Roma 21 settembre 2017

Nuove strategie terapeutiche

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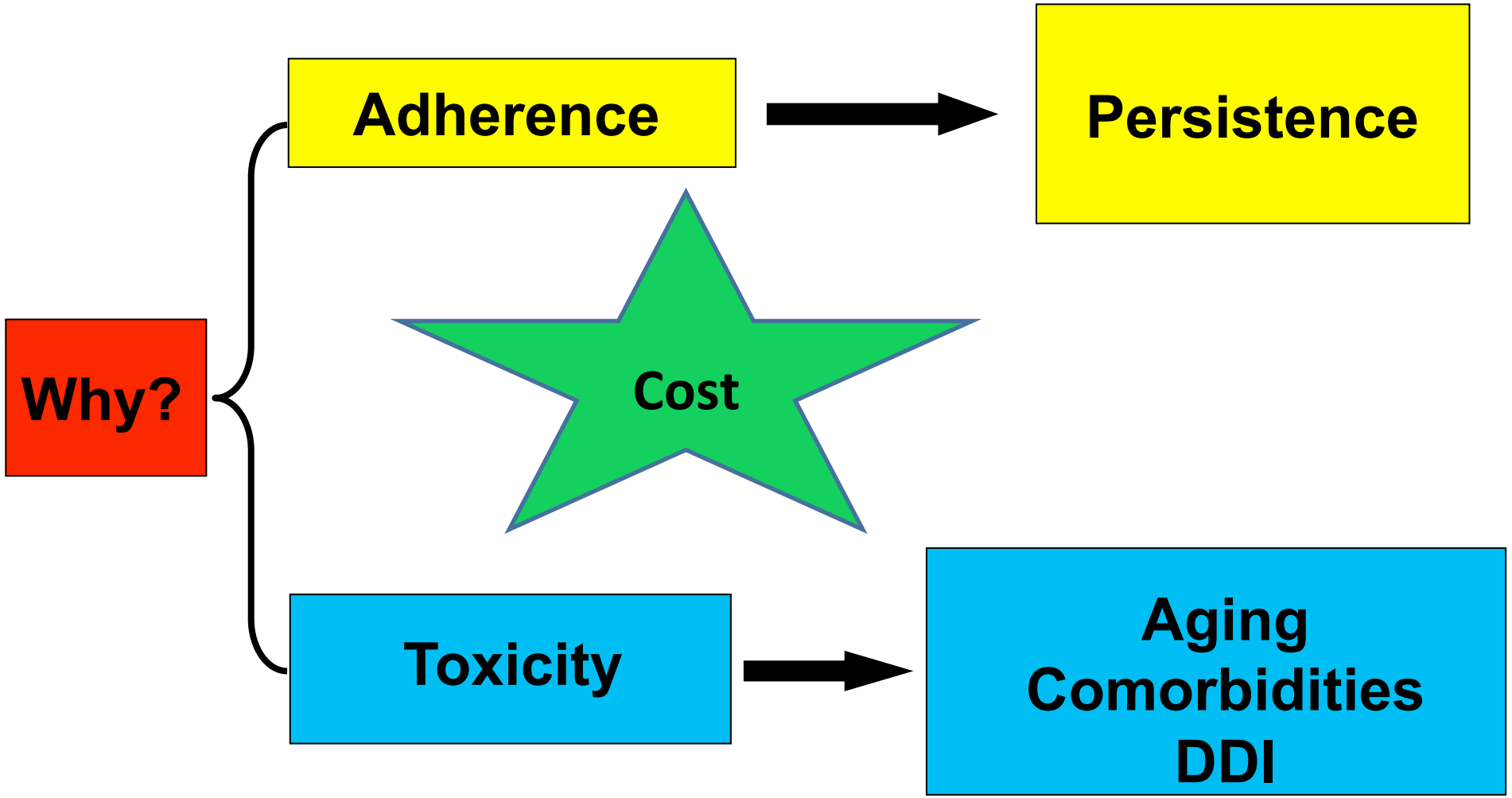
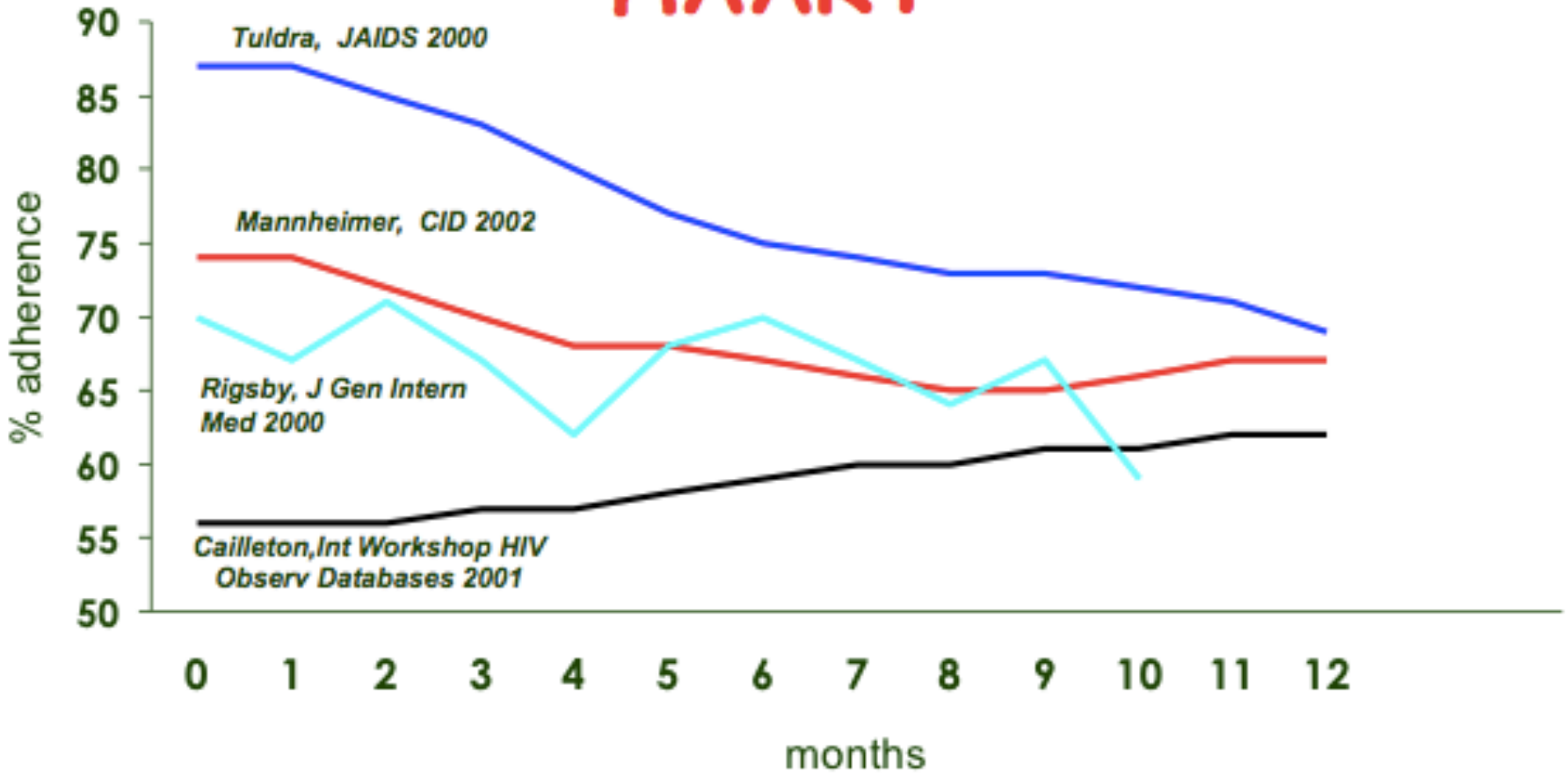
PTV
Azienda Ospedaliera Univers
POLICLINICO TOR VERGATA

Dual Therapy: starting from rationale



Andreoni M, June 2017

The adherence decline during HAART



KEEP THE DOCTOR AWAY

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

Ottobre 2011

Su mandato del Ministro della Salute

In collaborazione con

Ministero della Salute

Commissione Nazionale per la lotta contro l'AIDS
Consulta delle Associazioni per la lotta contro l'AIDS
e
SIMIT

2a. La riduzione del numero di dosi/somministrazioni e di compresse giornaliere: strategie di semplificazione gestionale

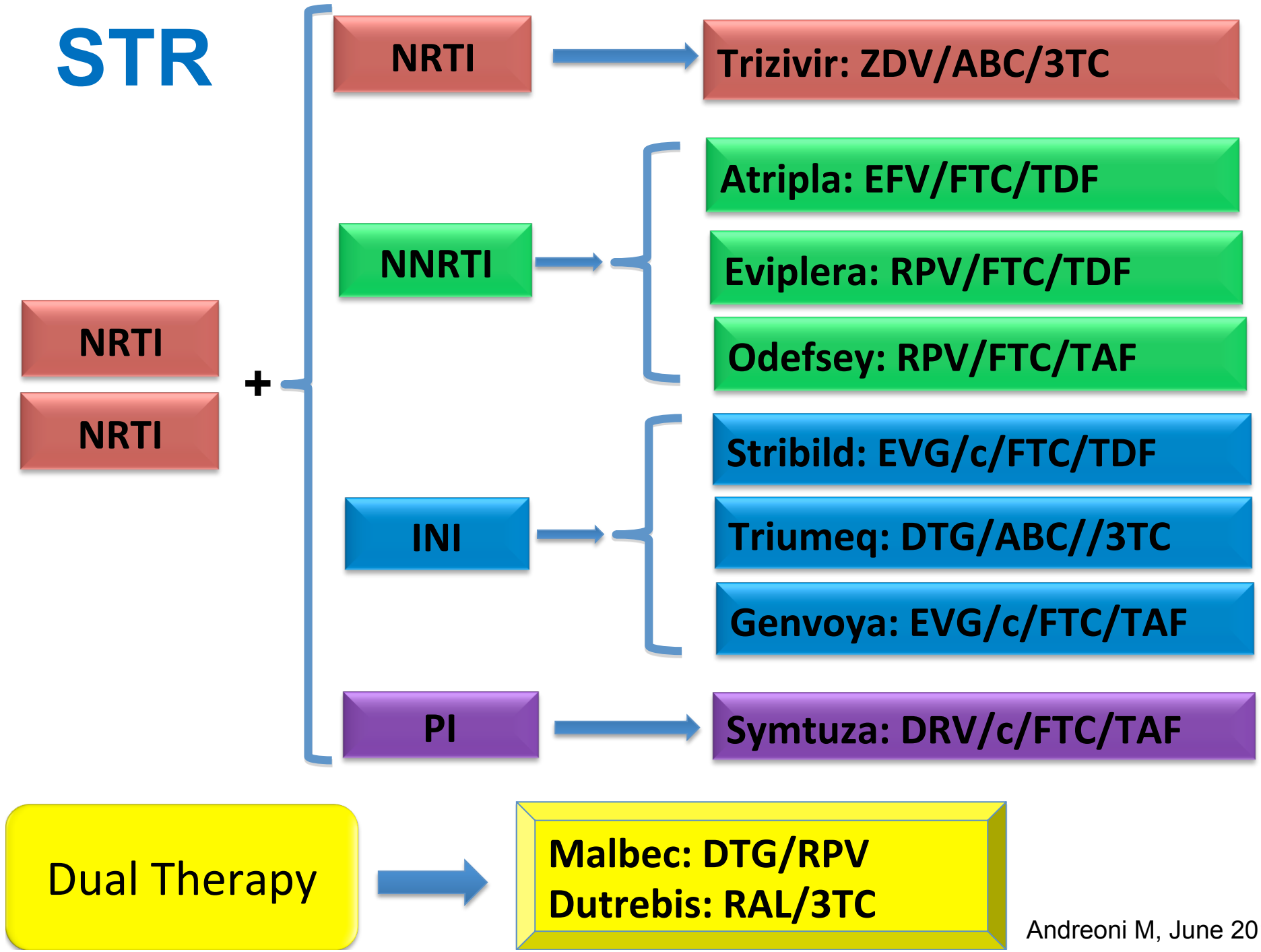
FDCs, Monosomministrazione giornaliera e regimi STR

Questi termini si riferiscono a concetti che favoriscono, nella pratica clinica, l'impiego di farmaci e/o regimi terapeutici che contemplano:

- L'utilizzo di FDCs (ossia Fixed-Dose Combinations) rispetto alle combinazioni estemporanee di singoli farmaci;
- La monosomministrazione giornaliera (QD invece che BID);
- La combinazione dei due precedenti concetti nota come STR (Single Tablet Regimen) ovvero la formulazione compatta di un regime terapeutico completo assunto una sola volta al giorno (una compressa una volta al giorno).

I regimi STR si sono mostrati più efficaci nella durata della soppressione virologica rispetto a quelli più complessi. In particolare, di recente è stato introdotto il concetto multifattoriale di 'resistenza di barriera', che riguarda l'analisi dell'intero regime terapeutico ed è basata sulla

L'uso di STR di per sé può essere un elemento chiave per contribuire a migliorare la qualità di vita e l'aderenza dei pazienti [AII]



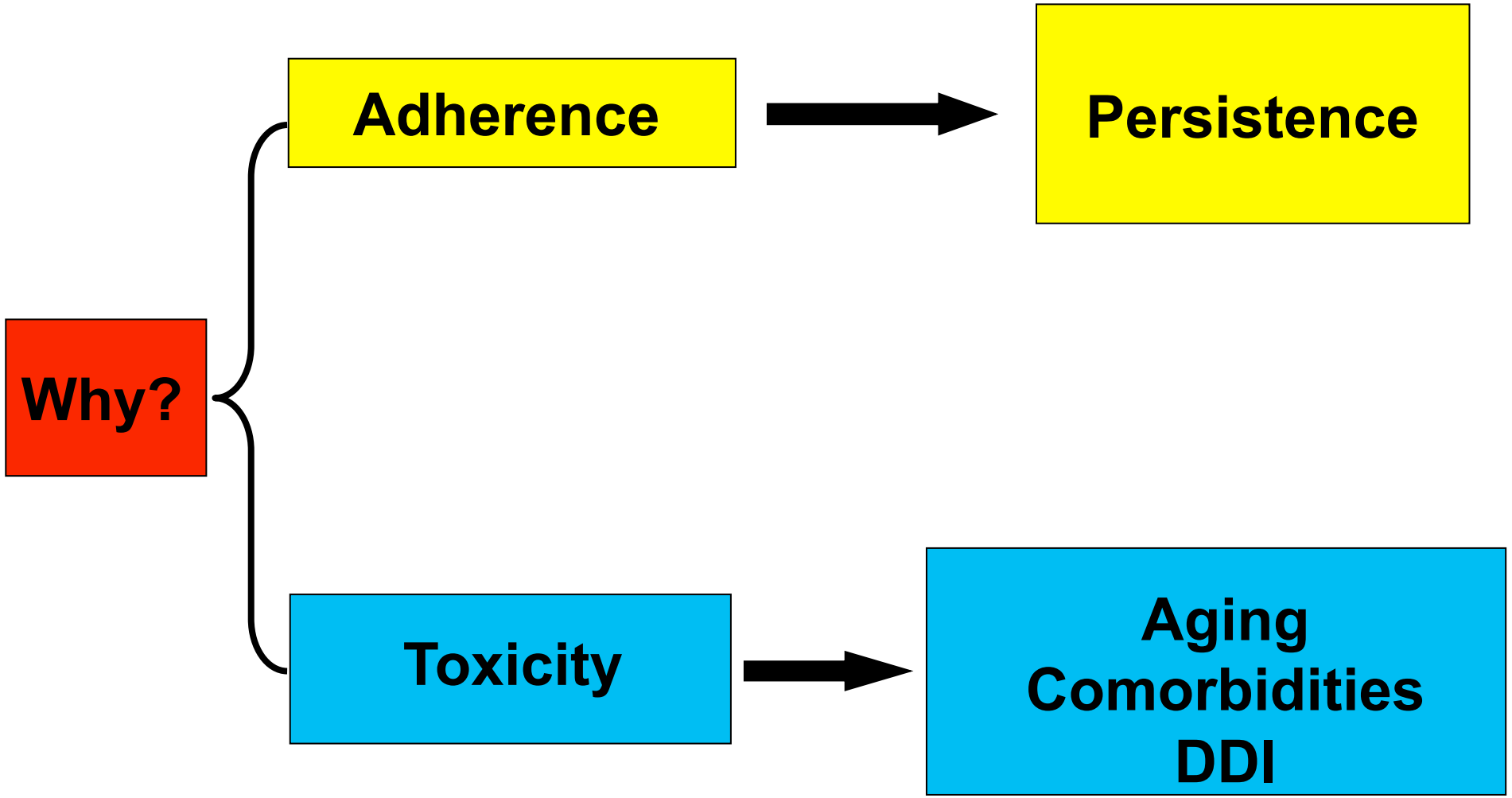
Andreoni M, June 2017

Recommended ART Regimens for Treatment-Naive Pts

Regimen	SIMIT	DHHS[1]	IAS-USA[2]	BHIVA[3]	EACS[4]	GeSIDA[5]
DTG/3TC/ABC						
DTG + FTC/TDF						
DTG + FTC/TAF						
EVG/COBI/FTC/TDF						
EVG/COBI/FTC/TAF						
RAL + FTC/TDF						
RAL + FTC/TAF						
ATV/RTV + FTC/TDF						
ATV/RTV + FTC/TAF						
DRV/RTV* + FTC/TDF						
DRV/RTV* + FTC/TAF						
RPV/FTC/TDF						
RPV/FTC/TAF						

Recommended Alternative Recommended in particular conditions Not included

Dual Therapy: starting from rationale



Andreoni M, June 2017

The challenge of medication toxicity

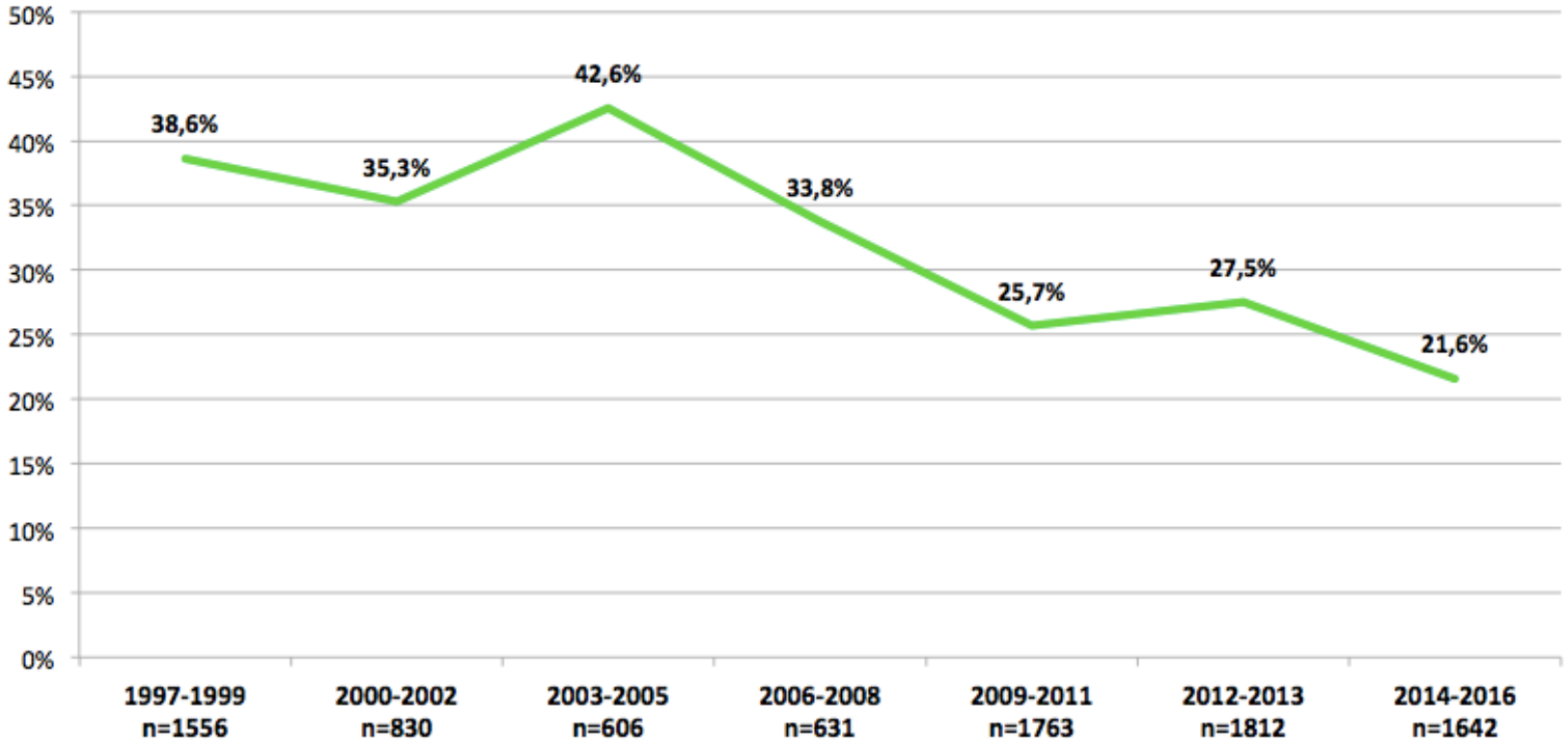
- Nausea[1]
- Diarrhoea[1]
- Metabolic disturbances[1]
- Body shape changes[1]
- Paraesthesia[1]
- Bone loss[2]
- Renal dysfunction[1]
- Cardiovascular disease[1]

1. Margolis AM et al. J Med Toxicol 2014;10:26–39; 2. Compston J J Intern Med. 2016 Oct;280(4):350-358

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Proportion of patients stopping at least one drug of their first ART regimen within 1 year, according to calendar period of starting



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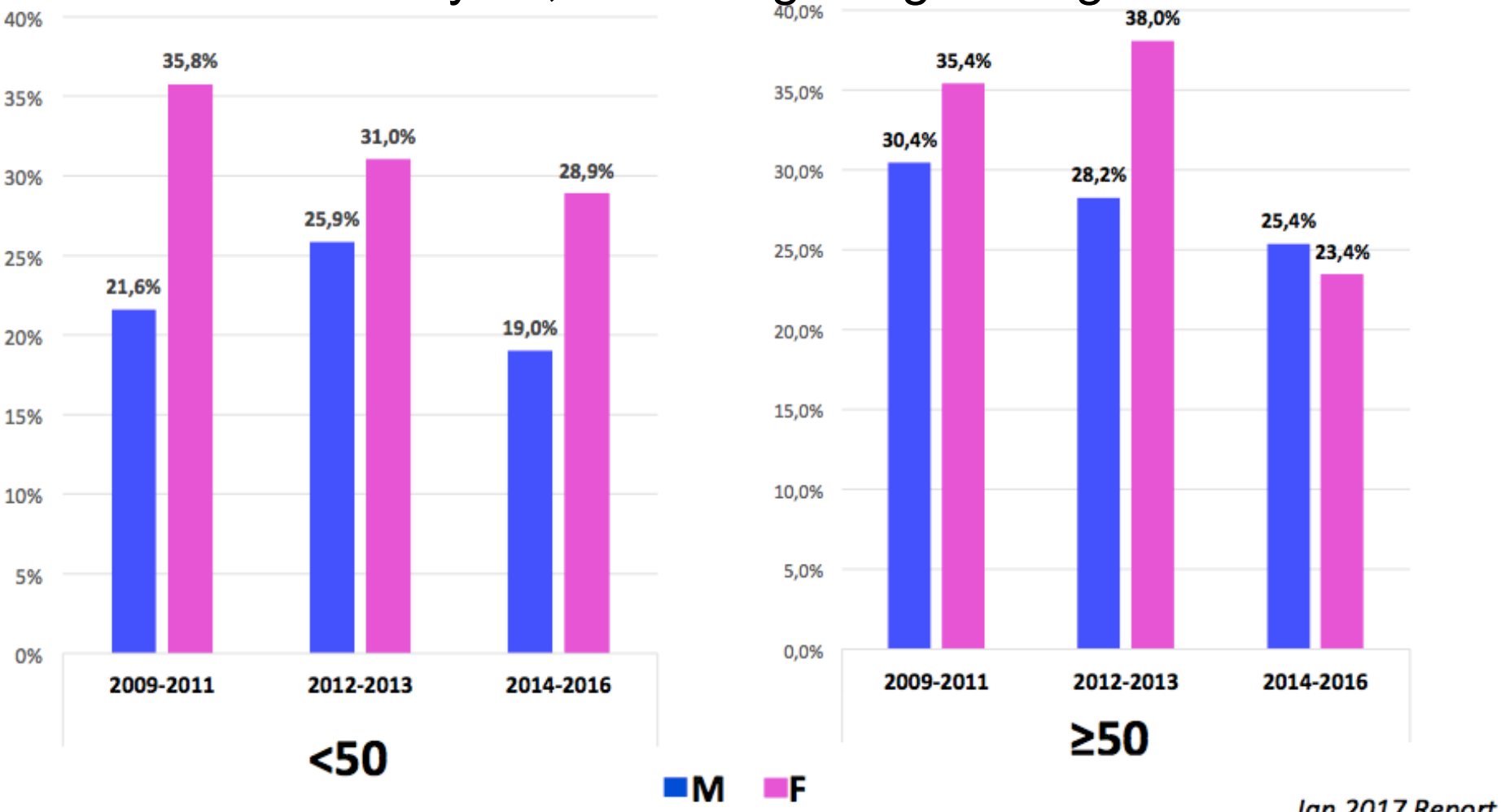
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of patients stopping at least one drug of first ART within 1 year, according to age and gender



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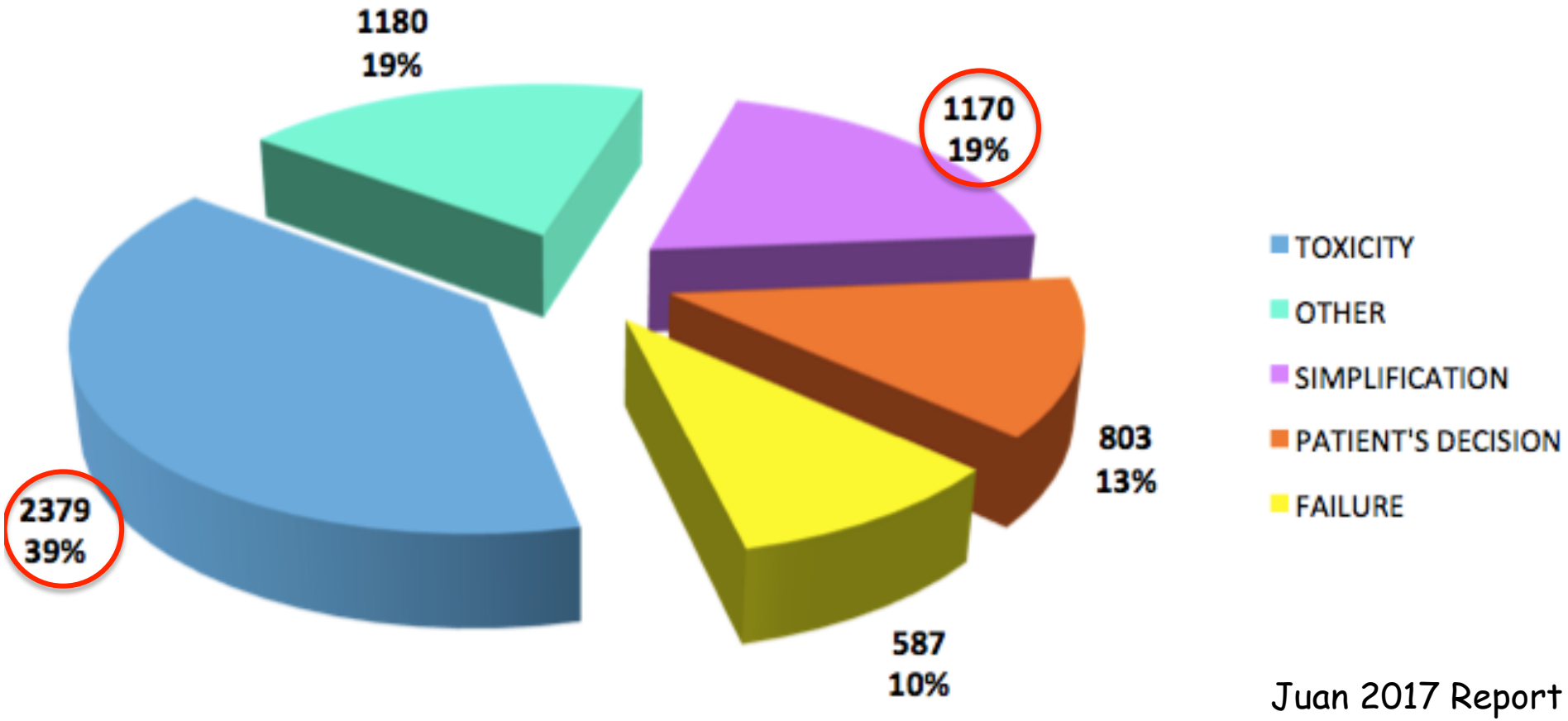
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Distribution of reasons for stopping at least one drug included in the first regimen (n.6119)



Juan 2017 Report

Multimorbidity, Polypharmacy, and ART Use in HIV+ Pts 75 Yrs of Age or Older

- **GEPPO**: prospective cohort study of geriatric HIV+ pts older than 75 yrs of age with matched group of HIV- pts
- Current cross-sectional analysis assessed polypharmacy, multimorbidity, and ART use by HIV status in pts 75 yrs of age or older (N = 492; HIV+: n = 292; HIV-: n = 200)
  - HIV+ pts stratified by duration of HIV infection
    - < 10 yrs, 10-20 yrs, > 20 yrs
  - Multimorbidity: ≥ 3 comorbidities (not due to infection)
  - Polypharmacy: ≥ 5 medications (excluding ART)

Guaraldi G, et al. International Comorbidities WS 2016. Abstract P05.

HIV+ > 20 Yrs Major Driver of Multimorbidity and Polypharmacy

- 35.3% of HIV+ pts on low-drug ART regimens
  - Dual therapy: 28.7%
  - Monotherapy: 6.6%
- 56.4% of HIV+ pts on NRTI-sparing regimens; 59.3% on booster-free regimens
- Statins prescribed more often in HIV+ vs HIV- pts (47.6% vs 22.3%), benzodiazepines prescribed less often (3.5% vs 18.4%)

Significant Predictors of Outcomes*	OR (95% CI)	*P* Value
Multimorbidity:		
▪ Male vs female	2.06 (1.12-3.793)	.02
▪ HIV+ > 20 yrs	2.31 (1.05-5.435)	.044
Polypharmacy:		
▪ HIV+ < 10 yrs	1.99 (0.989-4.011)	.05
▪ HIV+ > 20 yrs	2.36 (1.224-4.612)	.01
Dual/Mono ART Regimen:		
▪ Polypharmacy	3.09 (1.328-7.502)	.01

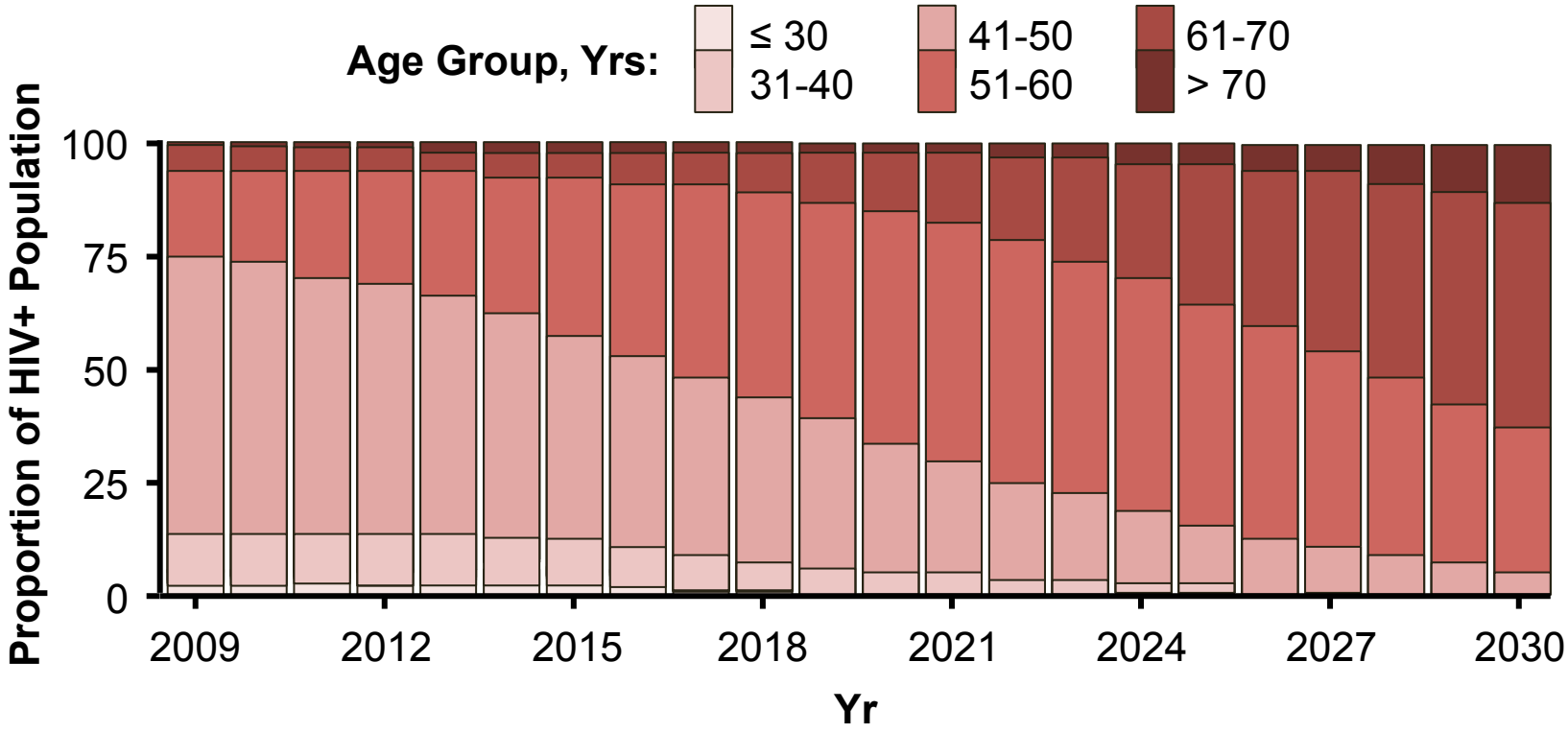
*Multivariate logistic regression.

Guaraldi G, et al. International Comorbidities WS 2016. Abstract P05.
Reproduced with permission.

Model Simulation Predicts Growth of Aging HIV+ Population

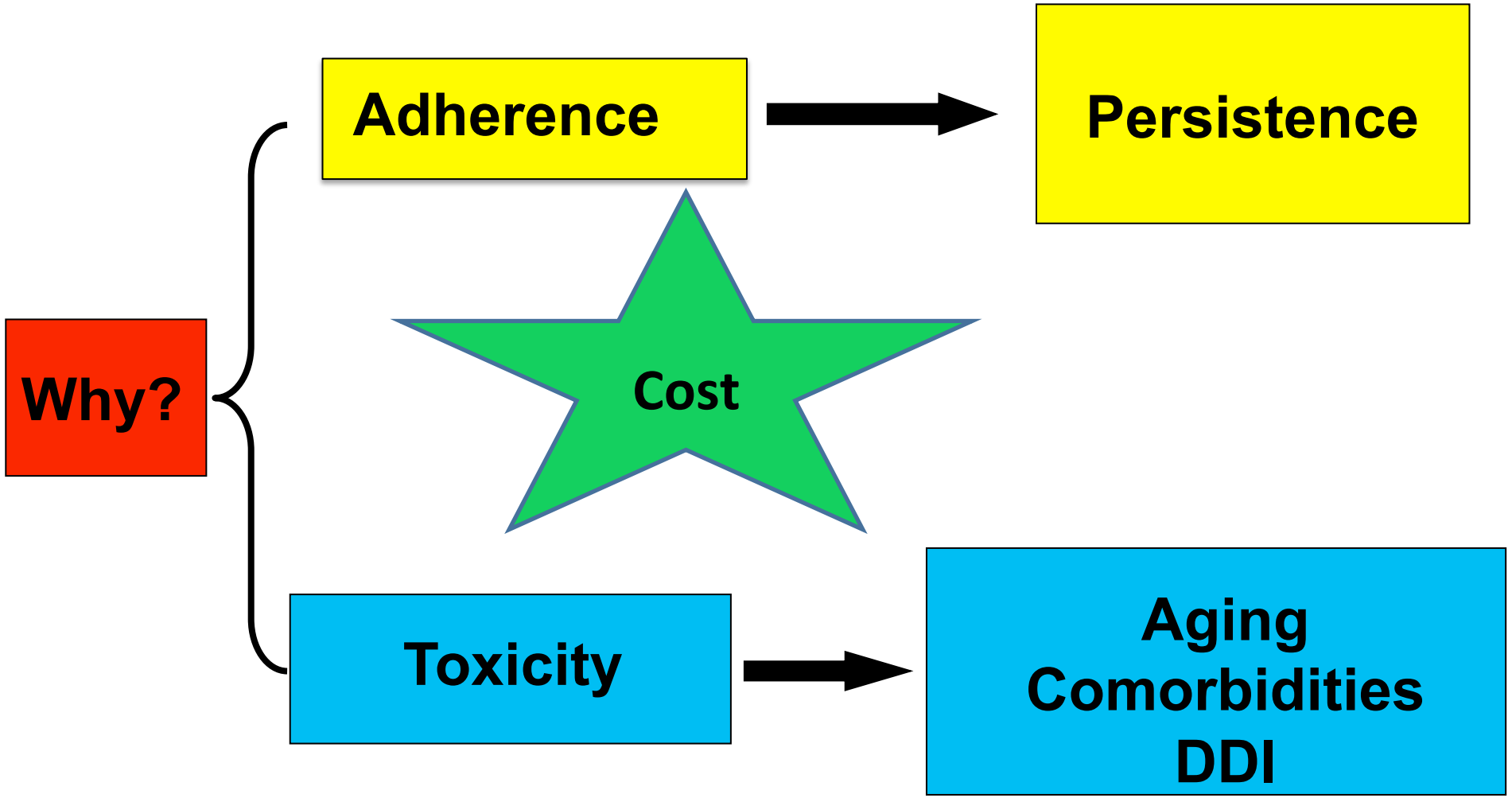
- By 2030, ~ 60% of HIV+ pts predicted to be older than 60 yrs of age, with ~ 10% older than 70 yrs of age

Observed (Red Box) and Projected Age Distribution of HIV+ Pts 2009-2030



Guaraldi G, et al. International Comorbidities WS 2016. Abstract P06.

Dual Therapy: starting from rationale

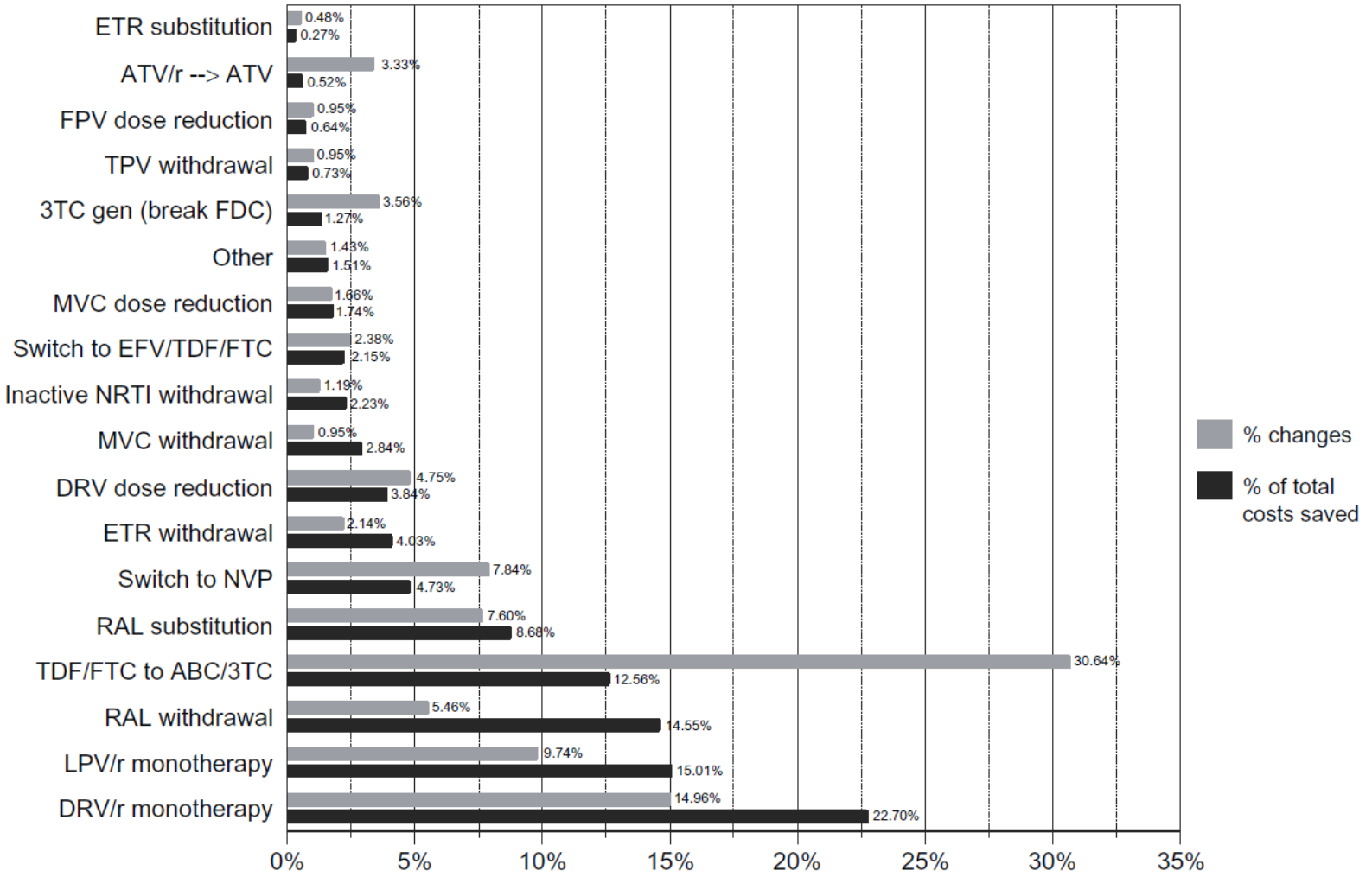


Andreoni M, June 2017

ClinicoEconomics and Outcomes Research

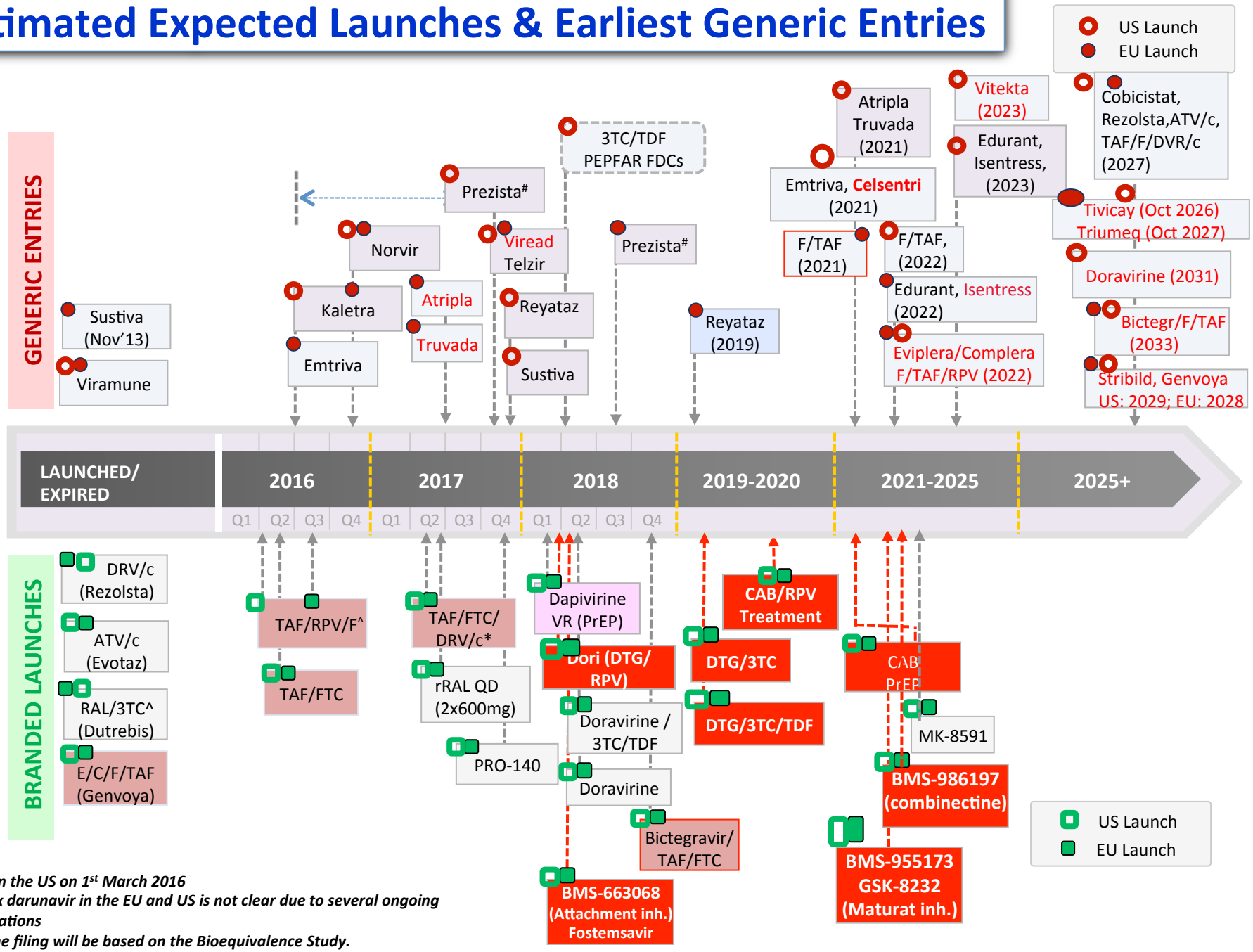
Antiretroviral treatment switch strategies for lowering the costs of antiretroviral therapy in subjects with suppressed HIV-1 viremia in Spain

Josep M Llibre,et al. 2013:5 215–221



Estimated Expected Launches & Earliest Generic Entries

Updated Mar 2016



^ Approved in the US on 1st March 2016

#Launch of gx darunavir in the EU and US is not clear due to several ongoing patent litigations

**Assuming the filing will be based on the Bioequivalence Study.*

Note: Estimates for generic entry do not reflect a determination regarding the validity of underlying IP

THE LANCET

Efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy: a systematic review and meta-analysis

Amit C Achhra, Gwamaka Mwasakifwa, Janaki Amin, Mark A Boyd

Lancet HIV May 31, 2016

21 studies comparing dual-therapy (from two independent classes) antiretroviral regimens as a first-line or a switch strategy (in virologically suppressed individuals) with standard triple-drug regimens.

Meta-analysis of the primary virological outcome* by trial type (first-line and switch studies), excluding maraviroc trials.

	Dual therapy (n/N)	Triple therapy (n/N)
First-line trials		
NEAT001[11]	47/398	38/400
RADAR[20]	15/40	7/43
GARDEL[19]	25/214	33/202
SPARTAN[21]	8/45	6/25
PROGRESS[23]	17/101	16/105
CCTG 589[24]	8/26	4/25
Kalead[34]	34/72	37/80
ACTG5142[13]	72/250	77/250
Subtotal (I^2=25·4%, p=0·226)	**226/1146**	**218/1130**
Switch trials		
PROBE[25]	1/30	3/30
OLE[26]	10/118	11/121
SALTZ[27]	30/140	33/141
ATLAS-M[29]	14/133	27/133
HARNESS[30]	22/72	5/37
SPARE[31]	4/28	1/30
KITE[32]	2/39	2/20
COOL[33]	13/71	2/72
Subtotal (I^2=61·0%, p=0·012)	**96/631**	**84/584**
Overall (I^2=45·1%, p=0·026)	**322/1777**	**302/1714**

In first-line studies, the RR of failure for dual-therapy versus control groups was 1.05 (0.86–1.28; I2=26%)

In switch studies, the RR of failure for dual-therapy versus control groups was 1.13 (0.64–1.99; I2=61%)

*Primary outcome: risk virological failure


THE LANCET

Meta-analysis of the primary virological outcome in naive patients with baseline viral loads of more than 100,000 copies per mL

	Dual therapy (n/N)	Triple therapy (n/N)	
MVC trials			
MODERN[17]	24/71	16/75	
A4001078[22]	5/16	5/22	
Subtotal (I^2=0·0%, p=0·815)	**29/87**	**21/97**	
Non-MVC trials			
NEAT001[11]	55/146	37/129	
RADAR[20]	7/14	6/19	
GARDEL[19]	12/94	19/86	
SPARTAN[21]	11/34	5/13	
PROGRESS[23]	5/15	6/19	
CCTG 589[24]	7/12	11/19	1·01 (0·55–1·86)
Kalead[34]	20/35	21/41	1·12 (0·74–1·69)
ACTG5142[13]	57/122	35/121	1·62 (1·15–2·26)
Subtotal (I^2=26·3%, p=0·219)	**174/472**	**140/447**	**1·18 (0·94–1·47)**
Overall (I^2=12·8%, p=0·325)	**203/559**	**161/544**	**1·24 (1·03–1·49)**

0·252 1 3·97

Favours dual therapy Favours triple therapy

In pts with viral load >100,000 cps/mL, RR of failure for dual-therapy versus control groups was 1.18 (0.94–1.47)

After excluding maraviroc-containing studies.

Lancet HIV May 31, 2016

THE LANCET

Efficacy and safety of c… …oviral regimens as first-line tr… strategy: a system…

Amit C Achhra, Gwamaka Mwasakifwa, Janaki Amin, …

Dual therapy with a greater risk of selecting resistance mutations compared with standard triple therapy.

	Primary virological outcome	SAEs	discontinuat…	
First-line	1·17 (0·94–1·47)	1·18 (0·90–1·53)	0·97 (0·65–1·45)	2·04 (1·23–3·39)
Switch*	1·14 (0·72–1·79)	1·19 (0·69–2·05)	0·55 (0·22–1·36)†	2·47 (0·78–7·86)
Overall	1·13 (0·91–1·40)	1·18 (0·93–1·49)	0·73 (0·46–1·16)†	2·11 (1·33–3·35)

Data are RR (95% CI) for the primary virological outcome, and OR (95% CI) for secondary outcomes (SAEs, AEs, and mutations). RR=relative risk, OR=odds ratio, SAE=serious adverse event, AE=adverse event. *We analysed the LATTE study as… …xclusion of the COOL study further reduced to 0·41 (0·…

Table 3: …ATTE study

We recorded the ORs for dual-therapy versus control groups for serious adverse events (1.16 [0.92–1.48]), adverse events (0.82 [0.52–1.28]), and mutations (2.11 [1.32–3.36]).

Lancet HIV May 31, 2016

Dual therapy in treatment-experienced HIV-positive individuals

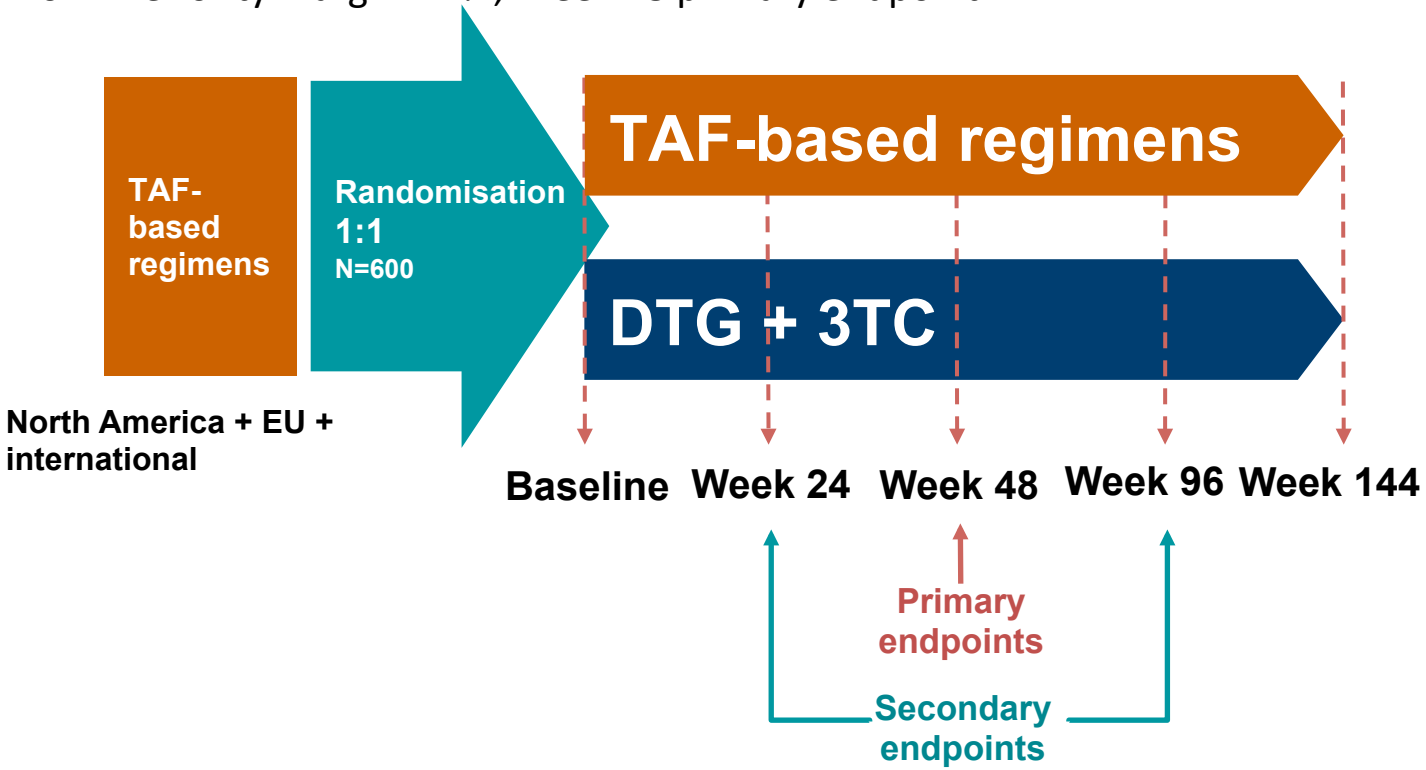
Virological Suppression

Study	N	Regimen	DUAL	Triple	
ATLAS-M[1,2]	266	**ATV/rtv + 3TC (96w)**	87.4%	65.4 %	
SALT[3,4]	286	**ATV/rtv + 3TC (48w)**	83.6 %	78.4 %	
NA[5†]	48	**DRV/rtv + 3TC (48w)**	98 %	/	
HARNESS[1]	109	**ATV/rtv + RAL (48w)**	69,4%	86,5%	
MARCH[2,3]	395	**DRV/rtv + MVC (48w)**	77,7 %	91,7 %	
DUAL Gesida	249	**DRV/rtv + 3TC (48w)**	89 %	93 %	
SWORD 1/2	513	**DTG + RPV**	95%	95%	
DOLULAM	27	**DTG + 3TC (36w)**	100%	/	
LAMIDOL	104	**DTG + 3TC (48w)**	97%	/	

TANGO: Switch Study Design

Phase III, randomised, multicentre, parallel-group, non-inferiority study

- **Objective:** to demonstrate non-inferior antiviral activity of switching to DTG + 3TC QD compared with continuation of current ARV regimen over 48 weeks in HIV-1-infected ART-experienced subjects
- **Primary endpoint:** the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the ITT-E population
  - non-inferiority margin = 4%; Week 48 primary endpoint



STUDIO TANGO (204862) - Protocollo emend. 1 del 06 Mag 2017

INCLUSION CRITERIA

Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening

Plasma HIV-1 RNA <50 c/mL at Screening.

Must be on uninterrupted ART for at least 6 months prior to screening

EXCLUSIONARY CRITERIA PRIOR TO SCREENING OR DAY 1

1. Any evidence of major NRTI mutation or presence of any DTG resistance mutation
2. Within the 6 to 12 month window prior to Screening any plasma HIV-1 RNA measurement >200 c/mL. or 2 or more plasma HIV-1 RNA measurements ≥50 c/mL.
3. Within 6 months prior to Screening any plasma HIV-1 RNA measurement ≥50 c/mL.
4. Any drug holiday during the 6 months prior to Screening
5. Any history of switch to another regimen due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA ≥400 c/mL.)

Dual therapy in treatment-naïve HIV-positive individuals

Virological Suppression

Study	N	Regimen	DUAL	Triple	
MODERN	797	**DRV/rtv +MVC (48W)**	87.3%	86.4 %	
A4001078	121	**ATV/rtv +MVC (48w)**	74.6 %	83.6 %	
MIDAS	24	**DRV/rtv + MVC (48w)**	91.7 %	/	
NEAT 001	805	**DRV/rtv + RAL (96w)**	82.2 %	86.2 %	
ACTG5262	112	**DRV/rtv + RAL (24w)**	61 %	/	
RADAR	85	**DRV/rtv + RAL (48w)**	62.5 %	83.7 %	
PROGRESS	206	**LPV/rtv + RAL (96w)**	66.3 %	68.4 %	
SPARTAN	93	**ATV + RAL BID (24w)**	74.6 %	63.3 %	
GEMINI 1/2	700	**DTG + 3TC**			?
Paddle*	20	**DTG + 3TC (48W)**	90%	/	

*One pt with SAE and one PDVF (virological failure as defined by protocol)

ACTG A5353: A Pilot Study of Dolutegravir (DTG) + Lamivudine (3TC) for Initial Treatment of HIV-1-Infected Participants With HIV-1 RNA <500,000 copies/mL

Babafemi O. Taiwo,[1] Lu Zheng,[2] Amesika N. Nyaku,[3] Andrei Stefanescu,[2] Paul E. Sax,[4] David Haas,[5] Baiba Berzins,[1] Carole L. Wallis,[6] Kimberly Y. Smith,[7] Belinda Ha,[7] Catherine Godfrey,[8] Johnstone Kumwenda,[9] Edward Acosta,[10] Beverly E. Sha,[11] Cornelius Van Dam,[12] Roy M. Gulick[13]

[1]Northwestern University, Chicago, U.S., [2]Harvard School of Public Health, Boston, U.S., [3]Rutgers, New Jersey Medical School, Newark, U.S., [4]Brigham and Women's Hospital, Boston, U.S., [5]Vanderbilt University, Nashville, U.S., [6]BARC-SA/Lancet Laboratories, Johannesburg, South Africa, [7]ViiV Healthcare, Research Triangle Park, U.S., [8]NIH, NIAID, Division of AIDS, Rockville, U.S., [9]College of Medicine, Johns Hopkins Project, Blantyre, Malawi, [10]University of Alabama, Birmingham, U.S., [11]Rush University Medical Center, Chicago, U.S., [12]Greensboro Clinical Research Site, Greensboro, U.S., [13]Weill Cornell Medicine, New York, U.S.

Study Objective and Primary Outcome: FDA Snapshot at Week 24

- Phase II, single-arm, 52-week, pilot study of DTG 50 mg + 3TC 300 mg daily in treatment-naïve participants with VL ≥1000 and <500,000 cpm

	Baseline HIV-1 RNA		
	>100,000 cpm N=37	**≤100,000 cpm N=83**	**Total N=120**
Virologic success	**33 (89%)**	**75 (90%)**	**108 (90%)**
HIV-1 RNA < 50 cpm **[95% CI, %]**	**[75%,97%]**	**[82%,96%]**	**[83%,95%]**
Virologic non-success	**3 (8%)**	**2 (2%)**	**5 (4%)**
HIV-1 RNA ≥ 50 cpm	3	0	3
Discontinued study treatment for other reasons while HIV RNA ≥ 50*	0	2	2
No virologic data in window	**1 (3%)**	**6 (7%)**	**7 (6%)**
Discontinued study treatment for other reasons#	1	5	6
On study but missing data in window	0	1	1

*Poor adherence; #Lost to follow-up, pregnancy

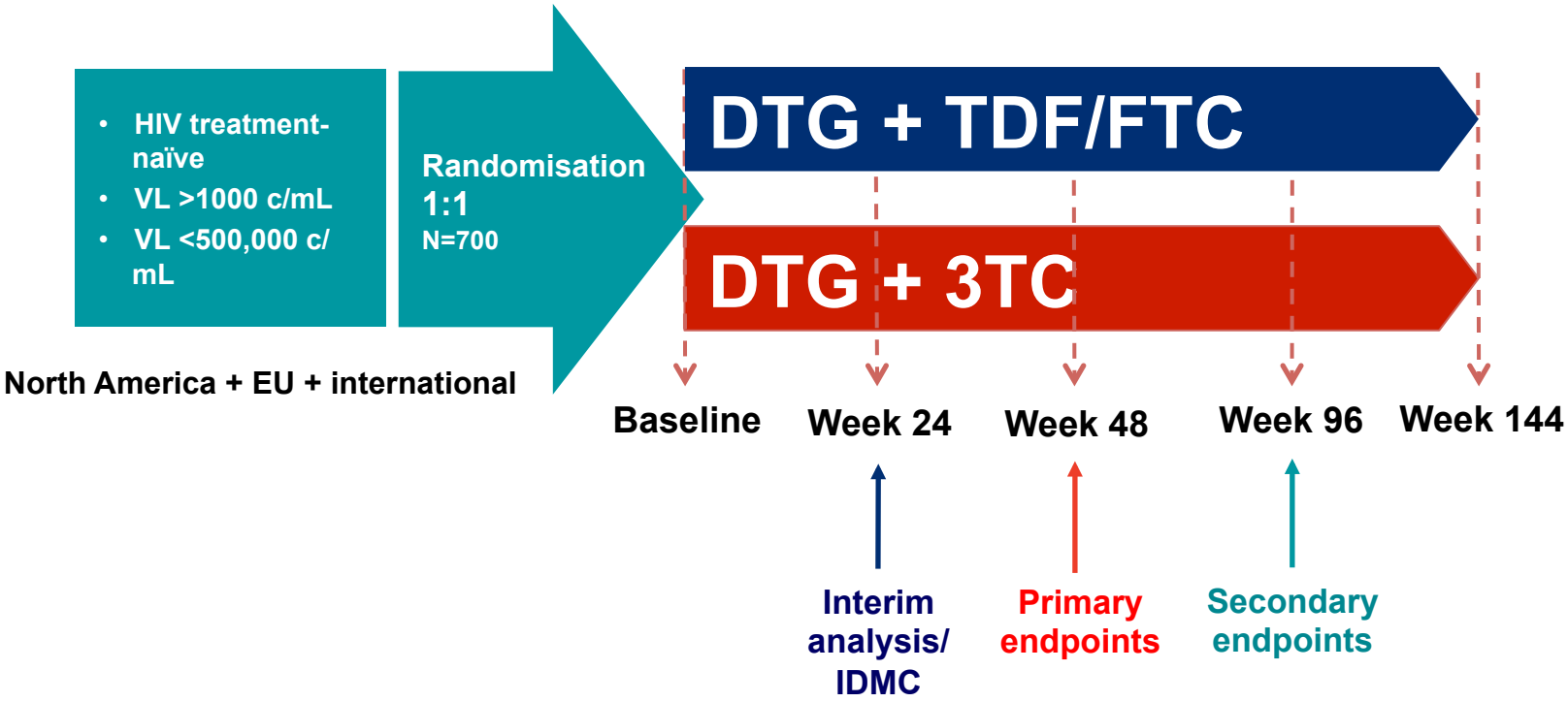
[95% Confidence intervals] for proportion of participants with virologic success at Week 24.

Taiwo et al. IAS 2017; Paris, France. Slides MOAB0107LB.

GEMINI-1 and -2: Study Design

Phase III, randomised, double-blind, multicentre, non-inferiority study[1,2]

- **Objective:** to demonstrate the non-inferior antiviral activity of DTG + 3TC QD compared with DTG + TDF/FTC QD over 48 weeks in HIV-1-infected ART-naïve subjects[1,2]
- **Primary endpoint:** the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (missing, switch or discontinuation = failure)[1,2]
  - non-inferiority margin: 10%[1,2]



IDMC, Independent Data Monitoring Committee

1. GEMINI-1. Available from: https://clinicaltrials.gov/ct2/show/NCT02831673. Accessed May 2017
2. GEMINI-2. Available from: https://clinicaltrials.gov/ct2/show/NCT02831764. Accessed May 2017

STUDI GEMINI (204861 & 205543)

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY

1. Screening plasma HIV-1 RNA of 1000 c/mL to ≤100,000 c/mL. If an independent review of accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen is supportive of the DTG plus 3TC treatment regimen, enrolment will be opened to subjects with Screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL

LABORATORY VALUES OR CLINICAL ASSESSMENTS AT SCREENING

1. Any evidence of pre-existing viral resistance
2. Any verified Grade 4 laboratory abnormality
3. Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound.
4. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin);
5. Creatinine clearance of <50 mL/min/1.73 m^2 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

GEMINI-1 and -2: Objectives

gemini 1
gemini 2

Primary objective[1,2]

To demonstrate the non-inferior antiviral activity of DTG + 3TC QD compared with DTG + TDF/FTC QD over 48 weeks in HIV-1-infected ART-naïve subjects

Secondary objectives[1,2]

- Antiviral activity of DTG + 3TC versus DTG + TDF/FTC at Weeks 24, 96 and 144
- Antiviral activity, immunological effects and disease progression up to study completion of ~7 years
- Viral resistance in subjects meeting CVW criteria
- Safety and tolerability over time
- DTG + 3TC compared with DTG + TDF/FTC: effects on renal and bone biomarkers
- Effects on fasting lipids
- Change in health-related QoL
- Effect of patient characteristics on response to DTG + 3TC or DTG + TDF/FTC over time

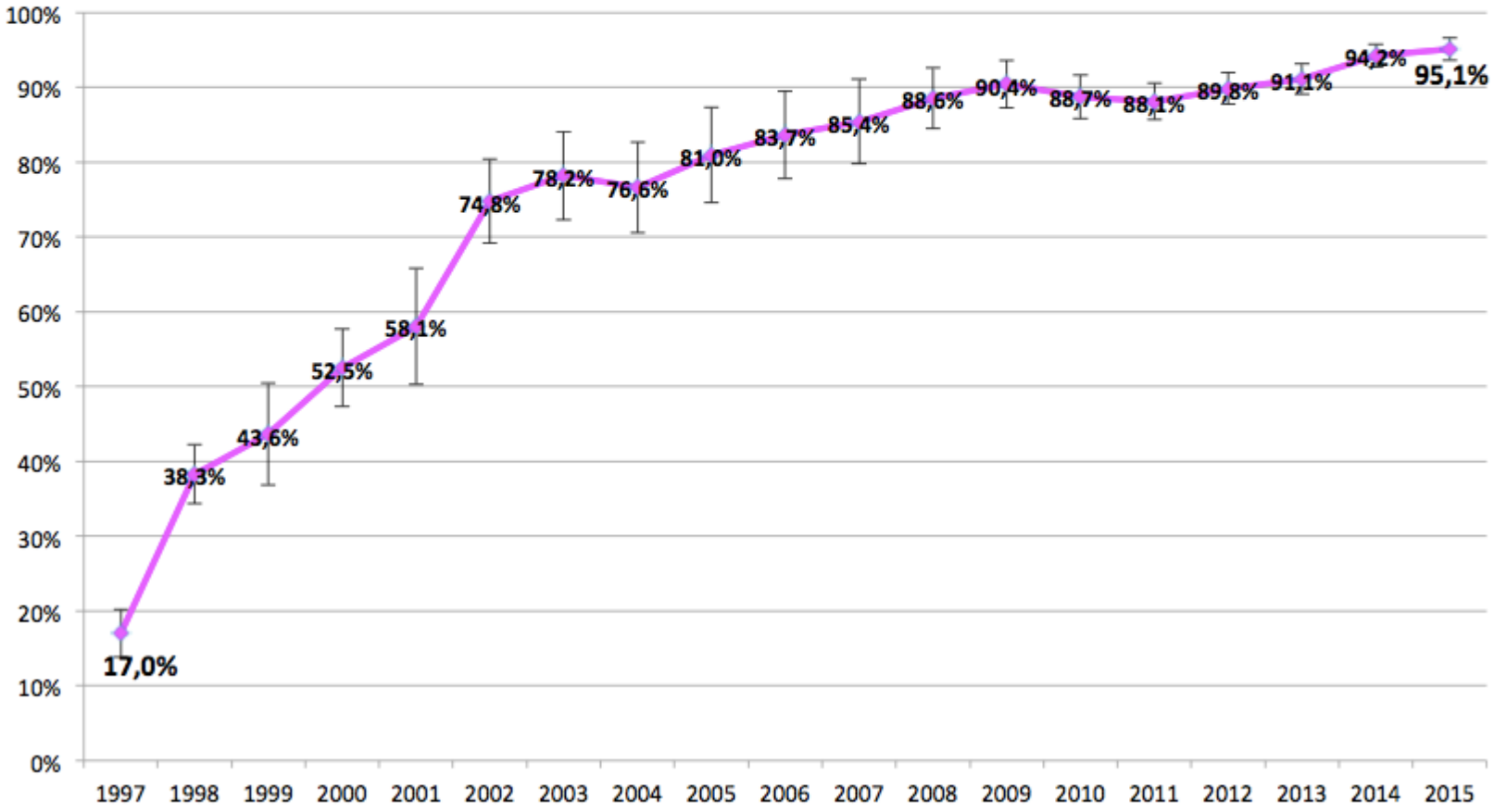
CVW, confirmed virologic withdrawal

1. GEMINI-1. Available from: https://clinicaltrials.gov/ct2/show/NCT02831673. Accessed May 2017
2. GEMINI-2. Available from: https://clinicaltrials.gov/ct2/show/NCT02831764. Accessed May 2017

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C O. N A. Naive Antiretrovirals

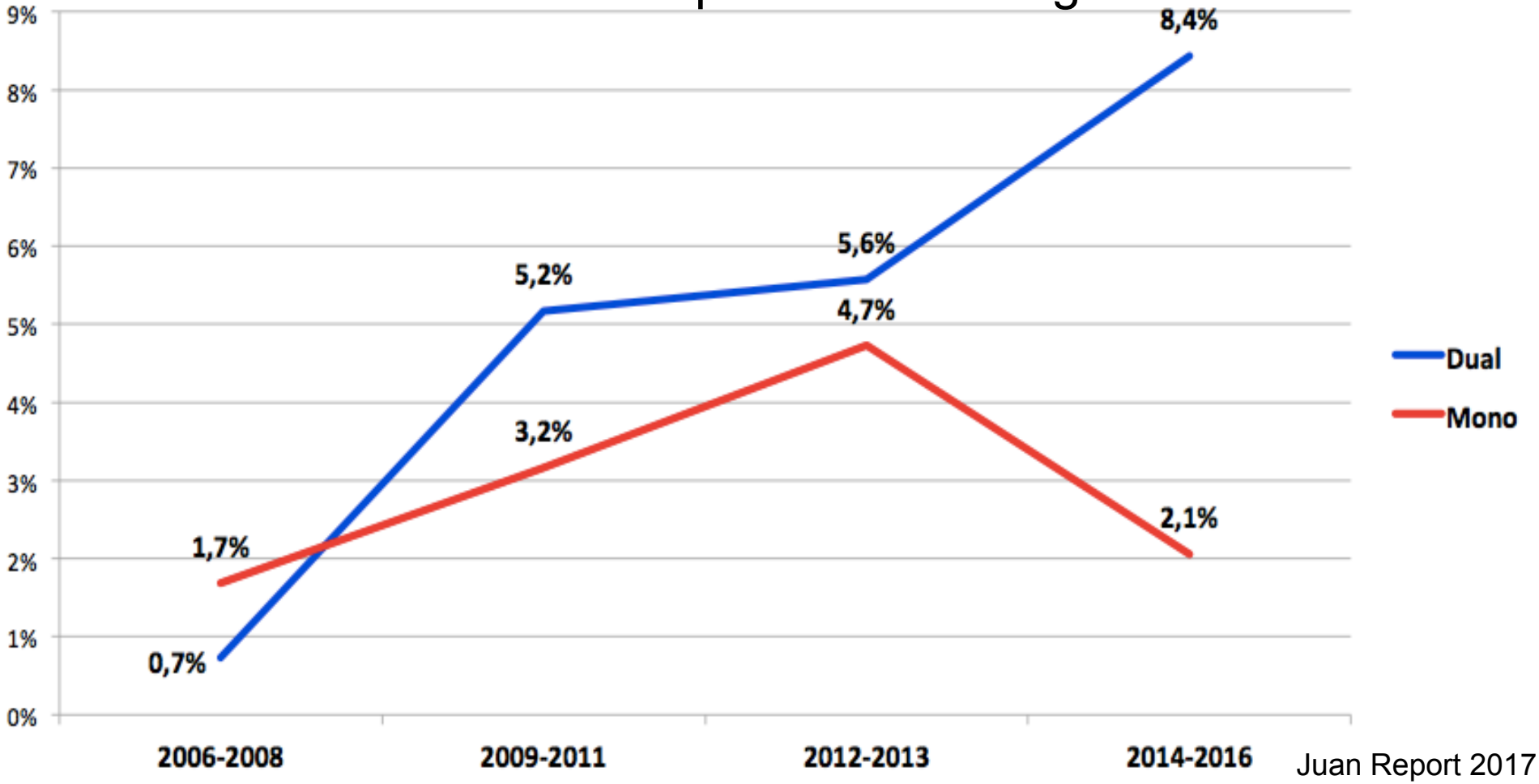
Proportion of patients with a VL<=80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation



Jan 2017 Report

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

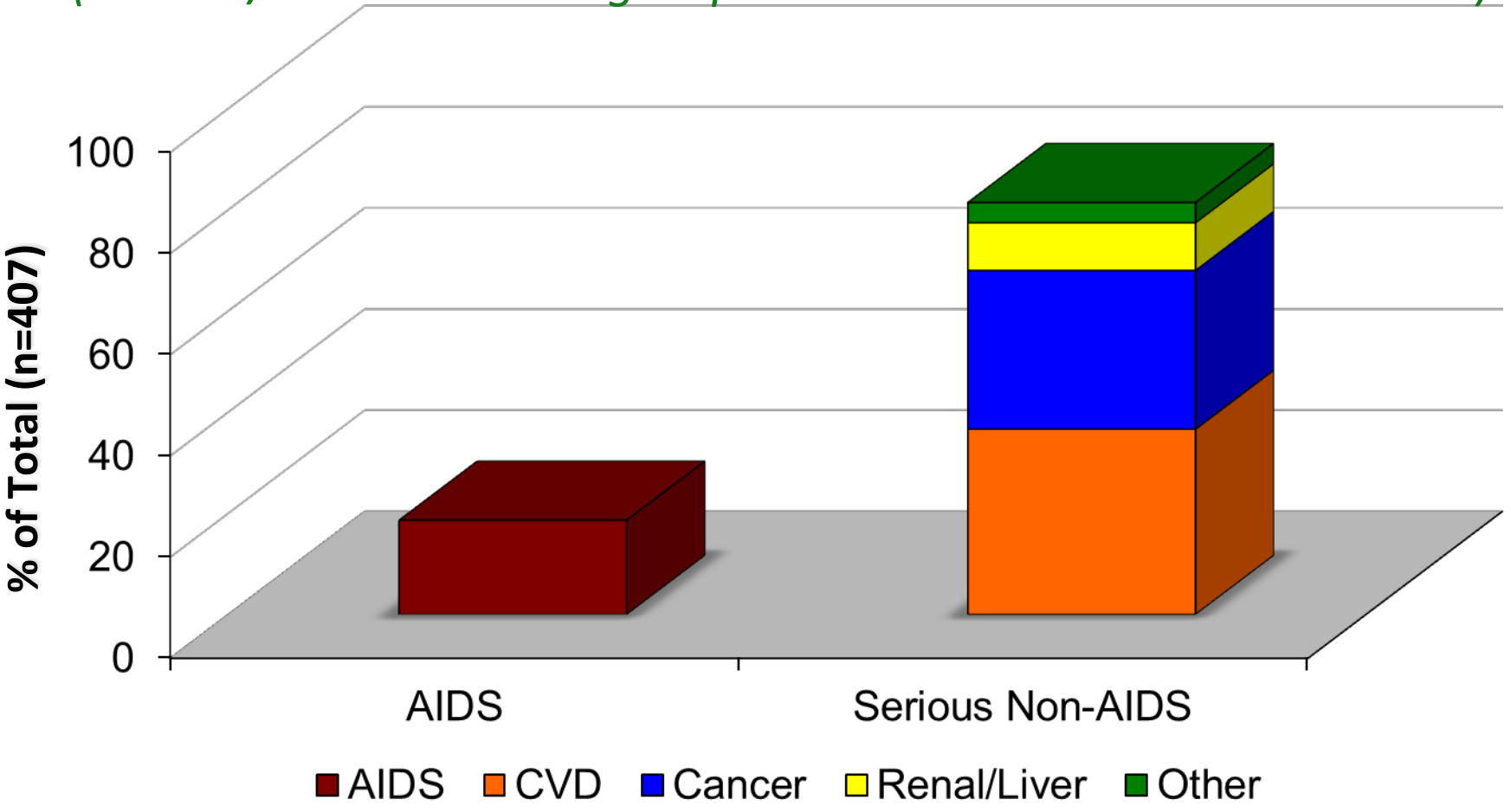
Proportion of Mono/Dual therapies according to calendar period of starting



Juan Report 2017

Events in ART-Treated Patients are largely Non-AIDS

(SMART/ESPRIT control groups: randomized to continuous ART)

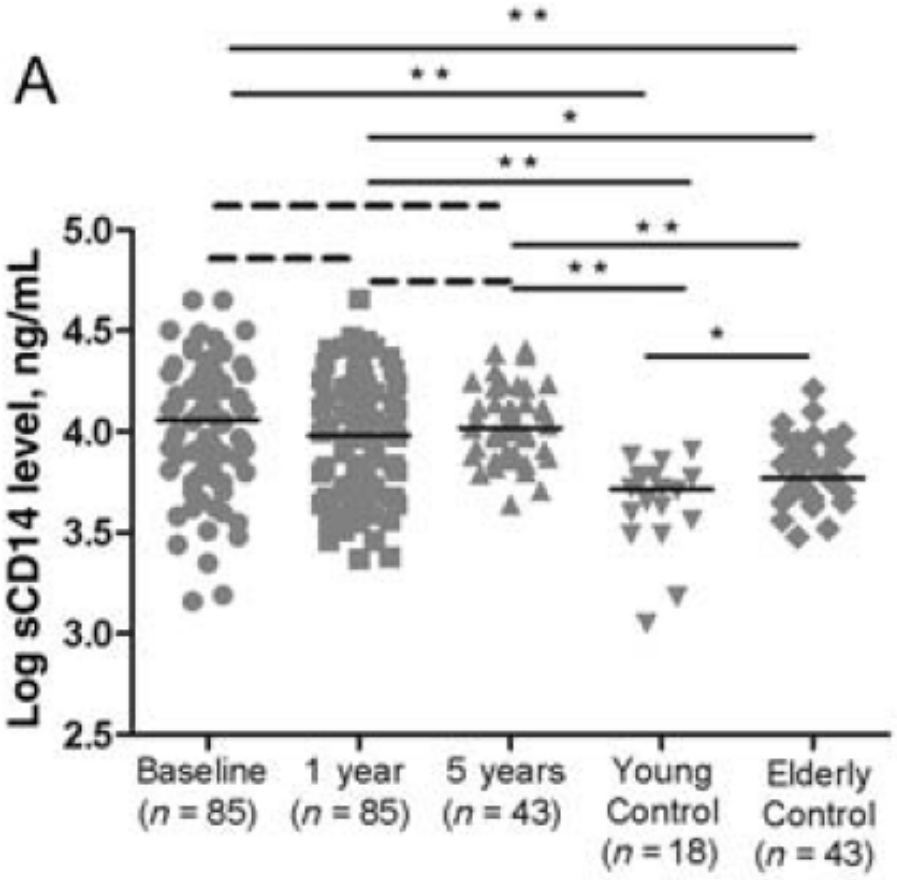


INSIGHT SMART & ESPRIT Study Groups

AIDS 2010; 24(12):1877, NEJM 2006; 355:2283-2296 , Ann Int Med 2008; 149:289-299

February 4, 2013

Long-Term Suppressive Combined Antiretroviral Treatment Does Not Normalize the Serum Level of Soluble CD14



HIV-infected group displayed a significantly higher sCD14 level at baseline (ie, before cART initiation), 1 year and 5 years after cART initiation, compared with both control groups.

G. Mendez-Lagares

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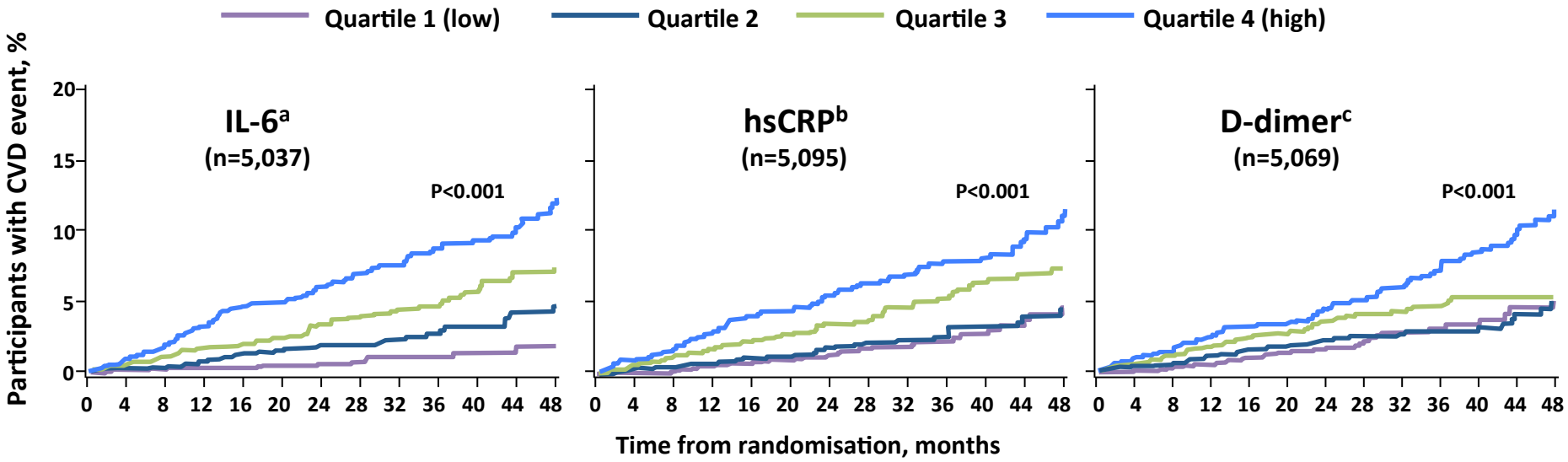
Elevated inflammatory biomarkers are associated with increased CVD risk in HIV-positive patients

Cumulative percent of participants developing CVD, by biomarker quartile levels

(SMART Study, 2002–2006)



hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6

[a] IL-6 quartiles are <1.10, 1.10–1.76, 1.77–3.01, >3.01 pg/mL; [b] hsCRP quartiles are <0.72, 0.72–1.71, 1.72–4.17, >4.17 µg/mL;

[c] D-dimer quartiles are <0.13, 0.13–0.21, 0.22–0.37, >0.37 µg/mL

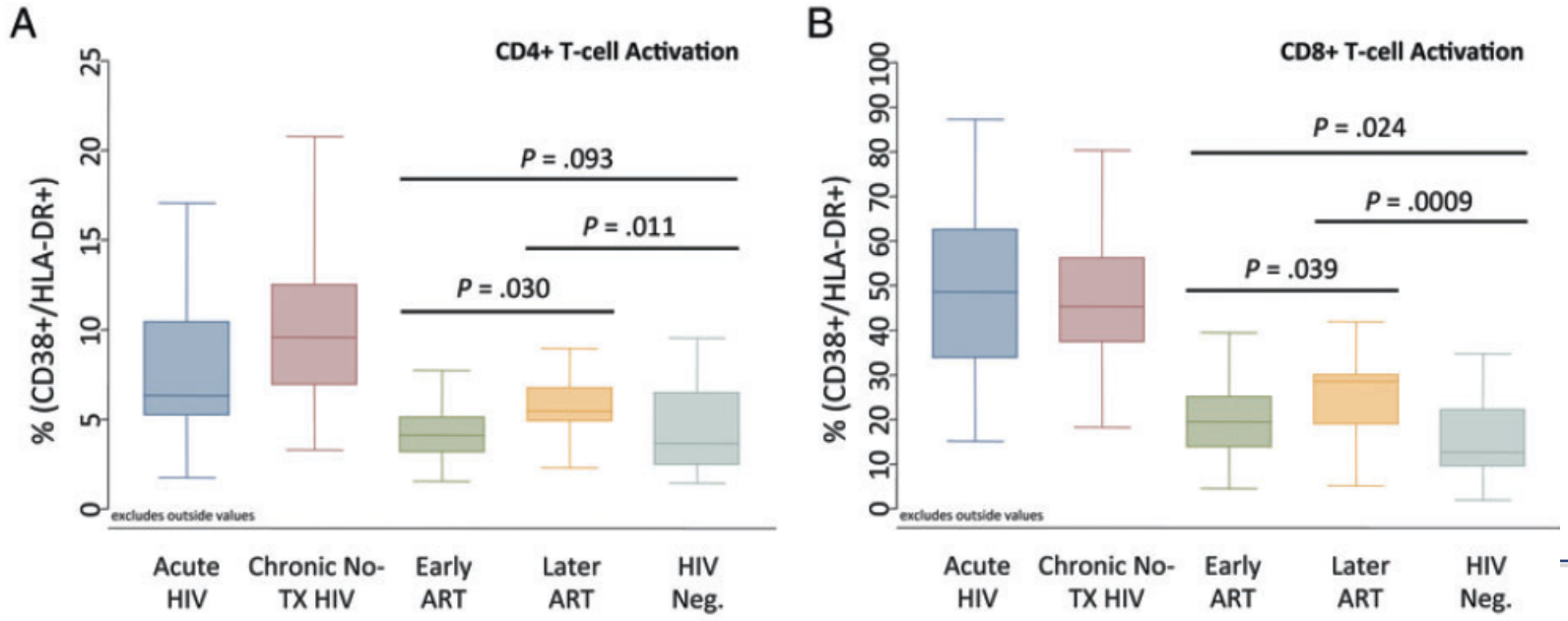
Duprez DA et al. PLoS One. 2012;7:e44454

Antiretroviral Therapy Initiated Within 6 Months of HIV Infection Is Associated With Lower T-Cell Activation and Smaller HIV Reservoir Size

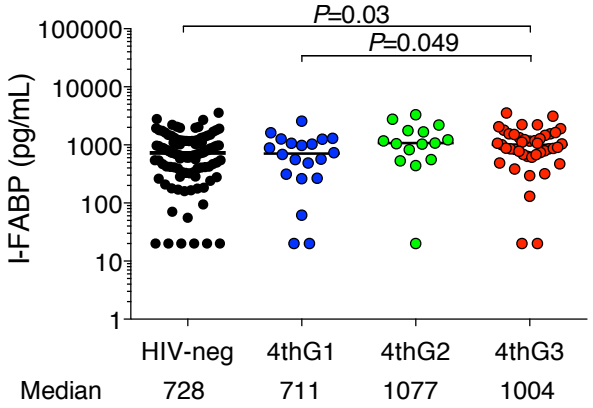
2013:208 (15 October) 1202

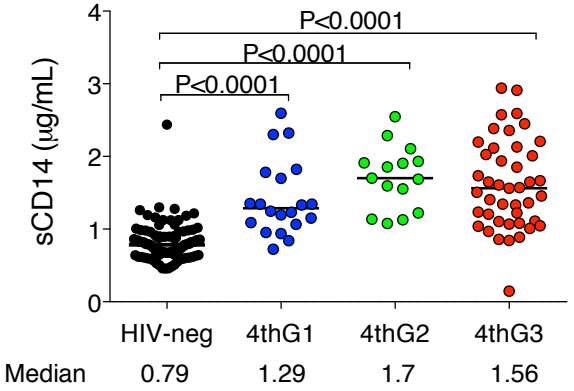
Vivek Jain,[1] Wendy Hartogensis,[1] Peter Bacchetti,[2] Peter W. Hunt,[1] Hiroyu Hatano,[1] Elizabeth Sinclair,[3] Lorrie Epling,[3] Tzong-Hae Lee,[4] Michael P. Busch,[4] Joseph M. McCune,[3] Christopher D. Pilcher,[1] Frederick M. Hecht,[1] and Steven G. Deeks[1]

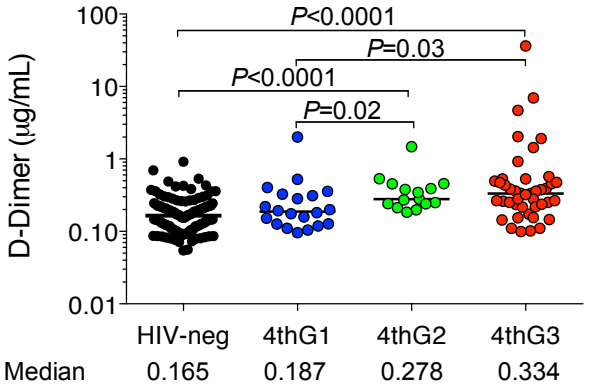
ART initiation <6 months after infection is associated with lower levels of CD4+ and CD8+ T-cell activation

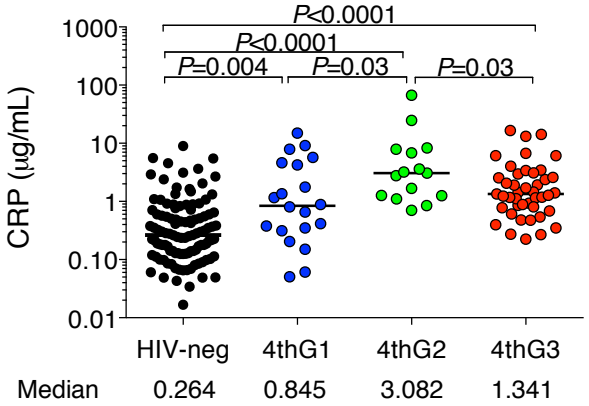


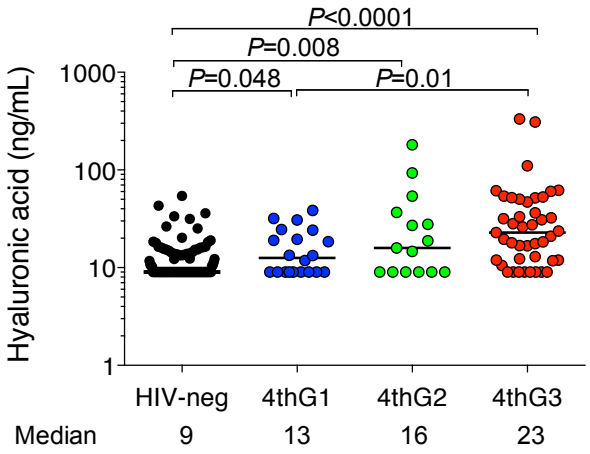
Inflammatory Biomarkers at Diagnosis of Acute HIV Infection









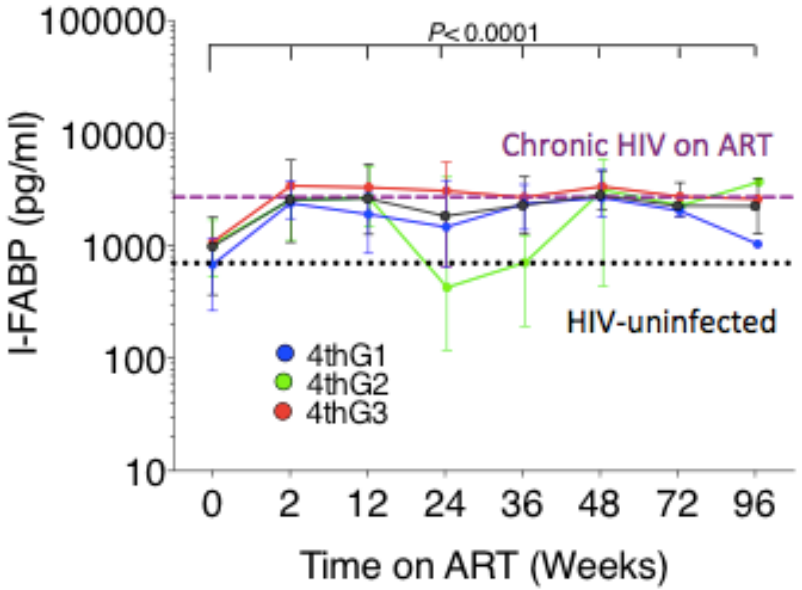


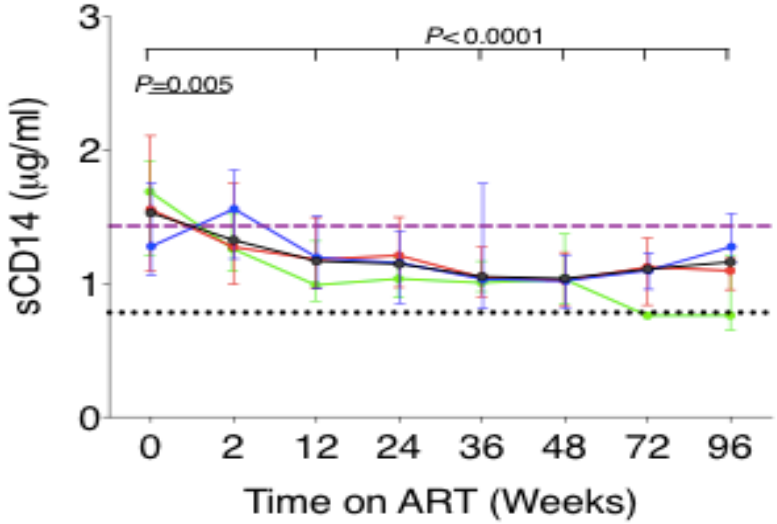
Compared to healthy controls, subjects with all stages of acute HIV infection have increased CRP, sCD14, and HA levels, and subjects with later stages of acute HIV infection have increased D-dimer and I-FABP levels.

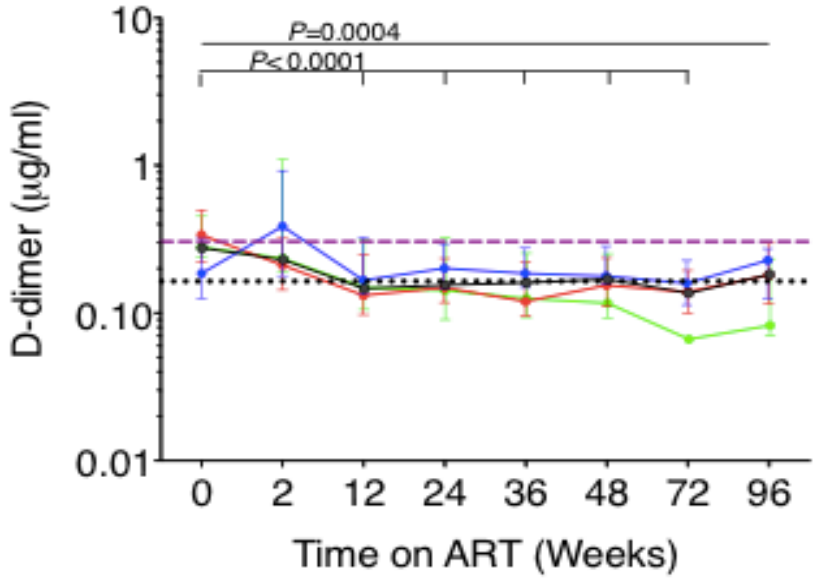
Sandler, CROI, 2014

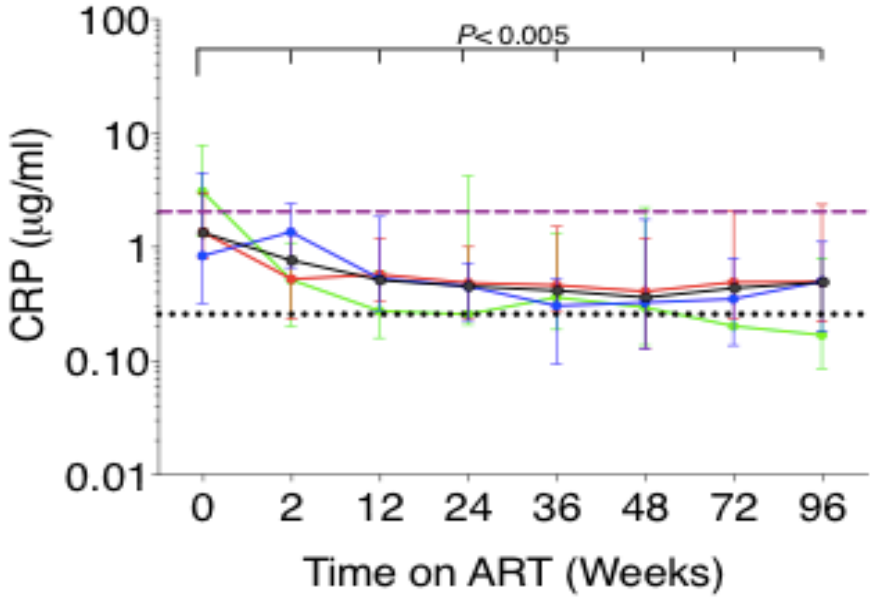
Inflammation persists despite early initiation of ART in acute HIV infection

NS Utay, CROI 2015

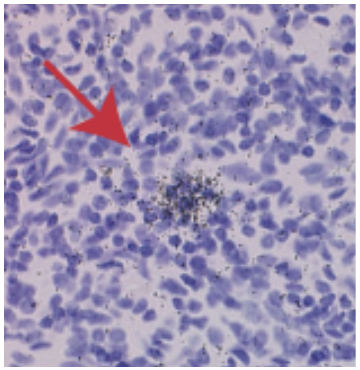




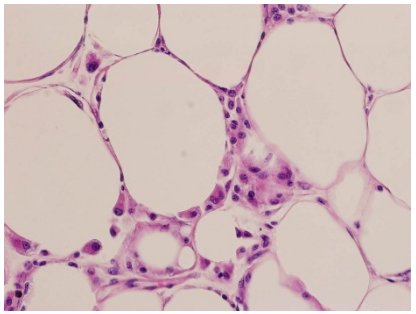




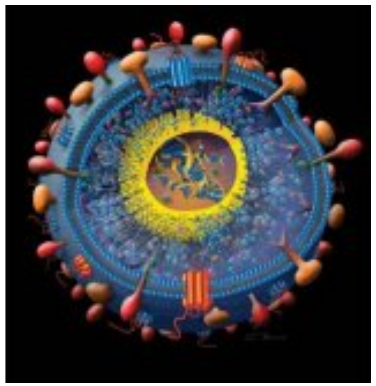
HIV production
HIV replication



HIV-associated fat
Metabolic syndrome



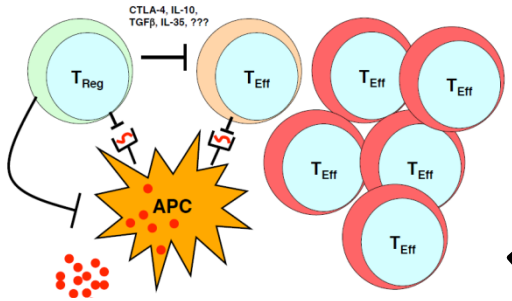
CMV- HCV
Excess pathogens



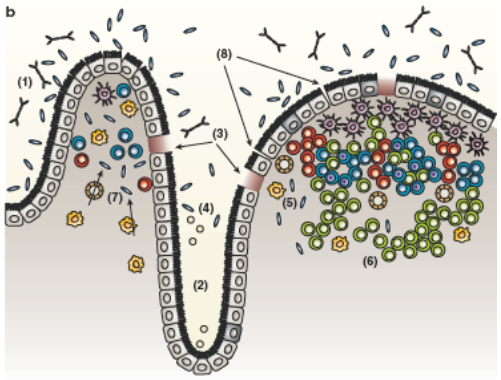
Inflammation

↑ Endothelium adhesion
↑ Monocyte activation
Dyslipidemia
Hypercoagulation/
thrombotic events
Endothelial dysfunction

Increased incidence of comorbidities and clinical disease

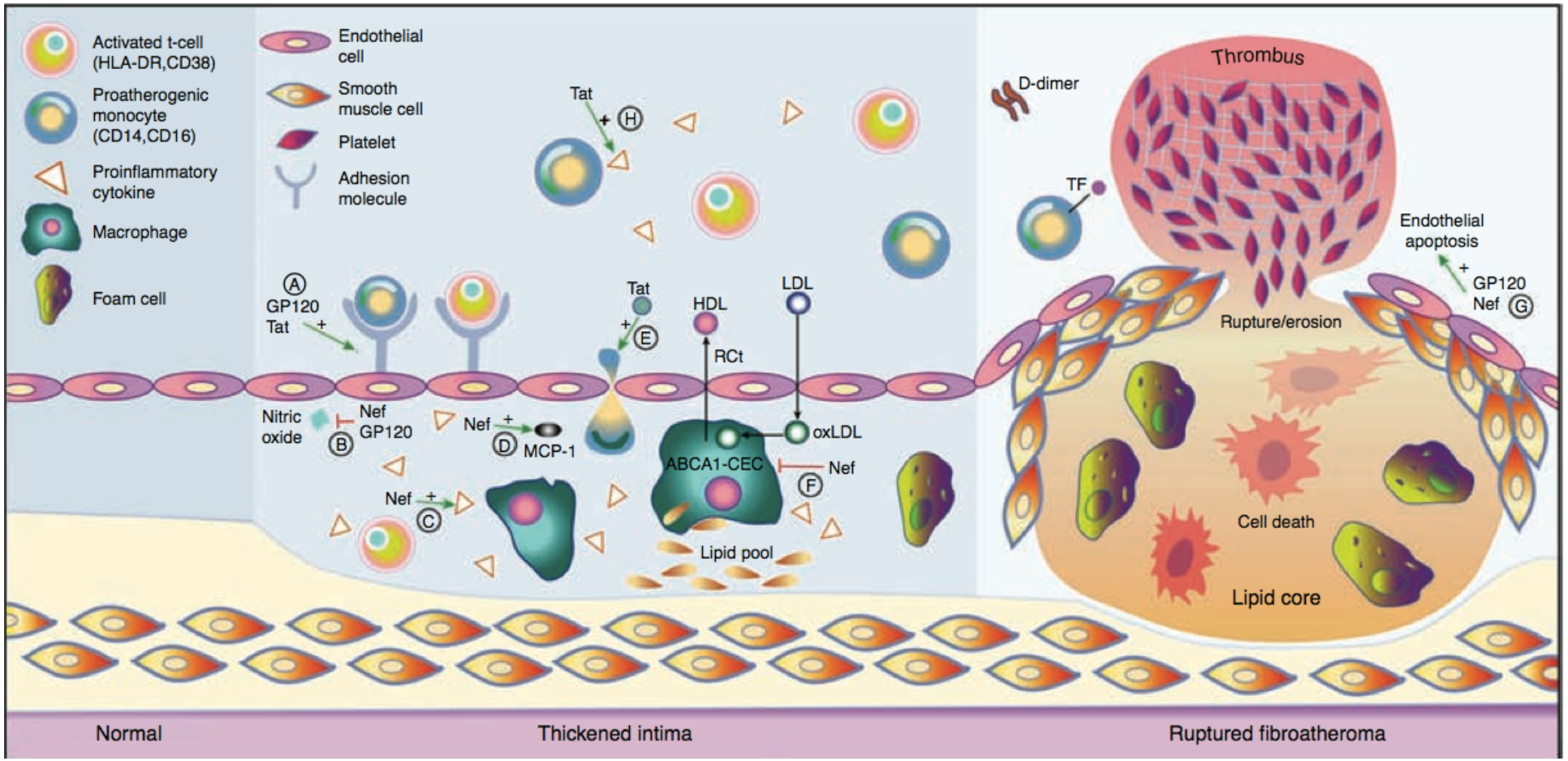


HIV-mediated loss of regulatory cells (Tregs)

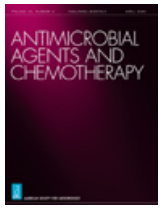


Microbial translocation

Effects of HIV viral proteins on the development of atherosclerosis



E. Nou AIDS 2016, Vol 30 No 10

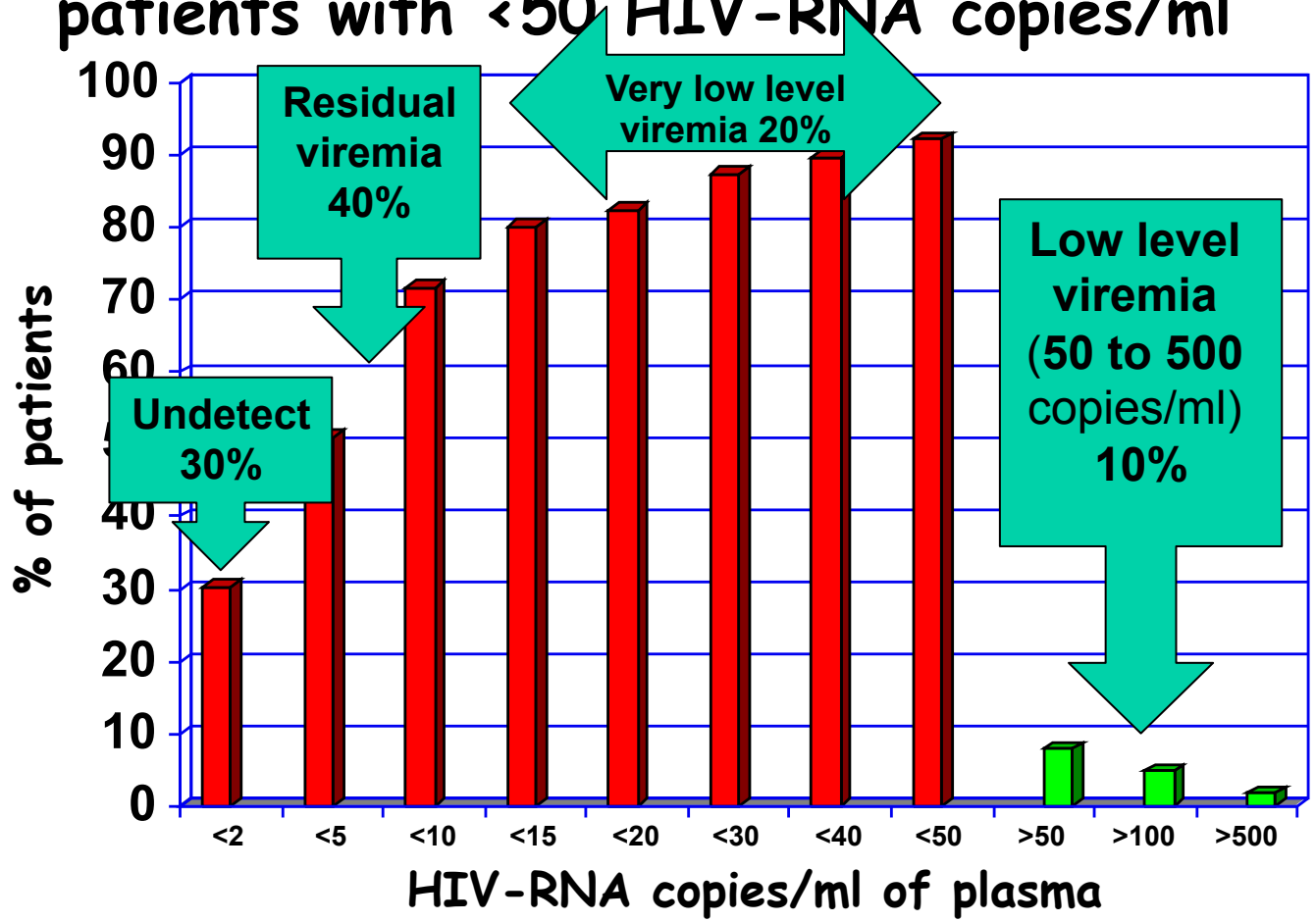


Nevirapine use, prolonged antiretroviral therapy and high CD4 nadir values are strongly correlated with undetectable HIV-DNA and -RNA levels and CD4 cell gain

2012

Loredana Sarmati[1]*, Saverio Giuseppe Parisi[2], Marco Montano[1], Samantha Andreis[2], Renzo Scaggiante[3], Andrea Galgani[4], Magdalena Viscione[1], Gaetano Maffongelli[1], Alessandra Ricciardi[1], Carolina Andreoni[5], Stefano Boros[6], Giorgio Palù[2] and Massimo Andreoni[1]

Detection of viral load by ultrasensitive method in 420 patients with <50 HIV-RNA copies/ml



OPEN ACCESS Freely available online October 2009 | Volume 4 | Issue 10 | e7658 PLoS one

HIV-1 Residual Viremia Correlates with Persistent T-Cell Activation in Poor Immunological Responders to Combination Antiretroviral Therapy

Maud Mavigner[1], Pierre Delobel[1,2,3], Michelle Cazabat[1,4], Martine Dubois[1,4], Fatima-Ezzahra L'Faqihi-Olive[1], Stéphanie Raymond[1,2,4], Christophe Pasquier[1,2,4], Bruno Marchou[2,3], Patrice Massip[2,3], Jacques Izopet[1,2,4]*

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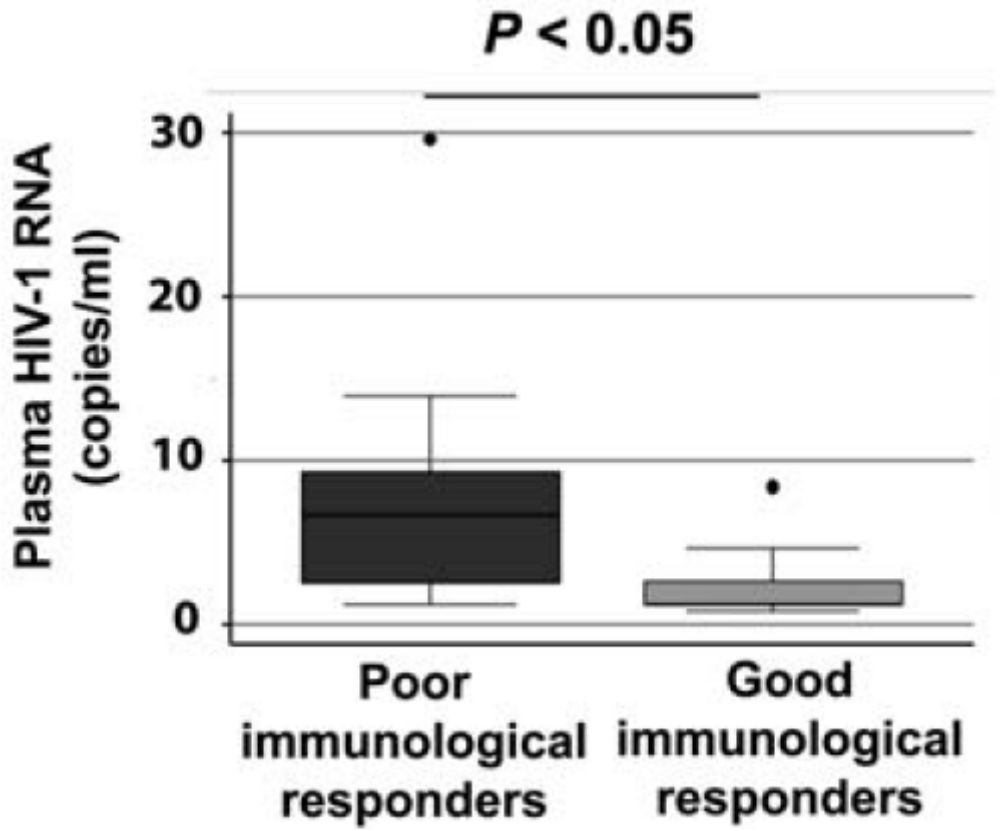
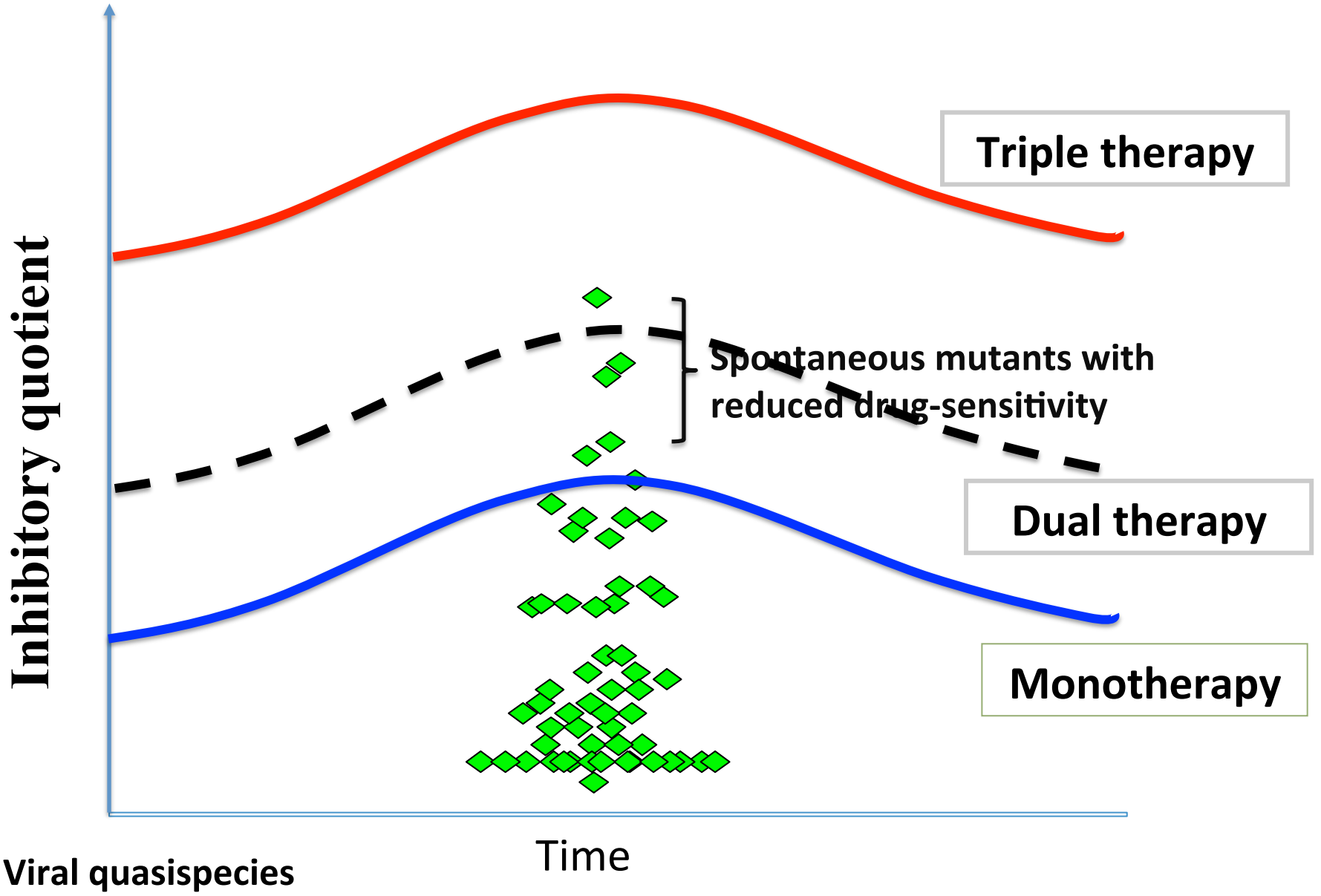
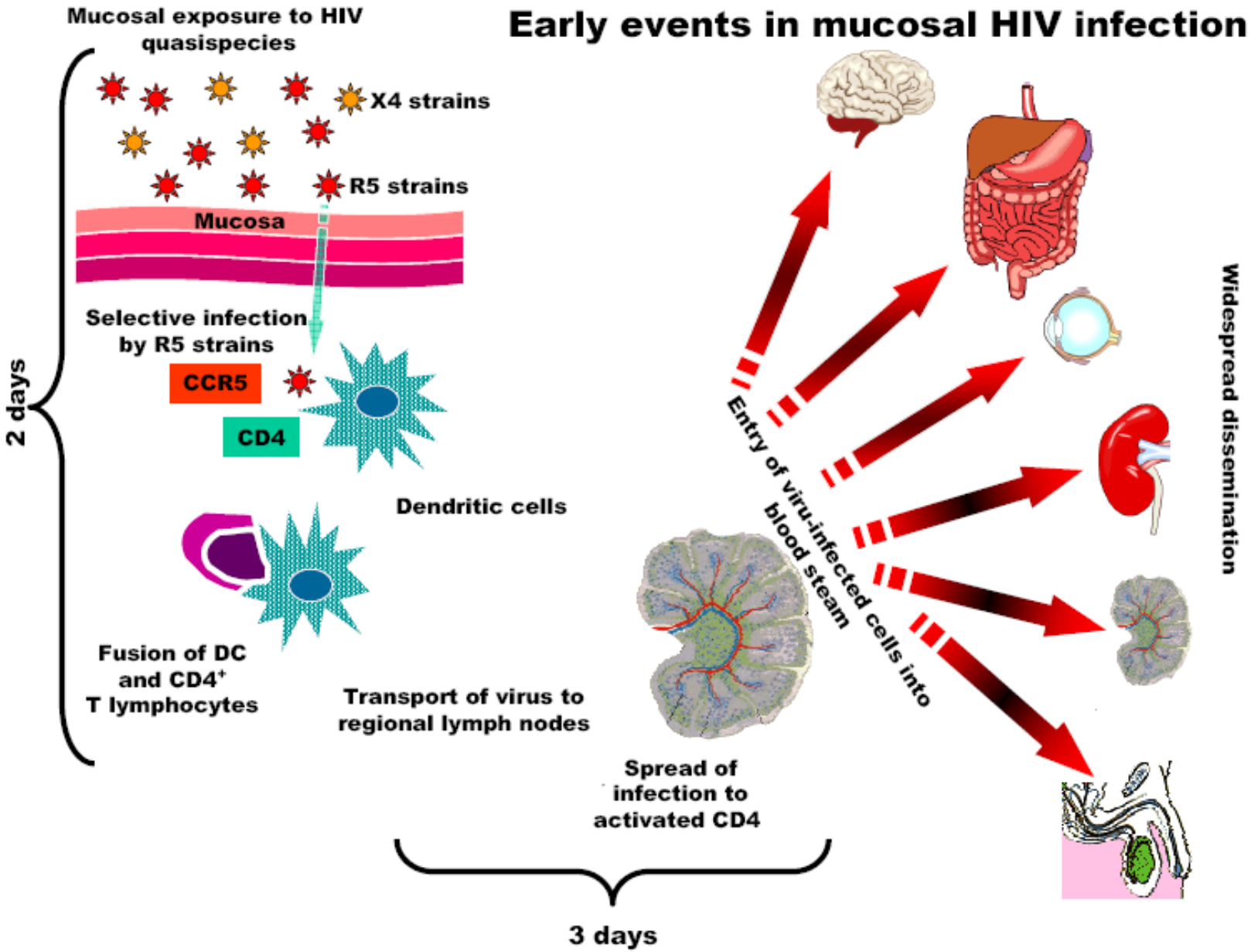
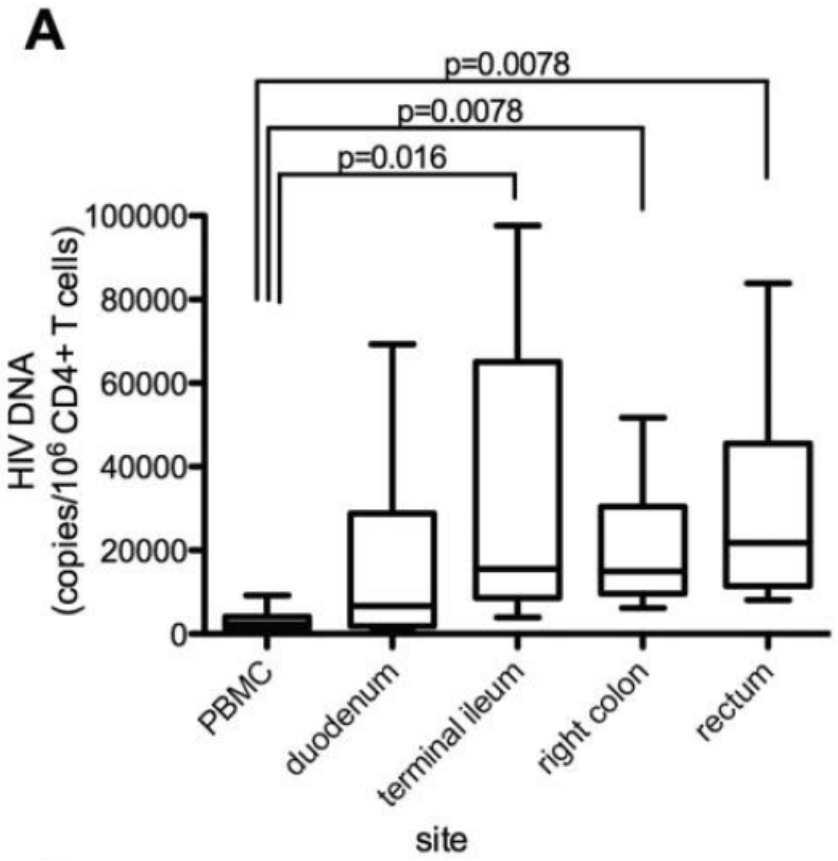


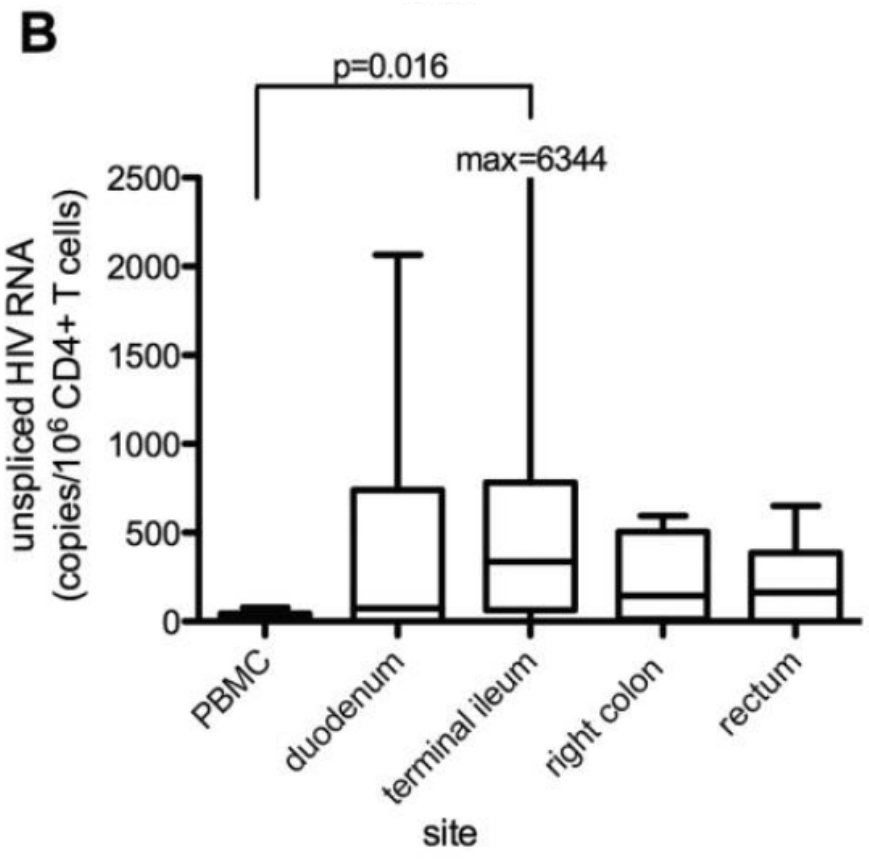
Dual Therapy: reaching clinical evidence



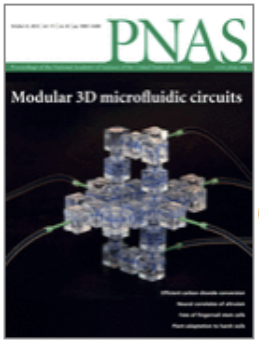

Early events in mucosal HIV infection
Mucosal exposure to HIV quasispecies
X4 strains
R5 strains
Mucosa
Selective infection by R5 strains
CCR5
CD4
Dendritic cells
Fusion of DC and CD4+ T lymphocytes
2 days
Transport of virus to regional lymph nodes
Spread of infection to activated CD4
3 days
Entry of viru-infected cells into blood steam
Widespread dissemination

HIV DNA and RNA levels per CD4+ T cell were higher in all 4 gut sites compared with those in the blood.





The Journal of Infectious Diseases 2010; 202(10):1553–1561



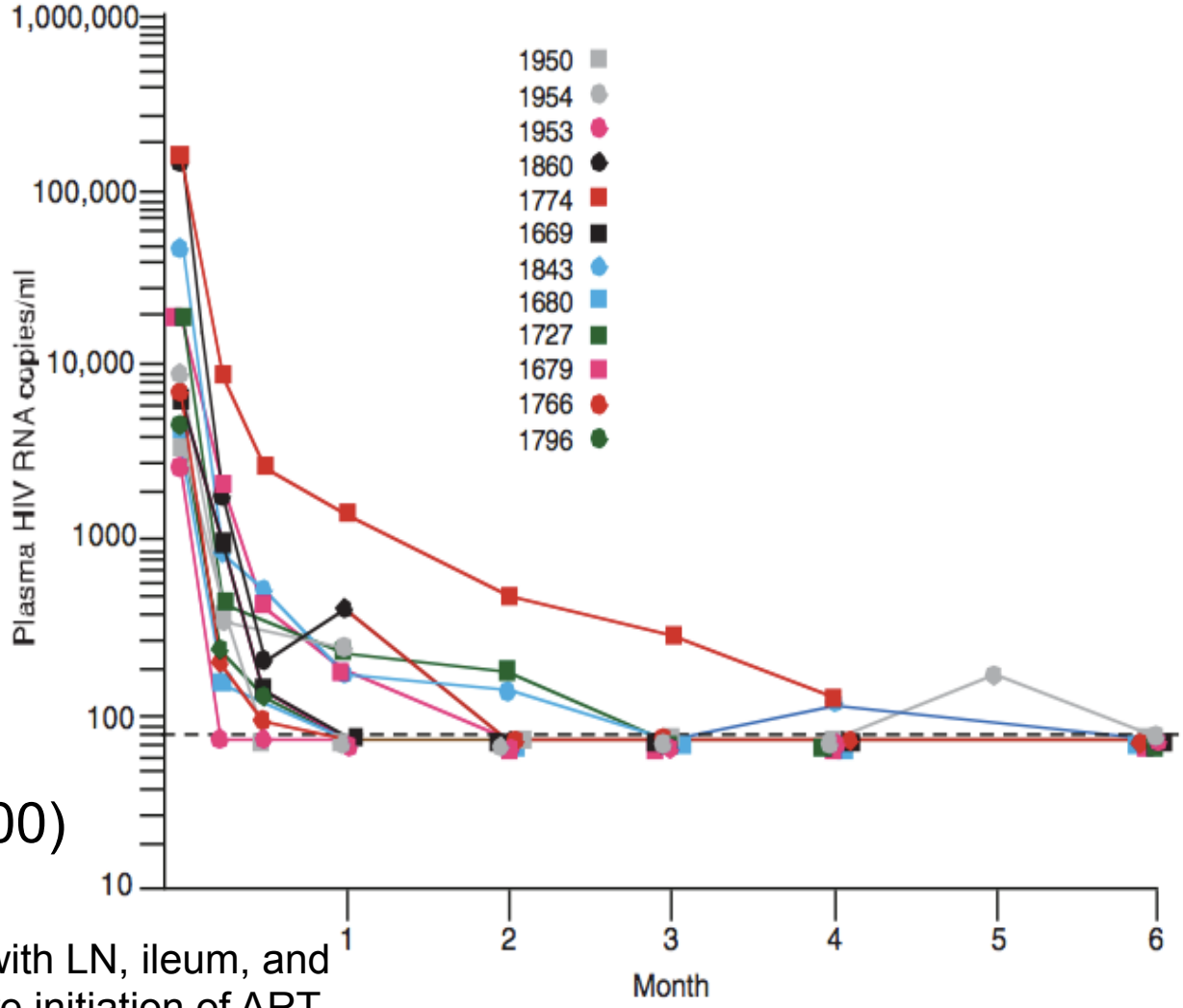
Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

12 Subjects received
TDF/FTC/EFV (n.6)
TDF/FTC/ATV/rtv (n.4)
TDF/FTC/DRV/rtv (n.2)

<u>At entry</u>

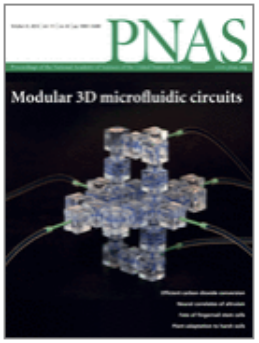
CD4: 467 μl (327-6220)

VL: 34,783 (2,530-157,000)



Subjects were followed for 6 mo with LN, ileum, and rectal biopsies obtained just before initiation of ART and again at months 1, 3, and 6.

C.V. Fletcher PNAS 11, 2014



Different rates of decay of HIV RNA from the FDCn of LN

No significant decrease

Initial decline and then decline more slowly at almost a flat rate

Continuous decay

FDCn: Follicular dendritic cell network

C.V. Fletcher PNAS 11, 2014

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

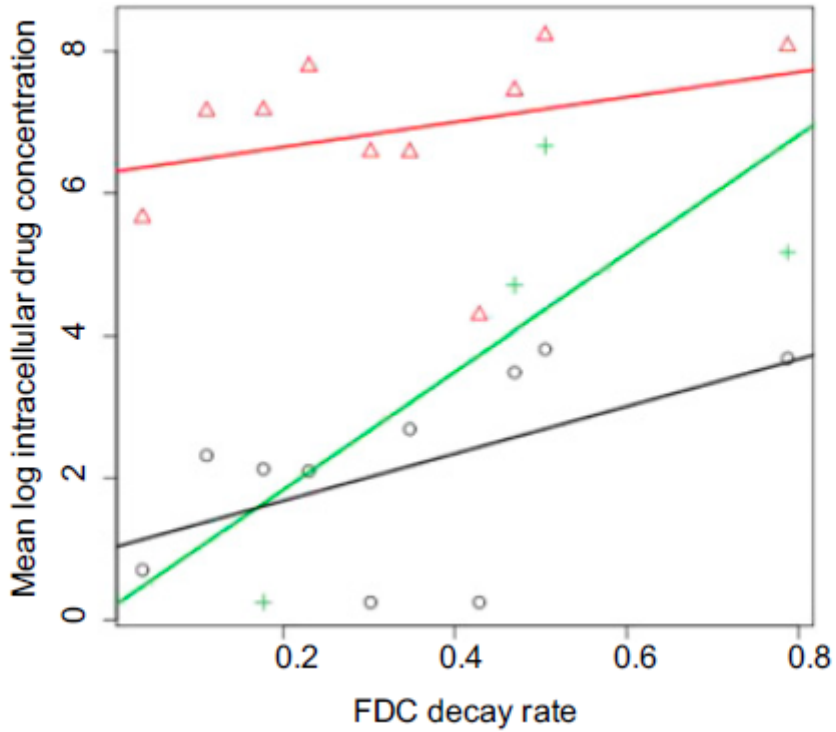
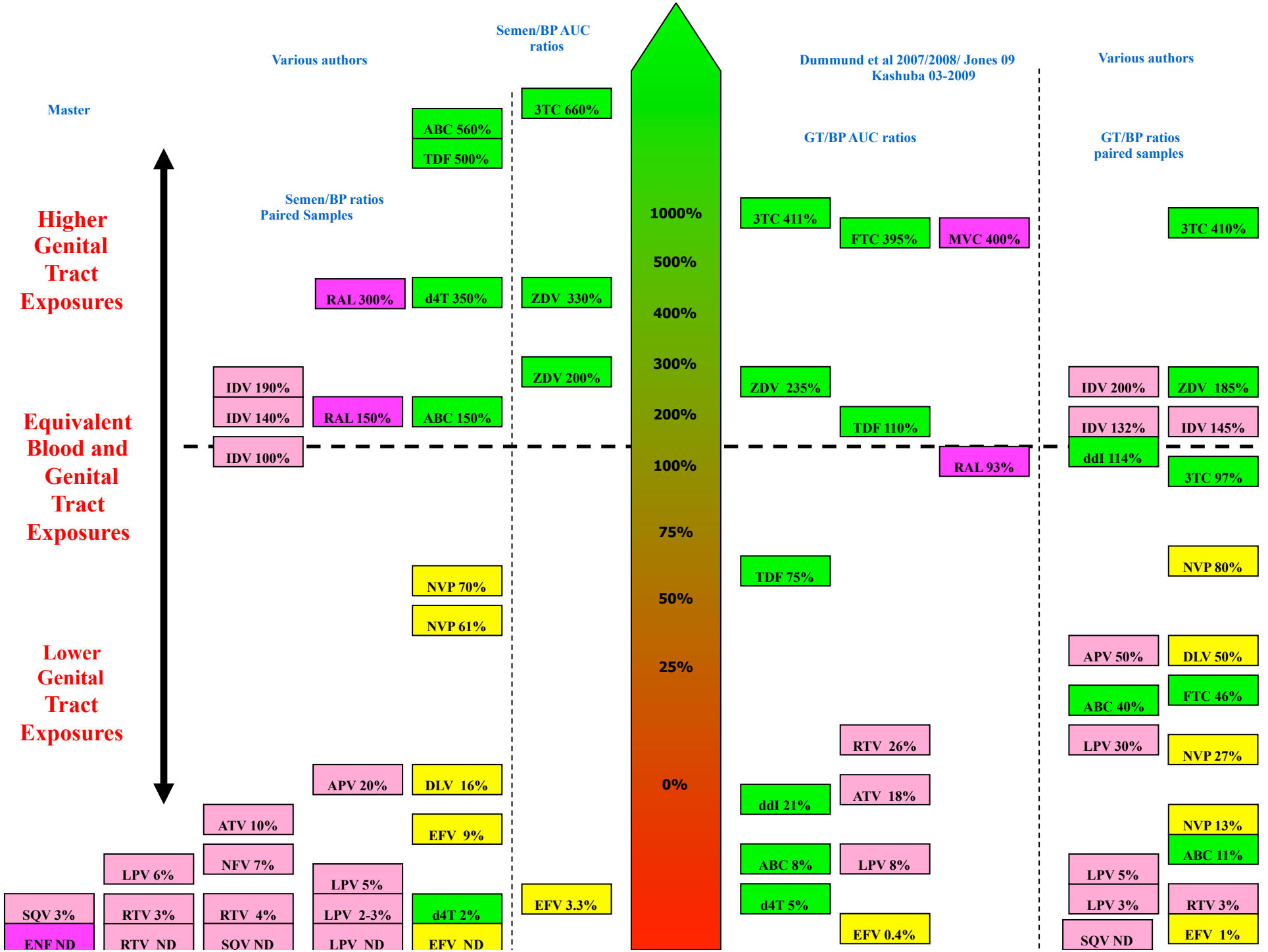


Fig. 5. Representation of the association between the decay rate of virions from the FDC pool and the mean quantity of drug for TFV-DP (black), FTC-TP (red), and EFV (green), showing faster decay of virions with higher concentrations of drug.

C.V. Fletcher PNAS 11, 2014


Master
Various authors
Semen/BP AUC ratios
Dummund et al 2007/2008/ Jones 09
Kashuba 03-2009
Various authors
GT/BP AUC ratios
GT/BP ratios paired samples
Semen/BP ratios Paired Samples
Higher Genital Tract Exposures
Equivalent Blood and Genital Tract Exposures
Lower Genital Tract Exposures
1000%
500%
400%
300%
200%
100%
75%
50%
25%
0%
3TC 660%
ABC 560%
TDF 500%
RAL 300%
d4T 350%
ZDV 330%
ZDV 200%
IDV 190%
IDV 140%
IDV 100%
RAL 150%
ABC 150%
NVP 70%
NVP 61%
APV 20%
DLV 16%
EFV 9%
ATV 10%
NFV 7%
LPV 6%
LPV 5%
SQV 3%
RTV 3%
RTV 4%
LPV 2-3%
d4T 2%
ENF ND
RTV ND
SQV ND
LPV ND
EFV ND
EFV 3.3%
3TC 411%
FTC 395%
MVC 400%
ZDV 235%
TDF 110%
RAL 93%
TDF 75%
RTV 26%
ddI 21%
ATV 18%
ABC 8%
LPV 8%
d4T 5%
EFV 0.4%
3TC 410%
IDV 200%
ZDV 185%
IDV 132%
IDV 145%
ddI 114%
3TC 97%
NVP 80%
APV 50%
DLV 50%
ABC 40%
FTC 46%
LPV 30%
NVP 27%
NVP 13%
ABC 11%
LPV 5%
LPV 3%
RTV 3%
SQV ND
EFV 1%

Different studies have highlighted that the level of HIV reservoir can influence the maintenance of virological success under simplification therapy

J Antimicrob Chemother. 2010 May;65(5):1005-7. doi: 10.1093/jac/dkq084. Epub 2010 Mar 18.

Impact of 48 week lopinavir/ritonavir monotherapy on blood cell-associated HIV-1-DNA in the MONARK trial.

Avettand-Fenoel V[1], Flandre P, Chaix ML, Ghosn J, Delaugerre C, Raffi F, Ngovan P, Cohen-Codar I, Delfraissy JF, Rouzioux C; MONARK Study Group.

HIV Clin Trials. 2013 May-Jun;14(3):120-6. doi: 10.1310/hct1403-120.

Long-term HIV-1 virologic control in patients on a dual NRTI regimen.

Prazuck T[1], Zucman D, Avettand-Fènoël V, Ducasse E, Bornarel D, Mille C, Rouzioux C, Hocqueloux L.

Role of Baseline HIV-1 DNA Level in Highly-Experienced Patients Receiving Raltegravir, Etravirine and Darunavir/ Ritonavir Regimen (ANRS139 TRIO Trial)

PLOS ONE | 2013

Charlotte Charpentier[1]*, Catherine Fagard[2,3], Céline Colin[2,3], Christine Katlama[4], Jean-Michel Molina[5], Christine Jacomet[6], Benoit Visseaux[1], Anne-Marie Taburet[7], Françoise Brun-Vézinet[1],

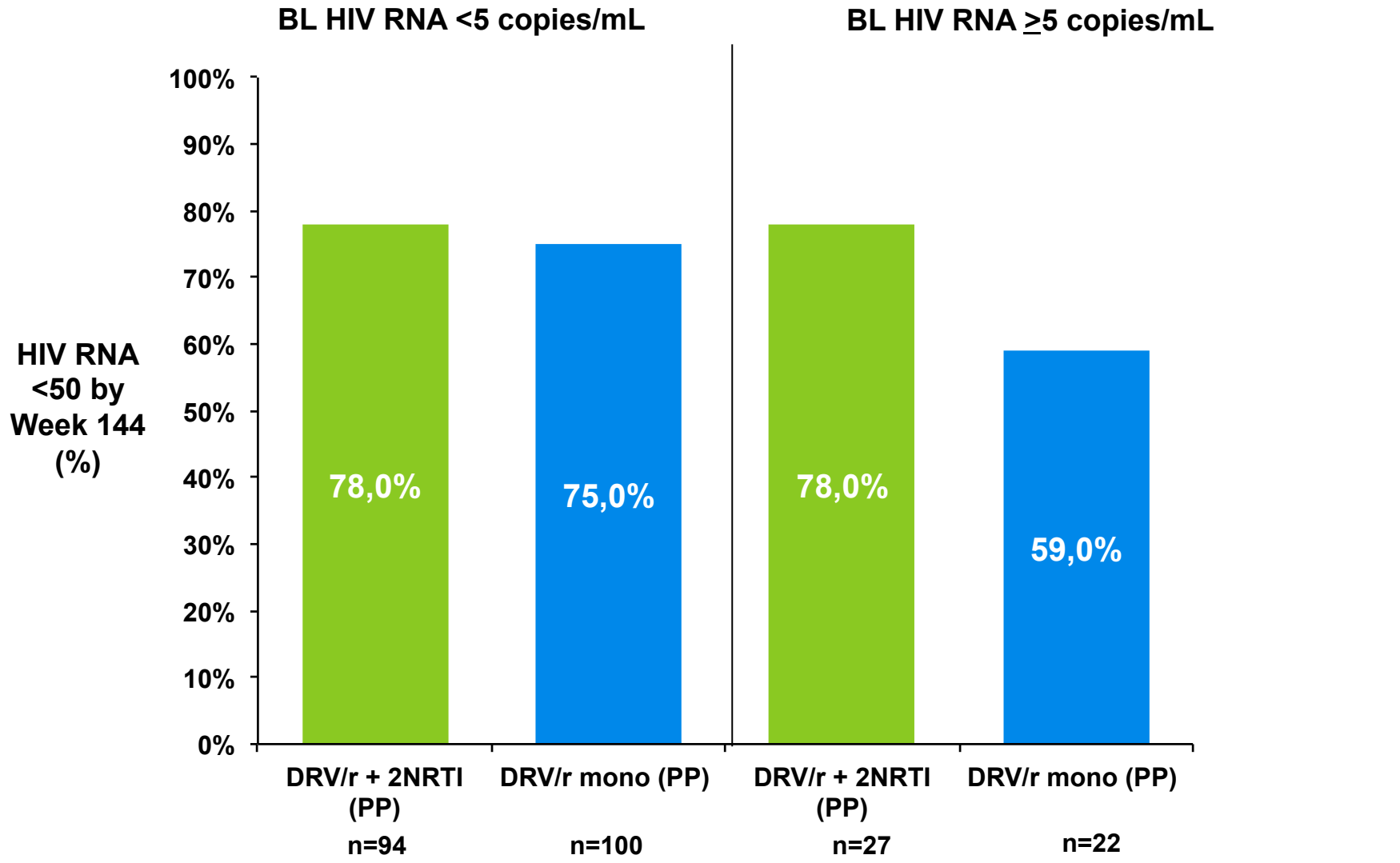
J Med Virol. 2007 Jul;79(7):880-6.

Cellular HIV-1 DNA quantitation in patients during simplification therapy with protease inhibitor-sparing regimens.

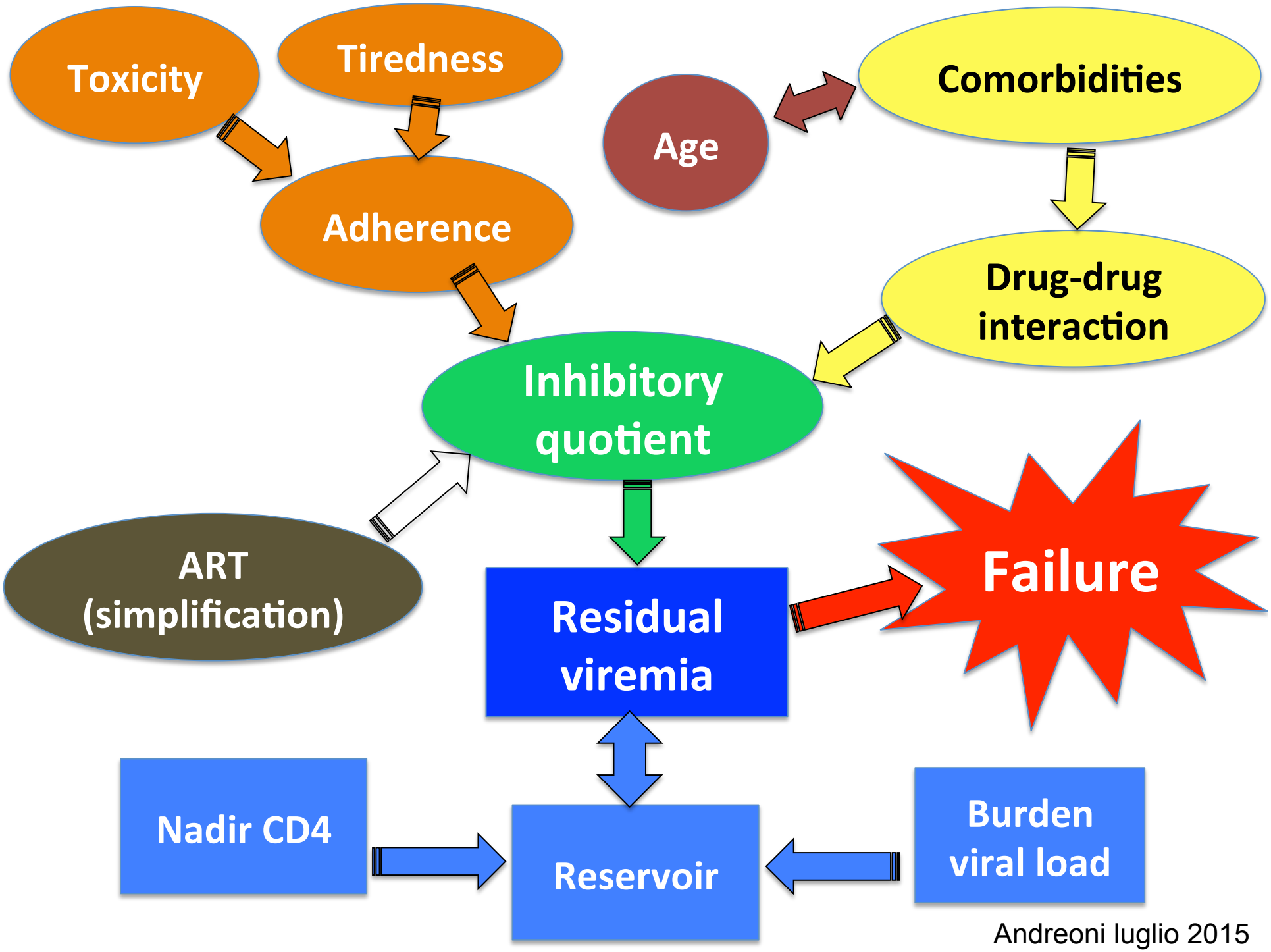
Sarmati L[1], Parisi SG, Nicastri E, d'Ettorre G, Andreoni C, Dori L, Gatti F, Montano M, Buonomini AR, Boldrin C, Palù G, Vullo V, Andreoni M.

At logistic regression analysis, high HIV-DNA levels (>226 copies/10^6 PBMCs) at baseline were associated independently to a increased risk of virological failure or viral blip during simplified therapy

HIV RNA <50 copies/mL at Week 144
by baseline HIV RNA (Per Protocol, TLOVR, Switch=Failure)
MONET study



Ref: Arribas et al, HIV Medicine 2012, 13:398-405


Toxicity
Tiredness
Adherence
Age
Comorbidities
Drug-drug interaction
Inhibitory quotient
ART (simplification)
Residual viremia
Failure
Nadir CD4
Reservoir
Burden viral load
Andreoni luglio 2015

Conclusions: Reasons to Switch to dual ART in Suppressed Pts

- Improve tolerability
- Avoid or minimize drug–drug interactions
- Reduce toxicity or avoid future toxicity
- Reduce costs

Principles of Switching dual Therapy in Suppressed Patients

- Essential to get a complete ARV treatment history for intolerance or virologic failure, and resistance tests results
  - Archival HIV DNA resistance testing may be helpful

Principles of Switching dual Therapy in Suppressed Patients

- Cross-class switching or from high to low barrier agents has greater risk
  - b-PI → RPV, DTG → EVG, ETR → RPV (?)
- Increase monitoring during first 3 mos after switch
- Don’t forget about HBV

Principles of dual Therapy in naive Patients

- An induction therapy with 3 DR can be useful
- A patient selection screen is needed
- Long term data (up to ~10 years) on antiviral activity, immunological effects and disease progression are needed