritonavir(**Prezista+Norvir**)
2015:darunavir/cobicistat ed atazanavir/cobicistat(**Rezolsta**, **Evotaz**)




alamy stock photo

Darunavir

-associato a ritonavir 800/100mgr una volta al giorno
-ben tollerato a livello gastrointestinale
-rash(<2%)
-ipertransaminasemia, **dislipidemia**
-cristalluria

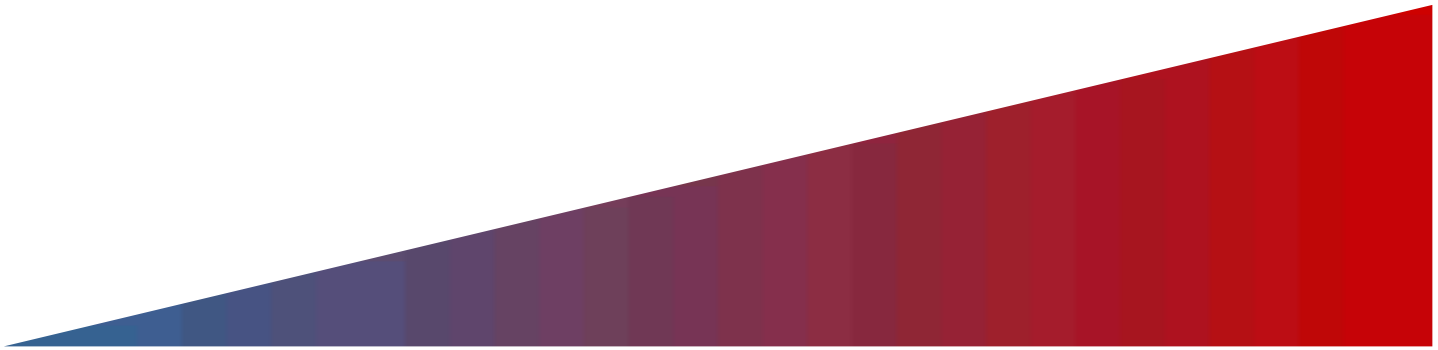
-associato a ritonavir 600/100mgr **DUE** volte al giorno
-da utilizzare in presenza di mutazioni associate a darunavir
-più indicato in presenza di alte cariche virali
-**>impatto metabolico per la doppia dose di ritonavir**
-possibile tossicità epatica
-interazioni farmacologiche

ATAZANAVIR

-vantaggi:assieme a ritonavir unica assunzione al dì, buon profilo lipidico, meno interazioni farmacologiche rispetto ad altri PI(es.con estroprogestinici, farmaci anti HCV, etc), uso in gravidanza
-svantaggi:**iperbilirubinemia indiretta**, **nefrolitiasi**, nefrotossicità

KALETRA(lopinavir già coformulato con ritonavir)
-dosaggio 2 cpr ogni dodici ore, meglio se a stomaco pieno
-vantaggi:elevata barriera genetica, buona penetrazione cerebrale, più studiato in gravidanza,nella PEP,già coformulato con il ritonavir, reperibile a basso costo in altri paesi, es.Africa sub-sahariana
-svantaggi:assunzione due volte al giorno, effetti gastrointestinali correlati al ritonavir, **dislipidemia associata, rischio cardiovascolare**

ART and Effects on Lipids



TDF

RAL
DTG

RPV
ETV

ABC

EFV

ATV/RTV or ATV/COBI
DRV/RTV or DRV/COBI
EVG/COBI

Inibitori dell'Integrasi

-raltegravir
-elvitegravir/cobi
-dolutegravir

Farmaci generalmente ben tollerati(tossicità neurologica, insonnia, irrequietezza)
Ottimo profilo lipidico
Rapida riduzione della carica virale
Non tossicità renale(solo modesto aumento della creatinina da blocco dell'OCT2 con dolutegravir ma clearance con ioexolo invariata, effetto "cosmetico")

SCARSE INTERAZIONI FARMACOLOGICHE(a parte elvitegravir/cobi)

Difetto:bassa barriera genetica per raltegravir ed elvitegravir

Pensando all'ultimo paziente con infezione da HIV che ho/abbiamo visto in ambulatorio qual è stato l'argomento principale della visita?

a) la casa, il lavoro, problematiche sociali

b) il fallimento della terapia

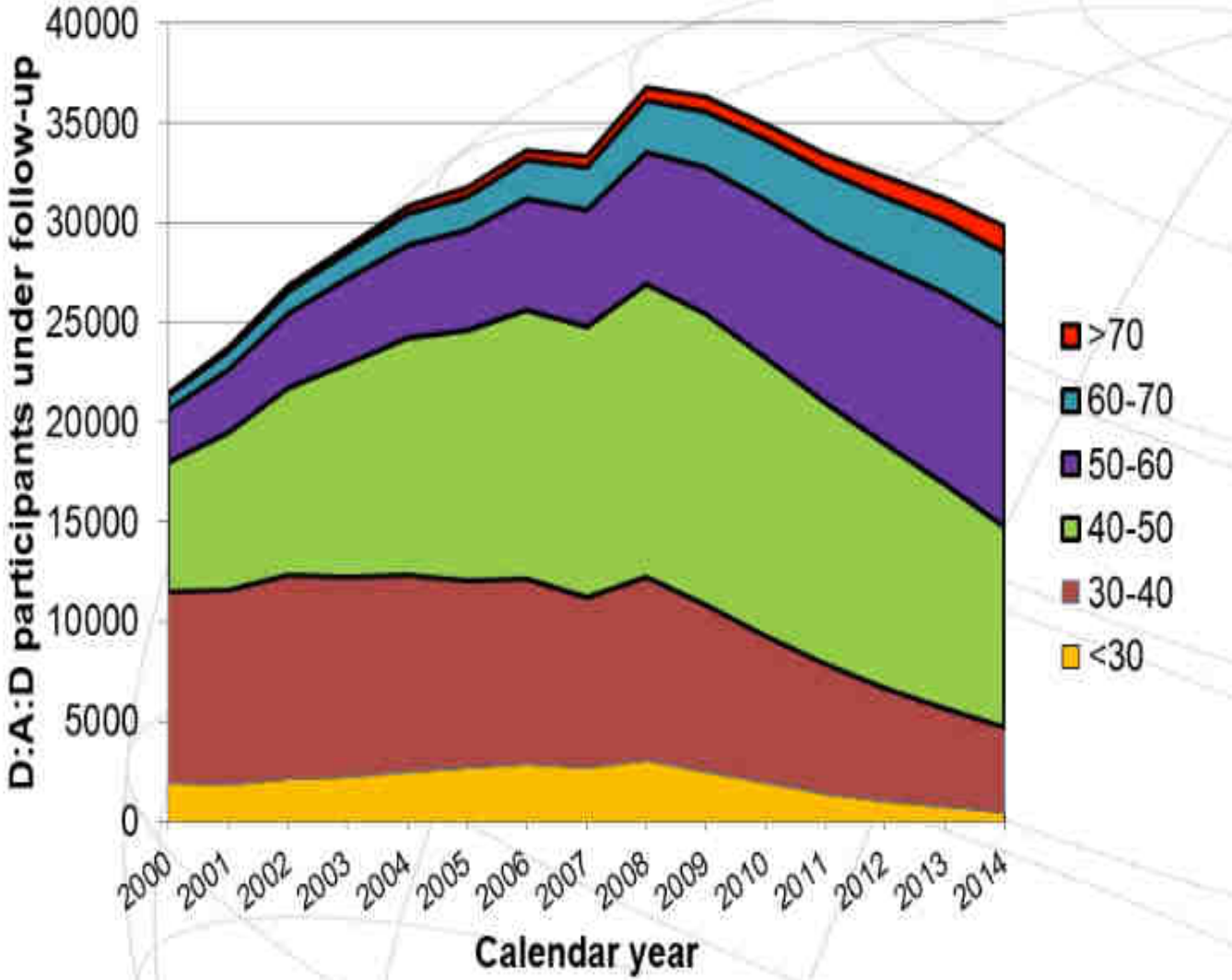
c) il cambiamento della terapia per tossicità o semplificazione

d) disturbi d'ansia, depressione, insonnia

e) fattori di rischio cardiovascolari o comorbidità come ipercolesterolemia, diabete, fumo, ipertensione, peso corporeo(prevenzione primaria o gestione clinica), interazioni farmacologiche

Rigshospitalet

Age distribution of HIV-positive participants in the D:A:D Study



D:A:D Merger 16 dataset

Background:l'HIV è una condizione a lungo termine

✔circa 120000 persone vivono con HIV in Italia

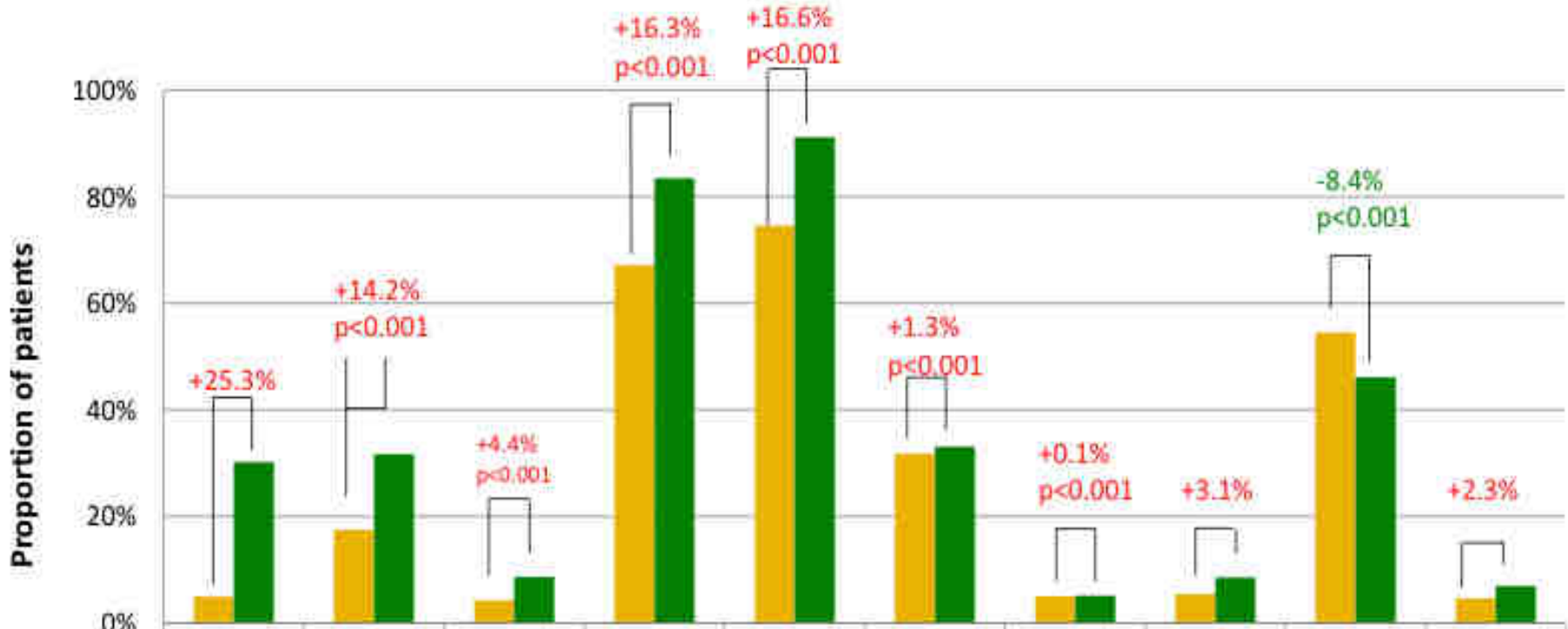
✔effetti e risultati della HART in una popolazione che invecchia

✔il 48% dei nostri pazienti è >50 anni

✔le comorbidità sono frequenti e ci si aspetta il loro incremento, soprattutto
- depressione
- rischio cardiovascolare

Evolution of comorbidities in HIV patients in Italian ICONA cohort: *cross sectional analysis in 2004 and 2014*

Figure 2– *Prevalence of patients' comorbidities and behavioral risk factors, in 2004 and 2014*



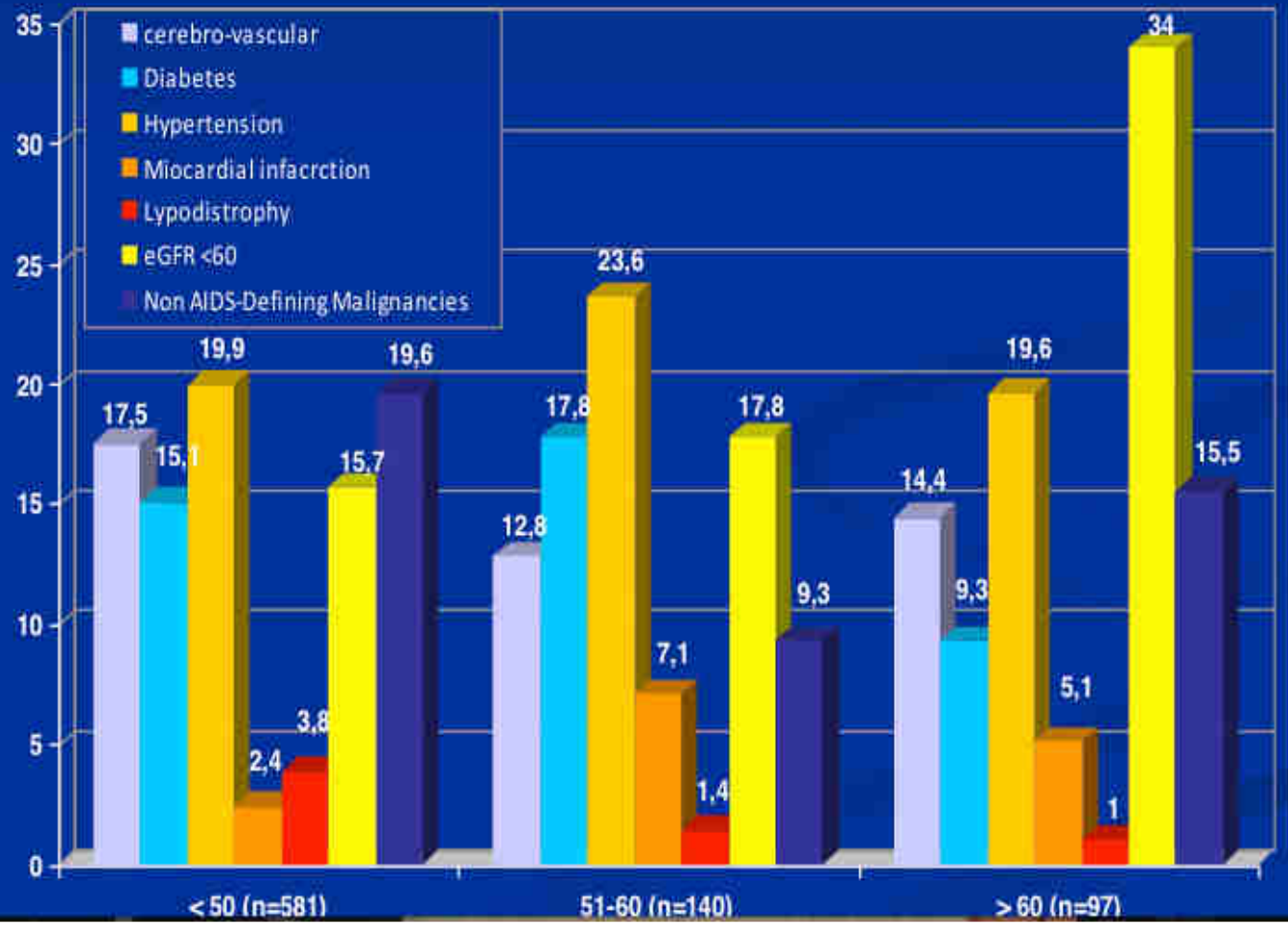
	eGFR<60	Cardiovascular event	Diabetes	Hypertension	Dyslipidemia	HCV	HBV	Obesity (BMI>30)	Current tobacco consumption	Abusive alcohol consumption
2004 (n=1,517)	4,90%	17,50%	4,20%	67,20%	74,60%	31,8%	5,0%	5,40%	54,50%	4,60%
2014 (n=1,517)	30,20%	31,70%	8,60%	83,50%	91,20%	33,1%	5,1%	8,50%	46,10%	6,90%

* p-value presented when calculated to the values presented in the graph.

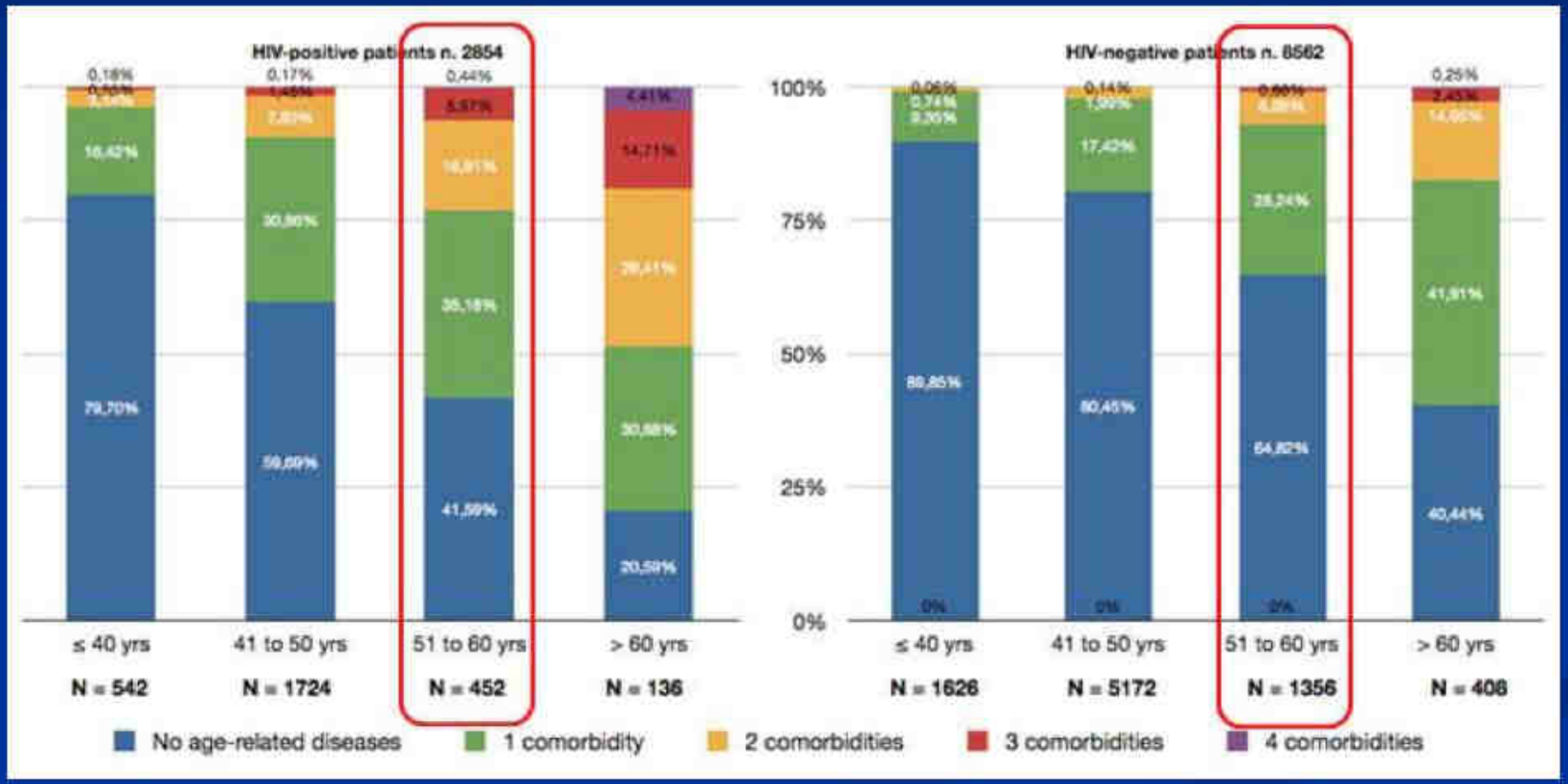
Fondazione Icona

Italian Cohort of Antiretroviral Naive Patients

Icona: prevalence of different non-AIDS related comorbidities according to age **in naive patients**

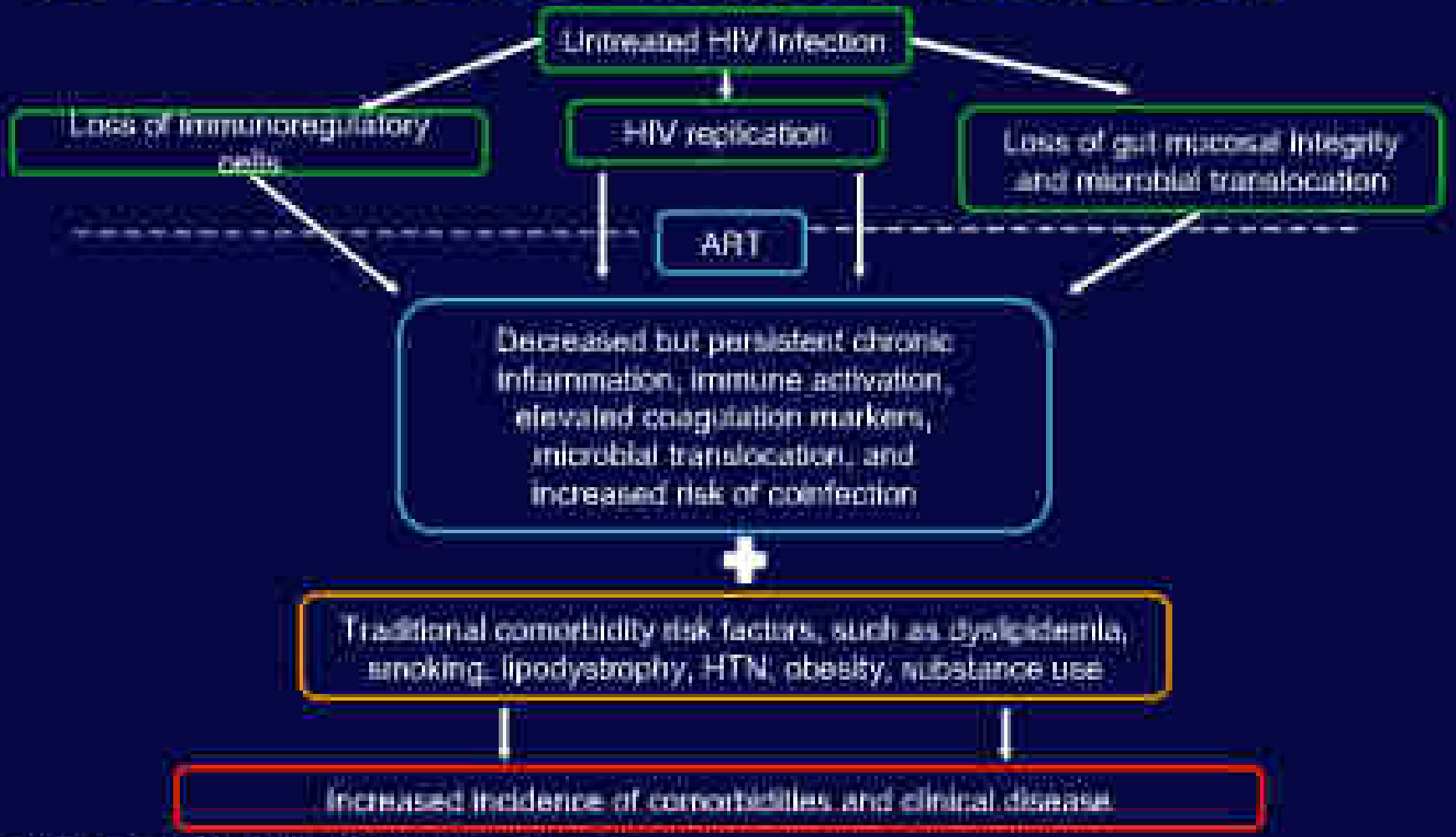


Confronto della prevalenza di poli-patologie tra la popolazione generale e una coorte di pazienti HIV-positivi



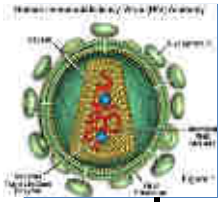
Guaraldi G et al, Clin Infect Dis 2011

Chronic Inflammation and Increased Risk for Comorbidities in HIV-Positive Pts



Deeks SG. Annu Rev Med. 2011;62:141-155.

Fattori implicati nella genesi del CVD nei pazienti HIV Positivi



rischi tradizionali

tossicità da ART

coinfezioni

attivazione monocitica e macrofagica

cascata proinfiammatoria e procoagulante

infiammazione cronica

CVD

Crowe, IAS 2014

Tassi di CVD più alti nei pazienti HIV positivi

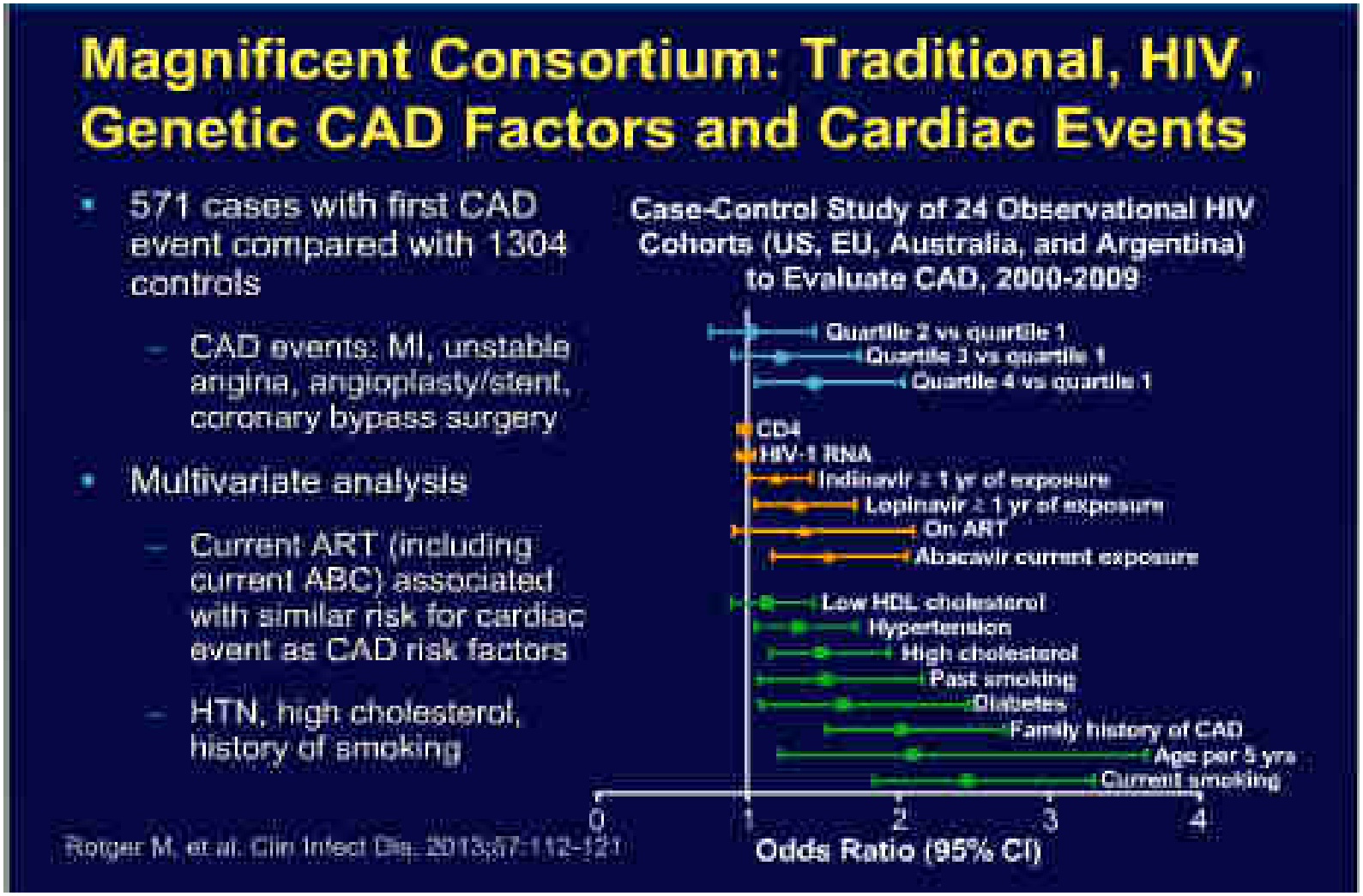
L'aumento del rischio permane anche dopo aver corretto per i più tradizionali fattori di rischio quali DM, HTN e iperlipemia

L'aumento del rischio permane anche nei pazienti in soppressione virologica

I drivers della CVD negli HIV+ includono la combinazione di più fattori fra cui la più alta prevalenza di rischi tradizionali(es.fumo) e non tradizionali(es.stress), gli effetti della ART e gli effetti dello stesso HIV

Freiberg MS, et al.JAMA Internal Medicine.2013;173:615-622

Contribution of traditional coronary artery diseases risk factors



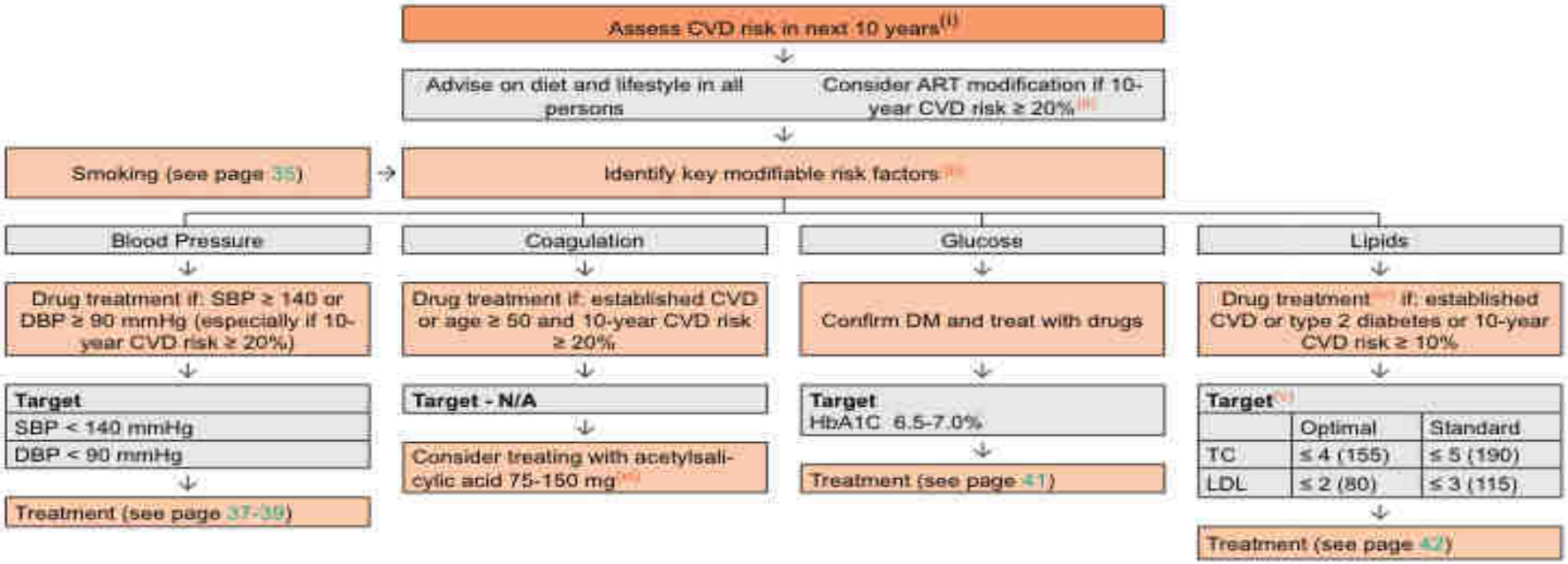
EACS European AIDS Clinical Society

GUIDELINES

Version 8.1
October 2016

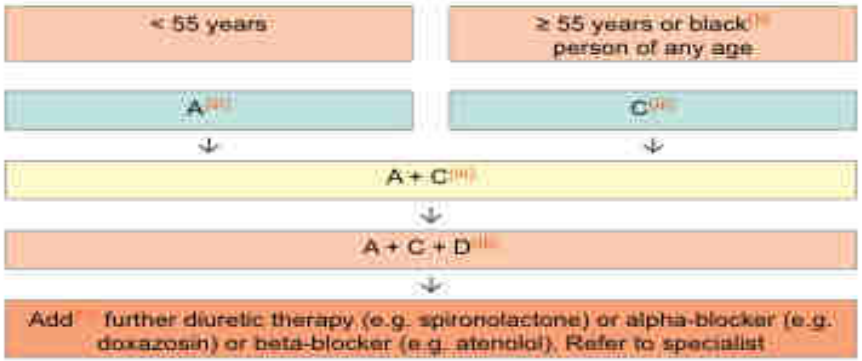
Prevention of CVD

Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated[1]. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in persons with a history of CVD.



Hypertension: Drug Sequencing Management

Choosing drugs[i] for persons newly diagnosed with hypertension



Abbreviations + details

A ACE inhibitor (e.g. perindopril, lisinopril or ramipril) or low cost angiotensin receptor blockers (ARB) (e.g. losartan, candesartan)

C Dihydropyridine calcium-channel blocker (e.g. amlodipine). If not tolerated or if deemed at high risk of heart failure, 'D' drugs can be used instead. Where a C drug is preferred but not tolerated, verapamil or diltiazem may be used (note: dose with caution with PIs as these may increase plasma concentrations of these calcium-channel blockers, potentially leading to toxic reactions)

D Thiazide-type diuretic* e.g. indapamide or chlorthalidone

i Some calcium-channel blockers interact marginally with the pharmacokinetics of ARVs, see Drug-drug interactions between Antihypertensives and ARVs

ii Black persons are those of African or Caribbean descent, and not mixed race, Asian or Chinese persons

iii Wait 4-6 weeks to assess whether target, see page 36, is achieved; if not, go to next step

iv Requirement of 4-5 drugs to manage hypertension needs specialist training

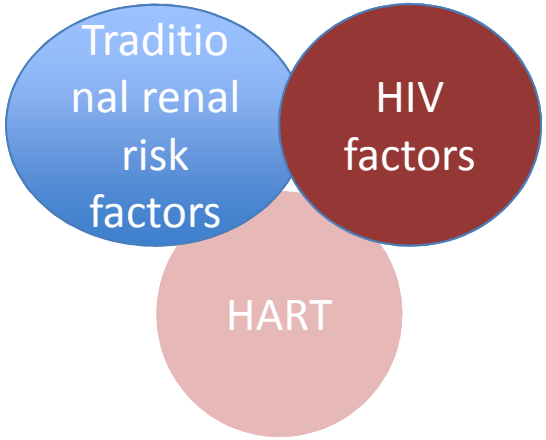
* This excludes thiazides (e.g. hydrochlorothiazide (HCTZ), bendroflumethiazide etc.)

Drug-drug Interactions between ARVs and Non-ARVs[i]

	Non-ARV drugs	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Cardiovascular drugs	atorvastatin	↑	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	fluvastatin	↔	↑	↔	↔	↑	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	pravastatin	↔	↑	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	rosuvastatin	↕213%	↑	↑48%	↑107%	↔	↔	↔	↔	↔	↔	↑38%	↔	↔	↔	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	amlodipine	↑*	↑	↑	↑*	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑*	↑	↑	↑*	↓69%	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑*	↑	↑	↑*	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑*	↑	↑	↑*	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	E	E	↔
	warfarin	↑ or ↓	↑	↓	↓	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔

http://www.hiv-druginteractions.org (University of Liverpool)

Potenziali fattori di rischio di CKD in HIV



Diabete, ipertensione, dislipidemia, fumo
Ageing
Etnia/Predisposizione genetica
Familiarità

Coinfezione HCV
Immunosoppressione
HIV
Uso di droghe
Infezioni opportunistiche e loro trattamenti

Terapia antiretrovirale (HART)

Kidney Disease: Definition, Diagnosis and Management

Diagnosis of kidney disease

		eGFR[1]		
		≥ 60 mL/min	30-59 mL/min	< 30 mL/min
Proteinuria[10]	UP/C[10] < 50	Regular follow-up		
	UP/C[10] 50-100	• Check risk factors for CKD[11] and nephrotoxic medicines including ART[5, 6] • Discontinue or adjust drug dosages where appropriate[5] • Perform renal ultrasound • If haematuria present with any level of proteinuria refer to nephrologist • Refer to nephrologist if new CKD or progressive decline in eGFR		• Check risk factors for CKD and nephrotoxic medicines including ART[5] • Discontinue or adjust drug dosages where appropriate[5] • Perform renal ultrasound • Urgent referral to nephrologist
	UP/C[10] > 100			

Management of HIV-associated kidney disease[5, 6]

Prevention of progressive renal disease	Comment
1. ART	Start ART immediately where HIV-associated nephropathy (HIVAN)[5, 6] or HIV immune complex disease strongly suspected. Immunosuppressive therapy may have a role in immune complex diseases. Renal biopsy to confirm histological diagnosis recommended
2. Start ACE inhibitors or angiotensin-II receptor antagonists if: a. Hypertension and/or b. Proteinuria	**Monitor eGFR and K^+ level closely on starting treatment or increasing dose** a. Blood pressure target: < 130/80 mmHg
3. General measures: a. Avoid nephrotoxic drugs b. Lifestyle measures (smoking, weight, diet) c. Treat dyslipidaemia[5, 11] and diabetes[12] d. Adjust drug dosages where necessary[5, 6]	CKD and proteinuria are independent risk factors for CVD

NNTH: At 5 years

D:A:D risk-score for CKD =

+	2	IDU
+	1	HCV antibody +ve
+	4	aged 35-50
+	7	aged 50-60
+	10	aged >60
+	6	baseline eGFR < 70
-	6	baseline eGFR > 90
+	1	female
+	1	nadir CD4 <200/mm^3
+	1	hypertensive
+	1	prior CVD
+	2	diabetic

Add zero if non-IDU, HCV antibody -ve, aged<35, baseline eGR 70-90, male, CD4 nadir ≥200/mm^3, non-diabetic, non-hypertensive or no prior CVD

CKD risk	Score	LPV/r, ATV	TDF, ATV/r, PI/r
Low	<0	1395	603
Medium	0-4	142	61
High	≥5	20	9

Mocroft for D:A:D, PLOS MED 2015

CASO CLINICO

CASO CLINICO
Roberto, 61 anni, Italiano
Fine 2014:ricovero per dimagrimento,febbre, tosse, dispnea
Quadro RX di interstiziopatia, all'EGDS candidosi esofagea

HIV POSITIVO! Late presenter(AIDS presenter!)
CD4+=176/mmc, HIV-RNA=389766 copie/ml

CASO CLINICO

Superate le infezioni opportunistiche inizia ART con 2 NRTI (abacavir/lamivudina)e 1 IP(darunavir/ritonavir b.i.d)
Terapia ben tollerata(diarrea), buon recupero immunologico e buon controllo virologico, sviluppo di ipercolesterolemia
Non fumatore, PA nei limiti, incremento ponderale
Lamenta DE

L'andrologo prescrive sildenafil a dosaggio basso 2 cpr/settimana che l'infettivologo riduce a 1 cpr/sett

Drug-drug Interactions between ARVs and Non-ARVs[1]

	Non-ARV drugs	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Cardiovascular drugs	atorvastatin	↑	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	fluvastatin	↔	↑	↔	↔	↑	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	pravastatin	↔	↑	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	rosuvastatin	↑213%	↑	↑48%	↑107%	↔	↔	↔	↔	↔	↔	↑38%	↔	↔	↔	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	amlodipine	↑*	↑	↑	↑*	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑*	↑	↑	↑*	↓69%	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑*	↑	↑	↑*	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑*	↑	↑	↑*	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	E	E	↔
	warfarin	↑ or ↓	↑	↓	↓	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
CNS drugs	diazepam	↑	↑	↑	↑	↓	↑	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	midazolam (oral)	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	triazolam	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	citalopram	↑*	↑	↑	↑*	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔	↔	↔	↔	↔
	sertraline	↓	↑	↓49%	↓	↓39%	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bupropion	↓	↔	↓	↓57%	↓55%	↔	↓	↔	↔	↔	↑?	↔	↔	↔	↔	↔	↔	↔
	pimozide	↑*	↑	↑	↑*	↑	↓	↓	↔*	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	carbamazepine	↑D	↑D	↑	↑D	↓27%D36%	D	↓D	D	D	D	D	D	↑	↔	↔	D	↔	↑*
	lamotrigine	↓32%*	↔	↓*	↓50%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenytoin	↓D	D	↓D	↓D	↓D	D	↓D	D	D	D	D	D	D	↔	↔	D	↔	↓
Anti-infectives	clarithromycin	↑*	↑	↑	↑*	↓	↓E	↓	E	E	↔	↑E	↔	↔	↔	↔	E	E	D
	fluconazole	↔	↑?	↔	↔	↔	E86%	E100%	E	↔	↔	↑?	↔	↔	↔	↔	E?	↔	E74%
	itraconazole	↑E	↑E	↑E	↑E	↓	↓E	↓61%	E	E	↔	↑E	↔	↔	↔	↔	E	E	↔
	rifabutin	↑	↑D	↑E50%	↑	↓38%	D37%	↑17%	D	-	↔	↑D	↔	↔	↔	↔	D	↔	↔
	rifampicin	D72%	D	D	D	D26%	D	D58%	D80%	D	D54%	D	D40%	D	↔	↔	D	↔	D47%
	voriconazole	↓	↑E	↓	↓	↓E	↑E	↓E	E	E	↔	↑E	↔	↔	↔	↔	↔	↔	↔
Miscellaneous	antacids	D	↔	↔	↔	↔	↔	↔	D	↔	D	D	D	↔	↔	↔	↔	↔	↔
	PPIs	D	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	E	↔	↔	↔	↔	↔	↔
	H2 blockers	D	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	E	↔	↔	↔	↔	↔	↔
	alfuzosin	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	beclometasone inhal.	↑*	↑?*	↓11%	↑*	↔	↔	↔	↔	↔	↔	↑*	↔	↔	↔	↔	↔	↔	↔
	buprenorphine	↑67%	↑	↑*	↔	↓50%	↓25%	↔	↔	↔	↔	↑35%	↔	↔	↔	↔	↔	↔	↔
	budesonide inhal.	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	ergot derivatives	↑	↑	↑	↑	↑	↑	↓	E	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	ethinylestradiol	↓*	↑	↓	↓	↔*	↔	↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
	fluticasone inhal.	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	methadone	↓*,**	↑?	↓16%	↓53%*	↓52%	↑6%	↓≈50%	↓16%	↔	↔	↔	↔	↓	↔	↔	↔	↔	E29-43%
	salmeterol inhal.	↑*	↑	↑	↑*	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	sildenafil (erec. dys.)	↑	↑	↑	↑	↓	↓37%	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	St John's wort	D	D	D	D	D	D	D	D	D	D	D	D?	↔	↔	↔	D	↔	↔
	varenicline	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

13 ottobre 2016, il caso continua

Persiste, in aumento, ipercolesterolemia nonostante dieta calibrata, attività fisica, etc.
In accordo con le linee guida (considerata l'età, rischio CVD, etc, non volendo introdurre le statine per pill burden) si cambia la terapia sostituendo l'IP con l'inibitore dell'integrasi
Nuova terapia:Triumeq(abacavir/lamivudina/dolutegravir) 1 cpr die
Paziente felice ma…..

Non è felice perchè è peggiorata la DE

http://www.hiv-druginteractions.org/

Report ID:
Date Produced: 18 November 2016

Antiretroviral Treatment	Co-medications
Abacavir Darunavir Lamivudine (3TC) Ritonavir	Sildenafil (Erectile Dysfunction)

This report lists the summaries of potentially clinically significant interactions (i.e. "red" and "amber" classifications for the drugs in the table above).

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown.

For full details of all interactions, see www.hiv-druginteractions.org .

Description of the interactions

Potential interaction - may require close monitoring, alteration of drug dose or timing of administration (AMBER)

Ritonavir + Sildenafil (Erectile Dysfunction)
Coadministration is contraindicated in pulmonary arterial hypertension patients. Coadministration substantially increases sildenafil concentrations and may increase sildenafil-associated adverse events. Coadministration of sildenafil (100 mg single dose) and ritonavir (500 mg twice daily) increased sildenafil AUC by 11-fold and Cmin by 4-fold. Coadministration is not recommended, but if given sildenafil should not exceed a maximum single dose of 25 mg in a 48-hour period.

Darunavir + Sildenafil (Erectile Dysfunction)
Note: this interaction was studied using a darunavir/ritonavir dose lower than that licensed. Coadministration of darunavir/ritonavir (400/100 mg twice daily) and a single dose of sildenafil (25 mg) resulted in comparable exposure to 100 mg sildenafil alone. If coadministration is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours can be used with increased monitoring for PDE-5 inhibitor associated adverse events.

No clinically significant interaction expected (GREEN)

Lamivudine (3TC) + Sildenafil (Erectile Dysfunction)

Abacavir + Sildenafil (Erectile Dysfunction)

www.hiv-druginteractions.org

University of Liverpool

Interaction Report

Report ID:
Date Produced: 18 November 2016

Antiretroviral Treatment	Co-medications
Abacavir Dolutegravir Lamivudine (3TC)	Sildenafil (Erectile Dysfunction)

This report lists the summaries of potentially clinically significant interactions (i.e. "red" and "amber" classifications for the drugs in the table above).

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown.

For full details of all interactions, see www.hiv-druginteractions.org .

Description of the interactions

No clinically significant interaction expected (GREEN)

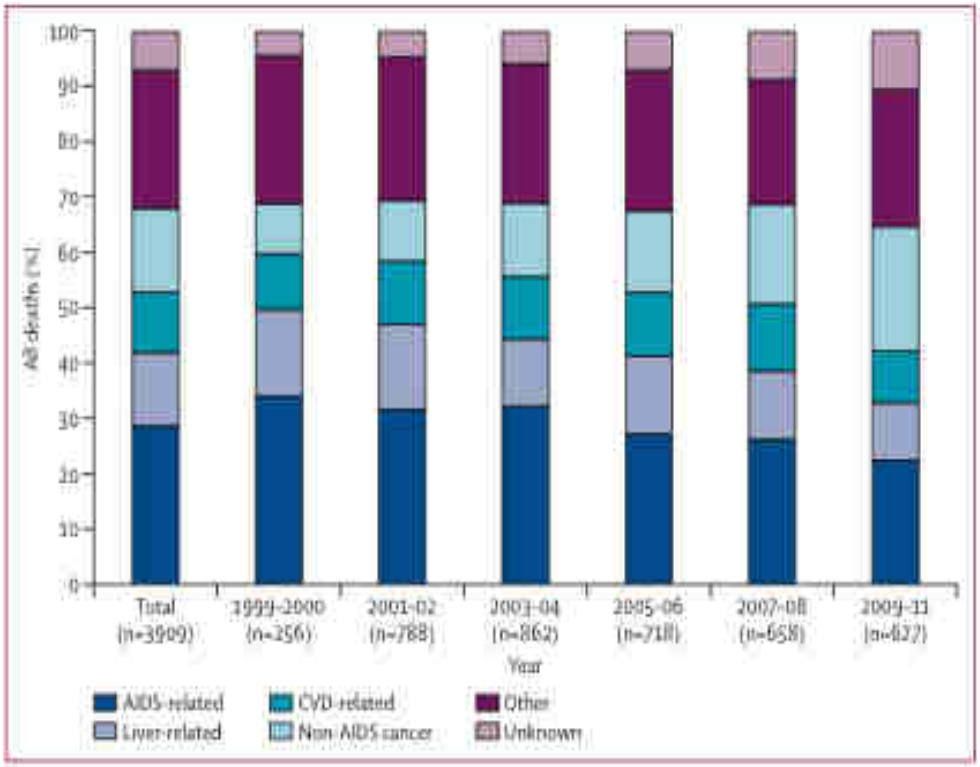
Lamivudine (3TC) + Sildenafil (Erectile Dysfunction)

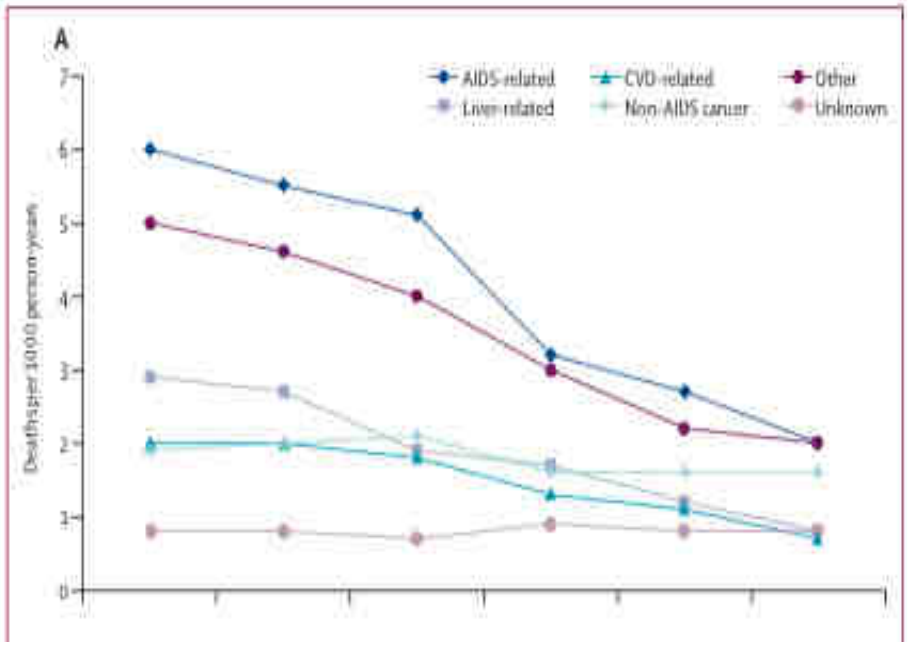
Abacavir + Sildenafil (Erectile Dysfunction)

Dolutegravir + Sildenafil (Erectile Dysfunction)

Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration

*Colette J Smith, Lene Ryom, Rainer Weber, Philippe Morlat, Christian Pradier, Peter Reiss, Justyna D Kowalska, Stephane de Wit, Matthew Law, Wafaa el Sadr, Ole Kirk, Nina Friis-Møller, Antonella d'Arminio Monforte, Andrew N Phillips, Caroline A Sabin, Jens D Lundgren, for the D:A:D Study Group**





National Toxicology Program

Headquartered at the
National Institute of Environmental
Health Sciences NIH-HHS

Cancer-Causing Viruses

Five viruses are being added to the Report on Carcinogens. All five are being listed as *known to be human carcinogens*, based on sufficient evidence from human studies. They all have been linked to cancer in humans. The viruses being added are:

- **Human immunodeficiency virus type 1 (HIV-1)**
- **Human T-cell lymphotropic virus type 1 (HTLV-1)**
- **Epstein-Barr virus (EBV)**
- **Kaposi sarcoma-associated herpesvirus (KSHV)**
- **Merkel cell polyomavirus (MCV)**

Given that about 12 percent of cancers worldwide are linked to viruses, and there are no vaccines available for any of these five viruses, prevention is critical for reducing potential cancer risks.

These five viruses are more likely to lead to cancer in people that have weakened immune systems, or immunosuppression.

These five viruses will be grouped with other viruses listed in previous reports, including hepatitis B, hepatitis C, and some human papillomaviruses.

Key Points

- *All five viruses are known to be human carcinogens*
- *These five viruses are linked to more than 20 types of cancers*
- *People with weakened immune systems are more likely to develop these cancers*

14th Report on Carcinogens

Viral exposures and cancers

Human immunodeficiency virus type 1 (HIV-1)
A virus spread through infected semen, vaginal fluids, or blood

Sufficient evidence of cancer:
- Cervical cancer
- Conjunctival eye cancer
- Hodgkin lymphoma
- Invasive anal cancer
- Kaposi sarcoma, a blood vessel cancer
- Non-Hodgkin lymphoma
- Non-melanoma skin cancer
- Penile cancer
- Vaginal/vulvar cancer

Limited evidence of cancer:
- Liver cancer
- Lung cancer
- Oral-related cancers

Human T-cell lymphotropic virus type 1 (HTLV-1)
A virus spread through contact with infected cells found in biological fluids or tissues

Sufficient evidence of cancer:
- Adult T-cell leukemia-lymphoma, a rare cancer

Epstein-Barr virus (EBV)
A herpes virus spread primarily by contact with infected saliva

Sufficient evidence of cancer:
- Burkitt lymphoma (endemic form)
- Extranodal natural killer/T-cell lymphoma (rare nasal type)
- Hodgkin lymphoma
- Immune-suppression-related non-Hodgkin lymphoma
- Nasopharyngeal carcinoma
- Some forms of stomach cancer

Limited evidence of cancer:
- Burkitt lymphoma (sporadic form)

Kaposi sarcoma-associated herpesvirus (KSHV or HHV-8)
A herpes virus spread through contact with infected saliva, blood, and bodily fluids

Sufficient evidence of cancer:
- Kaposi sarcoma, a blood vessel cancer
- Multicentric Castleman disease (plasmablastic variant)
- Primary effusion lymphoma

Merkel cell polyomavirus (MCV or MCPyV)
A virus where the spread is not fully understood, but close personal contact with infected saliva and skin, or from the environment, may contribute

Sufficient evidence of cancer:
- Merkel cell carcinoma, a rare skin cancer

PO Box 12233 • Research Triangle Park, NC 27709
Phone: 919-541-3345 • http://ntp.niehs.nih.gov

November 2016

GRAZIE!