Dati di ieri, dati di oggi: dove stiamo andando?

Proposta di un percorso ragionato, attraverso la lettura di quanto emerso ed ancora emerge dalla ricerca clinica, in merito all'evoluzione del trattamento.

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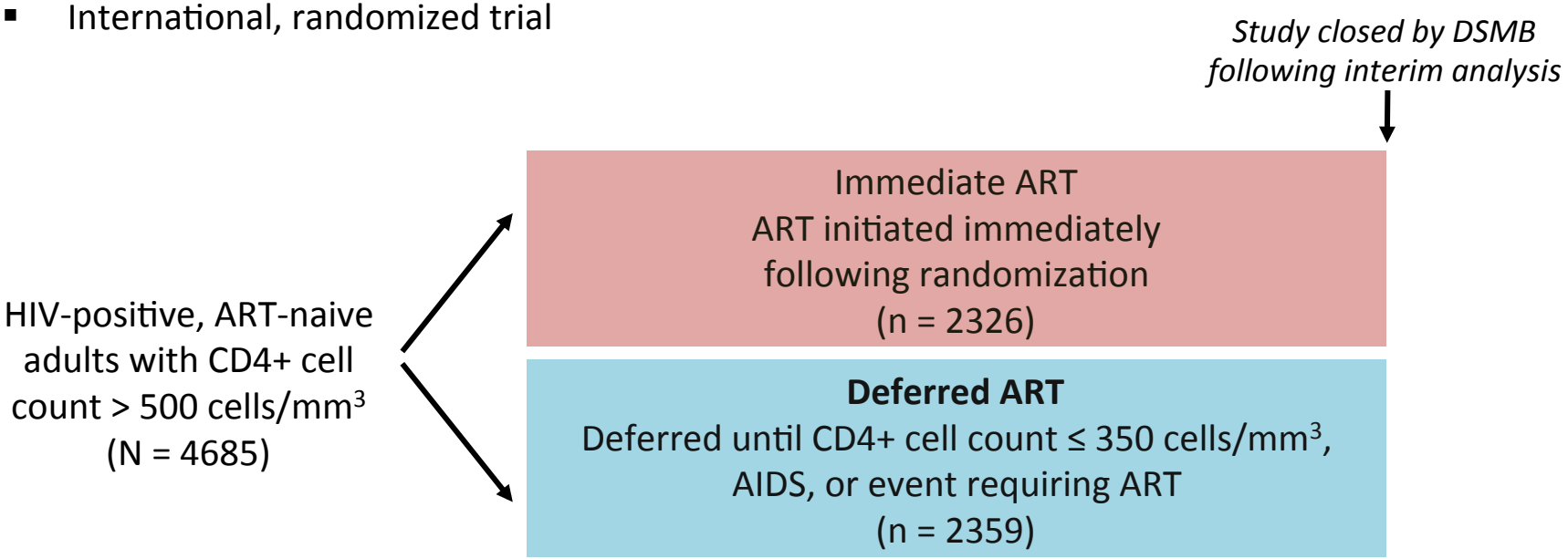
Andrea Antinori
Disclosure statement

- Personal fees for consultancy and lectures from Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck, ViiV.
- Travel grants from Abbvie, ViiV.
- Research grants from Bristol Myers Squibb, Gilead, Janssen, ViiV.

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial

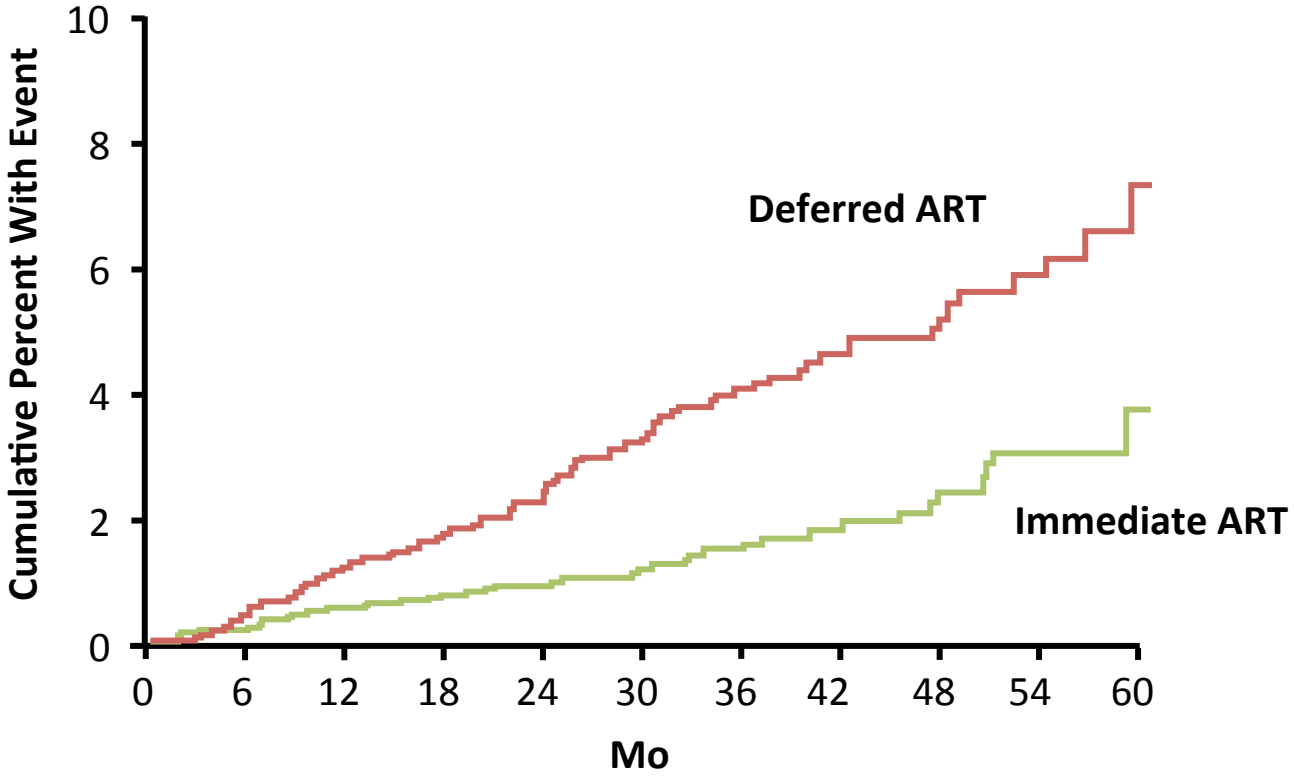


- Composite primary endpoint: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)
- Mean follow-up: 3 yrs; median baseline CD4+ cell count: 651 cells/mm^3; median baseline HIV-1 RNA: 12,759 copies/mL
- Median CD4+ cell count at initiation of ART for deferred group: 408 cells/mm^3

INSIGHT START Study Group. N Engl J Med. 2015;[Epub ahead of print]. Lundgren J, et al. IAS 2015. Abstract MOSY0302.

START: 57% Reduced Risk of Serious Events or Death With Immediate ART

- 4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death (HR: 0.43; 95% CI: 0.30-0.62; *P* < .001)



INSIGHT START Group. N Engl J Med. 2015;[Epub ahead of print]. Lundgren J, et al. IAS 2015. Abstract MOSY0302. Reproduced with permission.

Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy?

Evan Wood[a,b], Robert S. Hogg[a,b], Benita Yip[a], P. Richard Harrigan[a,d], Michael V. O'Shaughnessy[a,c] and Julio S.G. Montaner[a,d]

Objective: Therapeutic guidelines advise that 200–350 $\times 10^6$ cells/l may approximate an irreversible threshold beyond which response to therapy is compromised. We evaluated whether non-immune-based factors such as physician experience and adherence could affect survival among HIV-infected adults starting HAART.

Methods: Analysis of 1416 antiretroviral naive patients who initiated triple therapy between 1 August 1996 and 31 July 2000, and were followed until 31 July 2001. Patients whose physicians had previously enrolled six or more patients were defined as having an experienced physician. Patients who received medications for at least 75% of the time during the first year of HAART were defined as adherent. Cumulative mortality rates and adjusted relative hazards were determined for various CD4 cell count strata.

Results: Among patients with $< 50 \times 10^6$ cells/l the adjusted relative hazard of mortality was 5.07 [95% confidence interval (CI), 2.50–10.26] for patients of experienced physicians and was 11.99 (95% CI, 6.33–22.74) among patients with inexperienced physicians, in comparison to patients with $\geqslant 200 \times 10^6$ cells/l treated by experienced physicians. Similarly, among patients with $< 50 \times 10^6$ cells/l, the adjusted relative hazard of mortality was 6.19 (95% CI, 3.03–12.65) for adherent patients and was 35.71 (95% CI, 16.17–78.85) for non-adherent patients, in comparison to adherent patients with $\geqslant 200 \times 10^6$ cells/l.

Conclusion: Survival rates following the initiation of HAART are dramatically improved among patients starting with CD4 counts $< 200 \times 10^6$ cells/l once adjusted for conservative estimates of physician experience and adherence. Our results indicate that the current emphasis of therapeutic guidelines on initiating therapy at CD4 cell counts above 200×10^6 cells/l should be re-examined.

AIDS 2003, **17**:711–720

Keywords: CD4 cell count, HIV, adherence, antiretroviral therapy

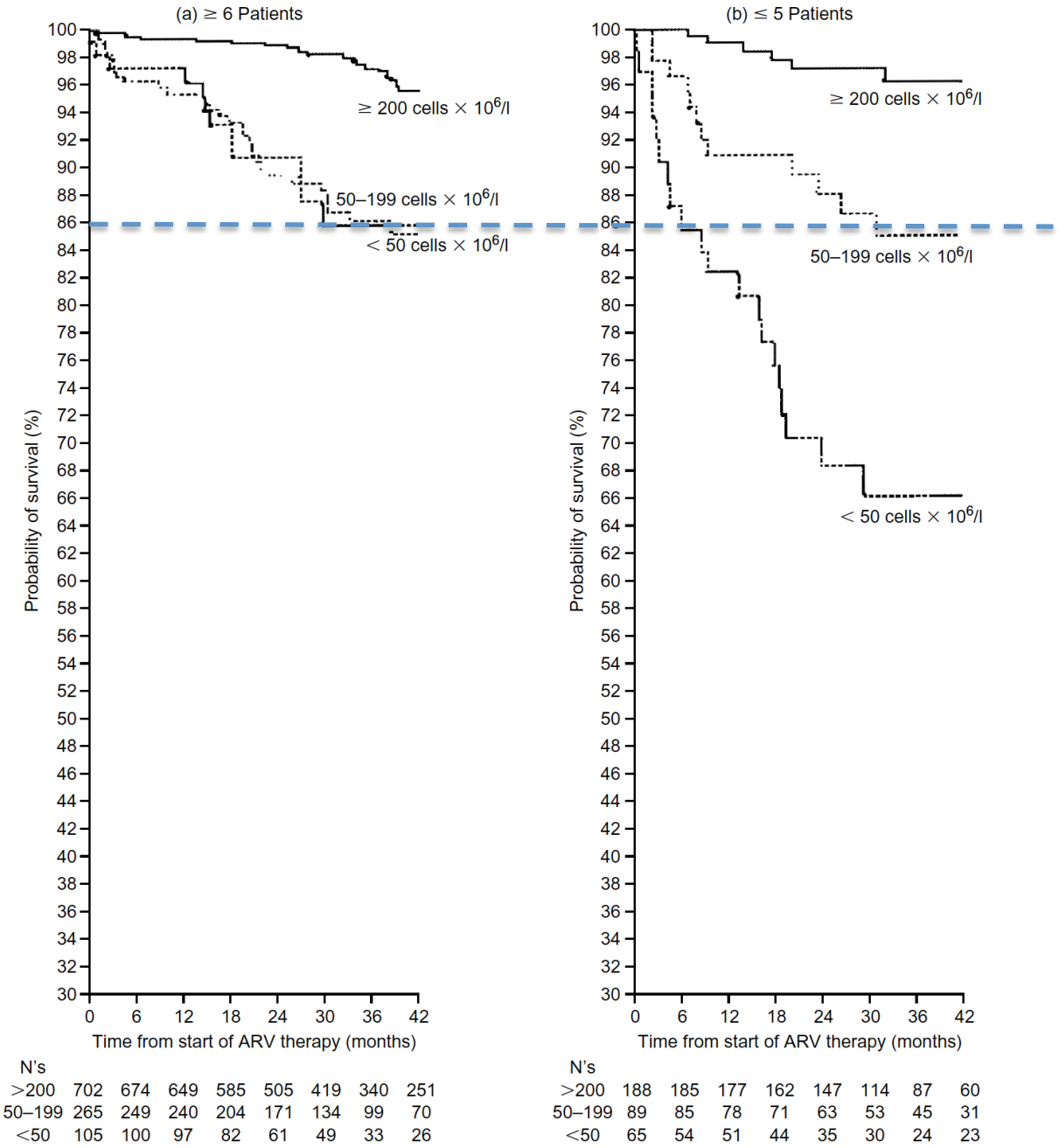


Fig. 2. Kaplan–Meier product limit estimates of cumulative progression to death among 1414 HIV-infected, antiretroviral-naive subjects who started antiretroviral therapy between 1 August 1996 and 31 July 2000, stratified by CD4 cell count groupings (< 50, 50–199, ⩾ 200 × 10^6 cells/l), and HIV-experienced (a) and non-experienced (b) categories.

SPECIAL COMMENTARY

Should HIV therapy be started at a CD4 cell count above 350 cells/μl in asymptomatic HIV-1-infected patients?

Caroline A. Sabin and Andrew N. Phillips

Research Department of Infection and Population Health, Division of Population Health, UCL Medical School, Royal Free Campus, London, UK

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Current Opinion in Infectious Diseases 2009, 22:191–197

Purpose of review

The aim is to review the available data that contribute to the debate on the optimal time to initiate highly active antiretroviral therapy (HAART) in HIV-infected individuals with a CD4 cell count more than 350 cells/μl.

Recent findings

Although few randomized data exist that can contribute to this debate, a number of findings from observational studies generally support earlier initiation of HAART. In particular, the findings that death rates remain higher in HIV-infected individuals than in uninfected individuals, even when successfully treated, and that both AIDS and several serious non-AIDS events are more common in those with a lower CD4 cell count (even when this count is above 350 cells/μl), suggest that earlier initiation of HAART may prevent much of the excess morbidity and mortality that remains in this patient group.

Summary

Currently, the data would generally support initiation of HAART in patients with CD4 cell counts more than 350 cells/μl. However, given the strong potential for confounding in observational studies and the lack of adjustment for lead-time bias in many analyses, it is not possible to rule out possible long-term detrimental effects of earlier use of HAART until the results from fully powered randomized trials that directly address this issue become available.

Keywords

antiretroviral therapy, CD4 cell count, HIV infection, when to start treatment

Curr Opin Infect Dis 22:191–197

0951-7375

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 17, 2013 VOL. 368 NO. 3

Short-Course Antiretroviral Therapy in Primary HIV Infection

The SPARTAC Trial Investigators*

ABSTRACT

BACKGROUND

Short-course antiretroviral therapy (ART) in primary human immunodeficiency virus (HIV) infection may delay disease progression but has not been adequately evaluated.

METHODS

We randomly assigned adults with primary HIV infection to ART for 48 weeks, ART for 12 weeks, or no ART (standard of care), with treatment initiated within 6 months after seroconversion. The primary end point was a CD4+ count of less than 350 cells per cubic millimeter or long-term ART initiation.

RESULTS

A total of 366 participants (60% men) underwent randomization to 48-week ART (123 participants), 12-week ART (120), or standard care (123), with an average follow-up of 4.2 years. The primary end point was reached in 50% of the 48-week ART group, as compared with 61% in each of the 12-week ART and standard-care groups. The average hazard ratio was 0.63 (95% confidence interval [CI], 0.45 to 0.90; P=0.01) for 48-week ART as compared with standard care and was 0.93 (95% CI, 0.67 to 1.29; P=0.67) for 12-week ART as compared with standard care. The proportion of participants who had a CD4+ count of less than 350 cells per cubic millimeter was 28% in the 48-week ART group, 40% in the 12-week group, and 40% in the standard-care group. Corresponding values for long-term ART initiation were 22%, 21%, and 22%. The median time to the primary end point was 65 weeks (95% CI, 17 to 114) longer with 48-week ART than with standard care. Post hoc analysis identified a trend toward a greater interval between ART initiation and the primary end point the closer that ART was initiated to estimated seroconversion (P=0.09), and 48-week ART conferred a reduction in the HIV RNA level of 0.44 $\log_{10}$ copies per milliliter (95% CI, 0.25 to 0.64) 36 weeks after the completion of short-course therapy. There were no significant between-group differences in the incidence of the acquired immunodeficiency syndrome, death, or serious adverse events.

CONCLUSIONS

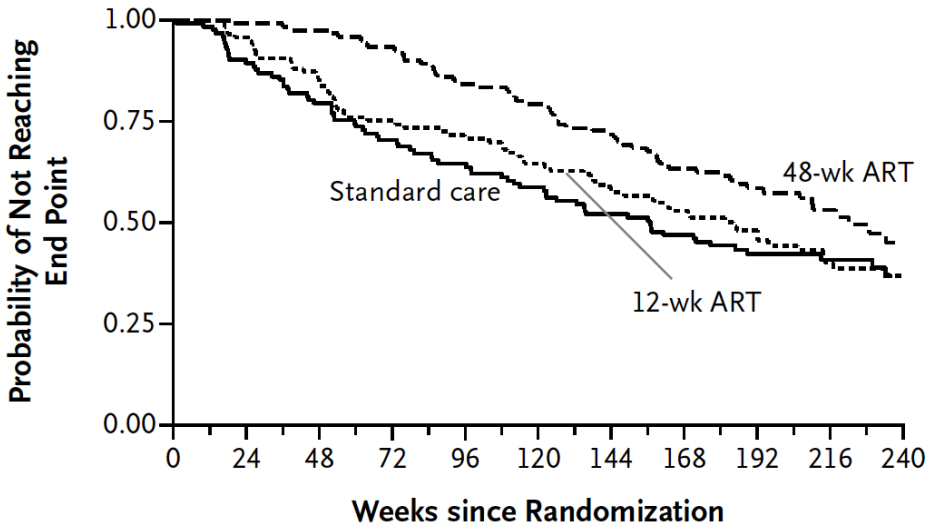
A 48-week course of ART in patients with primary HIV infection delayed disease progression, although not significantly longer than the duration of the treatment. There was no evidence of adverse effects of ART interruption on the clinical outcome. (Funded by the Wellcome Trust; SPARTAC Controlled-Trials.com number, ISRCTN76742797, and EudraCT number, 2004-000446-20.)

The members of the writing group are listed in the Appendix. Address reprint requests to Dr. Jonathan Weber at Imperial College London, Faculty of Medicine, St. Mary's Campus, Norfolk Pl., London W2 1PG, United Kingdom, or at j.weber@imperial.ac.uk.

*The Short Pulse Anti-Retroviral Therapy at Seroconversion (SPARTAC) Trial Investigators are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2013;368:207-17.
DOI: 10.1056/NEJMoa1110039

A Primary End Point (CD4+ count <350 cells/mm³ or long-term ART initiation)



No. at Risk

Standard care	123	110	96	85	78	70	62	55	38	27	17
12-wk ART	120	112	100	86	81	73	66	59	40	28	17
48-wk ART	123	121	118	113	101	95	85	75	54	32	17

HPTN 052: Partner Infections With Early vs Delayed ART

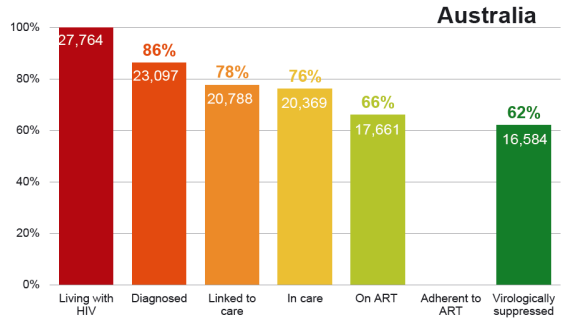
- ***No linked HIV transmissions observed when index participant stably suppressed on ART***

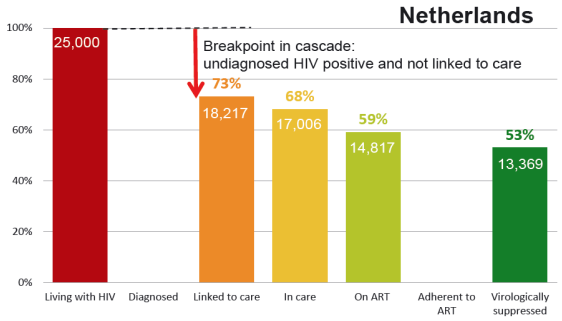
	April 2005 - May 2011		May 2011 - May 2015		Overall (April 2005 - May 2015)	
Partner Infections, n (rate/100 PY)	Early (1751 PY F/U)	Delayed (1731 PY F/U)	Early (2563 PY F/U)	Delayed (2449 PY F/U)	Early (4314 PY F/U)	Delayed (4180 PY F/U)
All	4 (0.23)	42 (2.43)	15 (0.59)	17 (0.69)	19 (0.44)	59 (1.41)
Linked	1 (0.06)	36 (2.08)	2 (0.08)	7 (0.29)	3 (0.07)	43 (1.03)
Risk Reduction With Early ART, %						
All infections	91	--	14	--	69	--
Linked infections	97	--	72	--	93	--

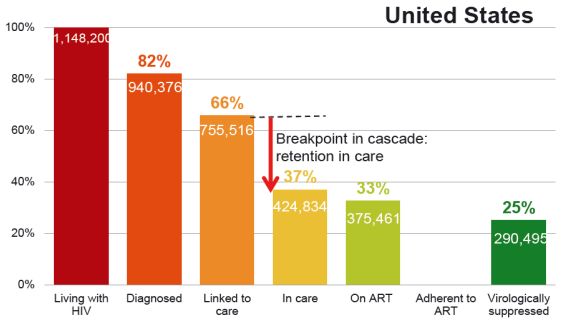
- 8 linked HIV infections diagnosed after seropositive pt started ART
  - 4 infections likely occurred before, or soon after, ART initiation, and 4 infections occurred after ART failure in seropositive pt
- Unlinked partner infection rates similar between study arms

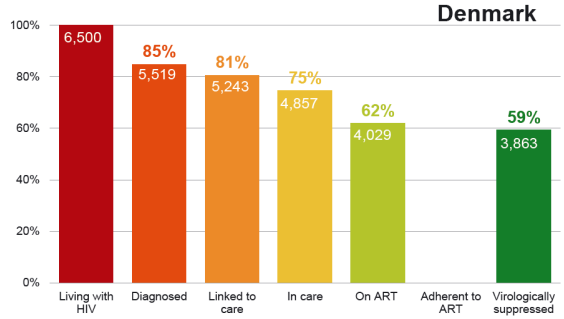
Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.

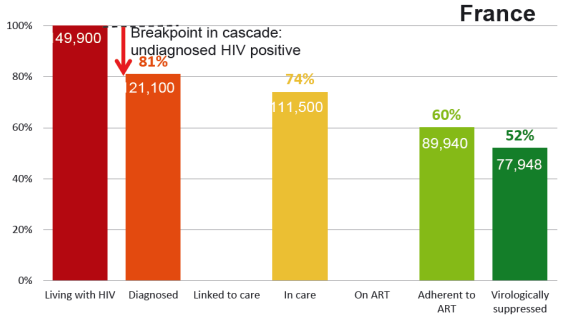
Large disparities in HIV treatment cascades between eight European and high-income countries

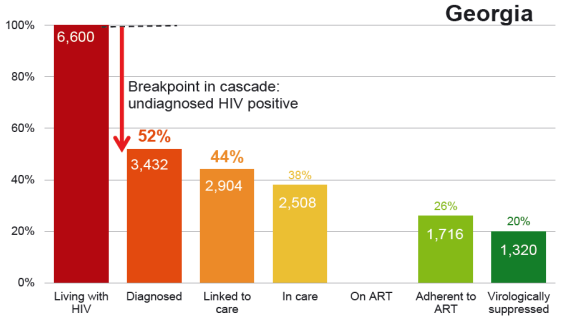


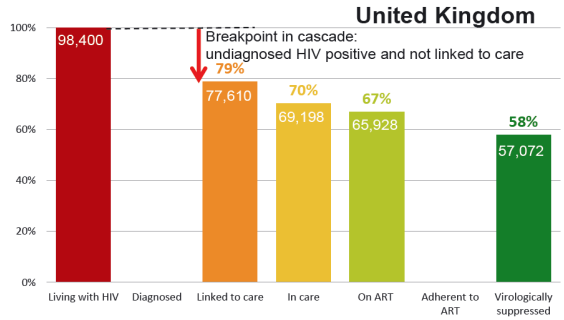


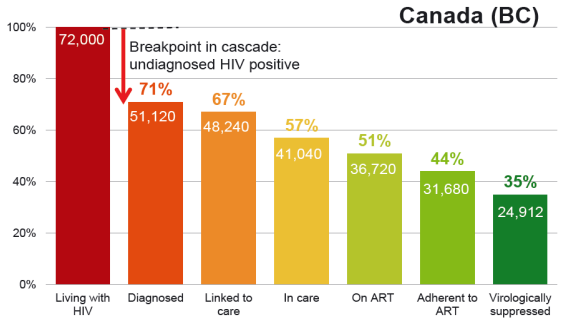


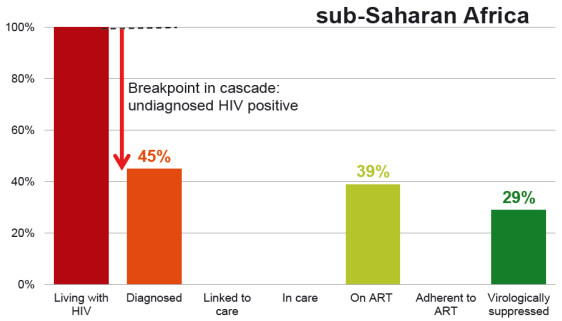








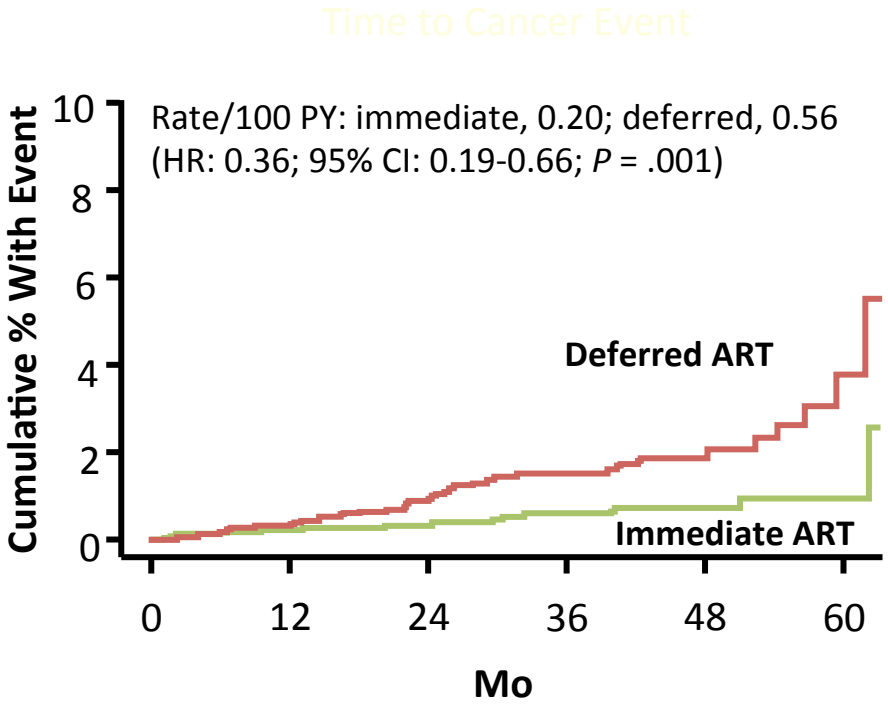




Raymond A, et al. HIV Drug Therapy; Glasgow, 2014. Abst.#O237

START: Cancer Events With Immediate vs Deferred ART

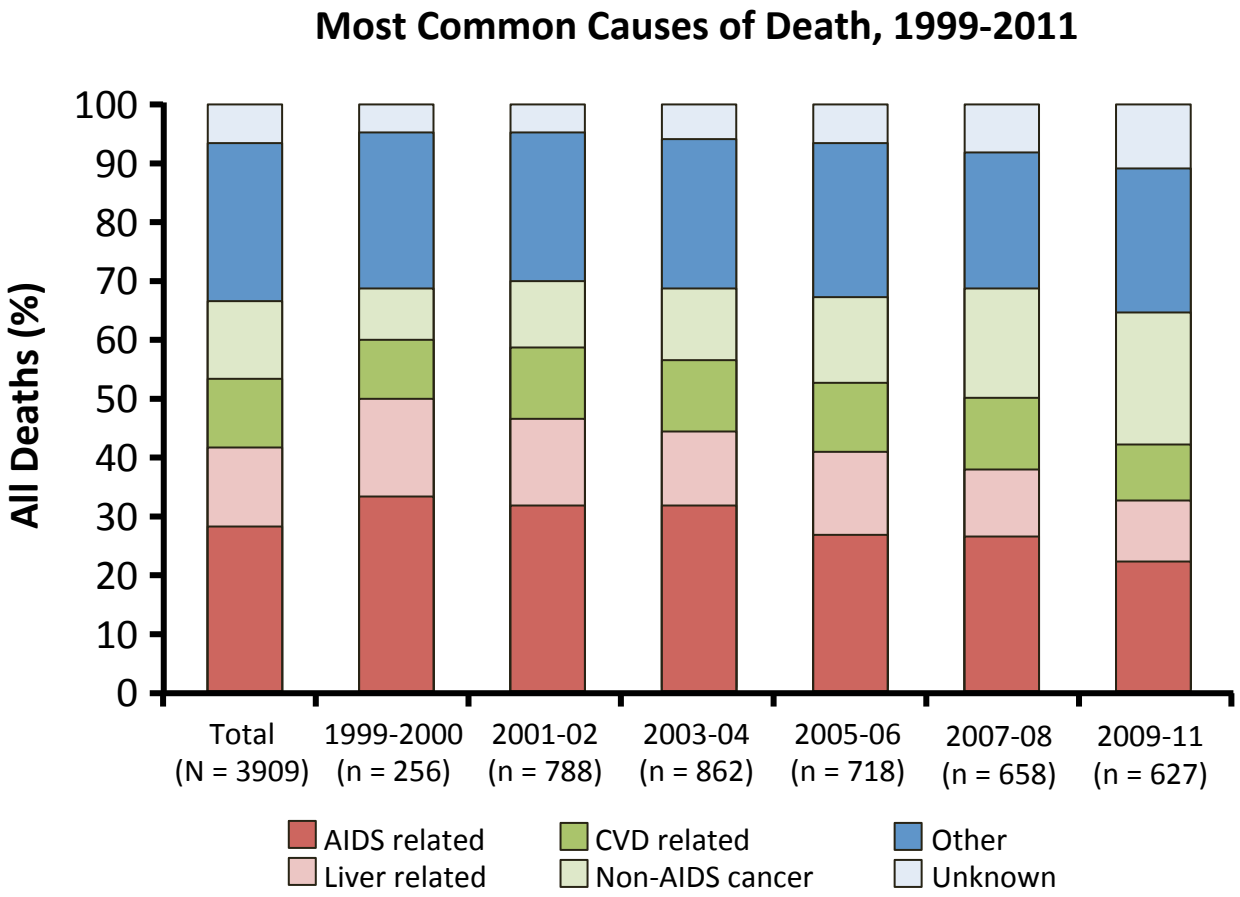
Cancer Event, n	Immediate ART (n = 2326)	Deferred ART (n = 2359)
Total	14	39
Kaposi's sarcoma	1	11
Lymphoma, NHL + HL	3	10
Prostate cancer	2	3
Lung cancer	2	2
Anal cancer	1	2
Cervical or testis cancer	1	2
Other types*	4	9



*Immediate ART: squamous cell carcinoma, plasma cell myeloma, bladder cancer, fibrosarcoma.
Deferred ART: gastric adenocarcinoma, breast cancer, ureteric cancer, malignant melanoma, myeloid leukemia, thyroid cancer, leiomyosarcoma, liver cancer, squamous cell carcinoma of head and neck.

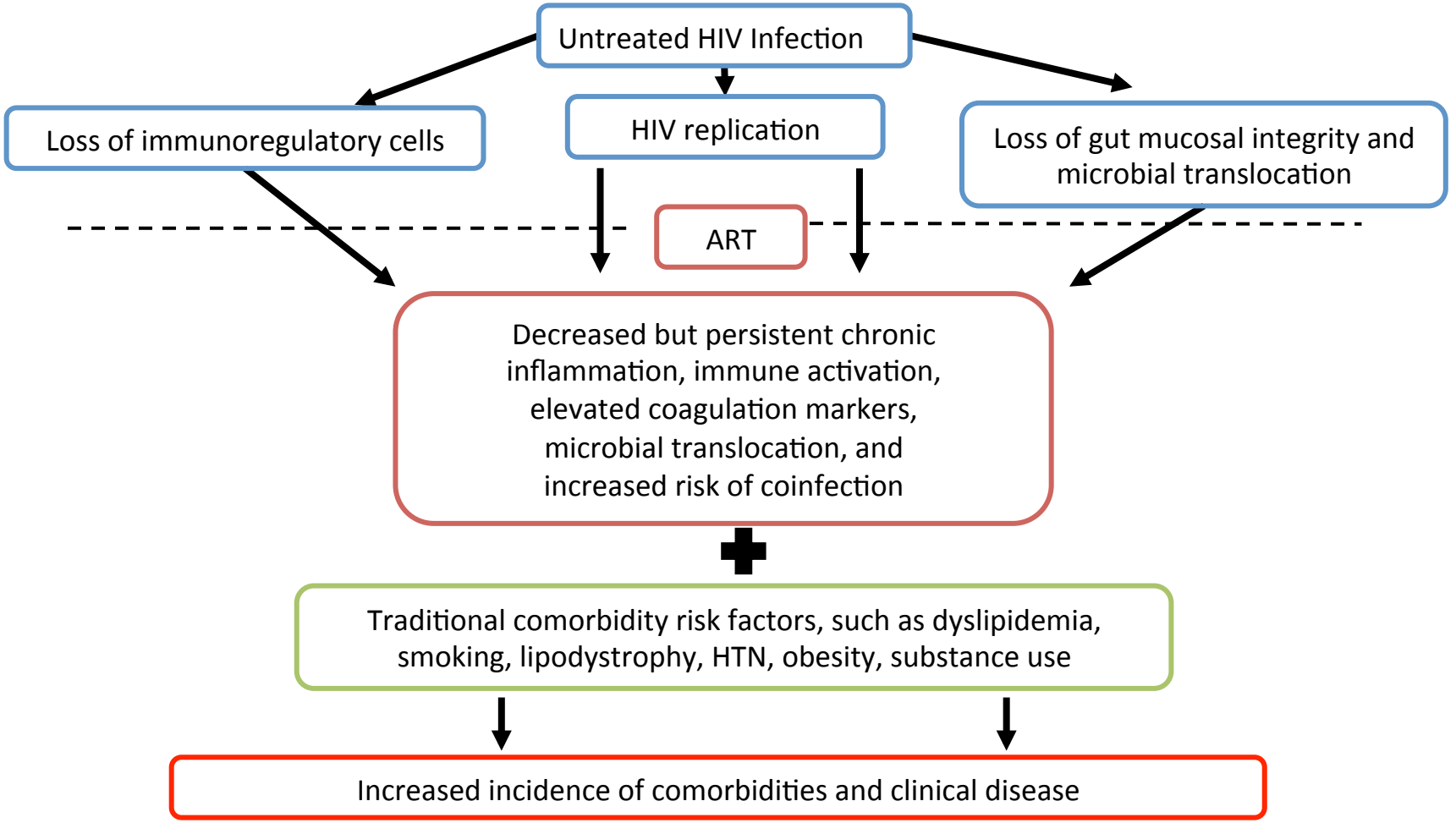
INSIGHT START Group. N Engl J Med. 2015;[Epub ahead of print]. Lundgren J, et al. IAS 2015. Abstract MOSY0302. Reproduced with permission.

D:A:D:
Non-AIDS cancer is now the leading non-AIDS cause of death



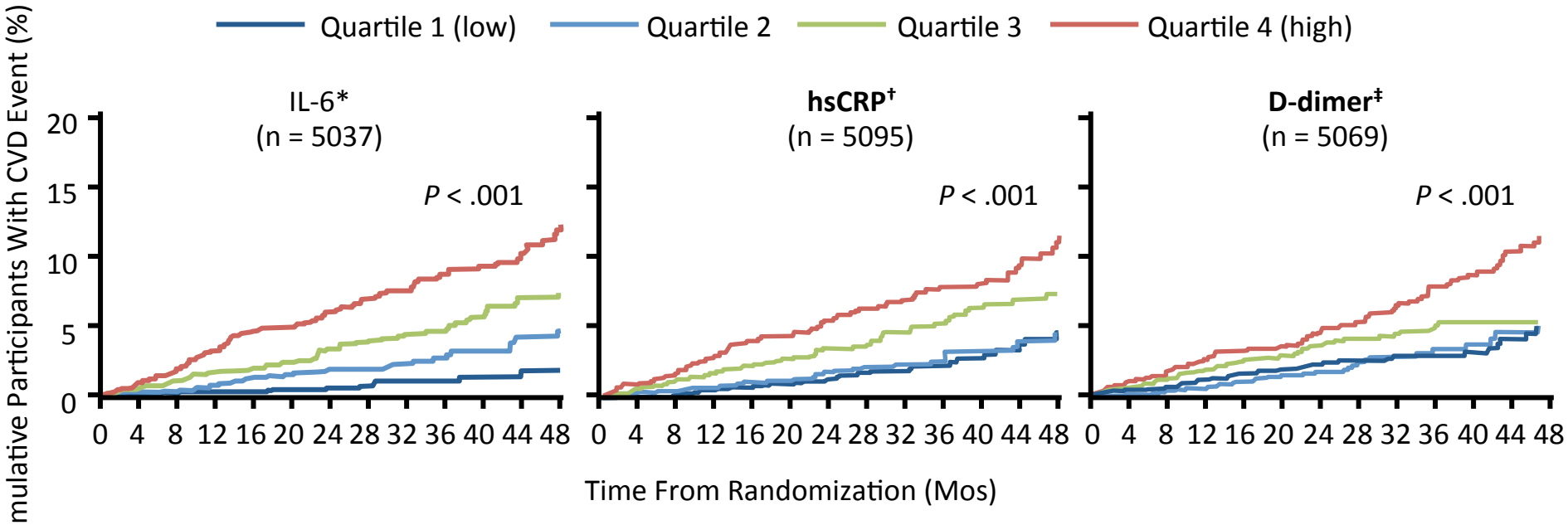
Smith C, et al Lancet. 2014:384:241-248.

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



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

SMART
High Levels of Inflammation Markers Associated With Risk of CVD



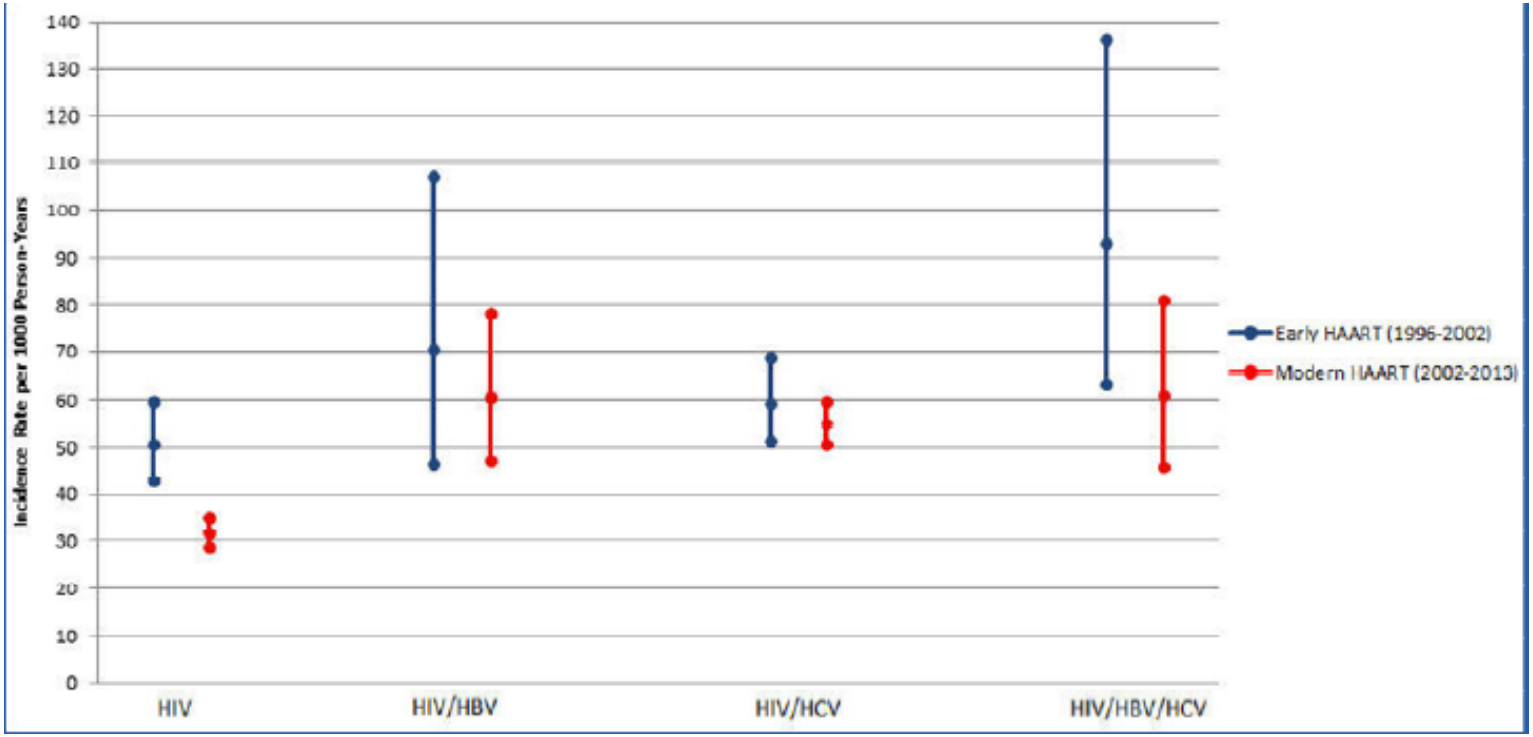
- Time-to-event methods were used to study associations of the baseline level of IL-6, hsCRP, and D-dimer with a CVD event

*IL-6 quartiles are < 1.10, 1.10-1.76, 1.77-3.01, > 3.01 pg/mL.
†hsCRP quartiles are < 0.72, 0.72-1.71, 1.72-4.17, > 4.17 µg/mL.
‡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.

Association of Co-Infection with HBV, HCV or both on survival among HIV infected adults

Prospective cohort study of 4819 patients with HIV and known HBV and HCV status receiving care at the Johns Hopkins HIV Clinic from 1996 to March 2013



In the modern cART era ,after adjusting for HIV disease and treatment, mortality was significantly increased among HIV/HBV, HIV/HCV and HIV/HBV/HCV co-infected patients when compared to HIV monoinfected.

Wansom T et al CROI 2014 poster# 686

Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial

Jürgen K Rockstroh, Mark Nelson, Christine Katlama, Jay Lalezari, Josep Mallolas, Mark Bloch, Gail V Matthews, Michael S Saag, Philippe J Zamor, Chloe Orkin, Jacqueline Gress, Stephanie Klopfer, Melissa Shaughnessy, Janice Wahl, Bach-Yen T Nguyen, Eliav Barr, Heather L Platt, Michael N Robertson, Mark Sulkowski

Lancet HIV 2015

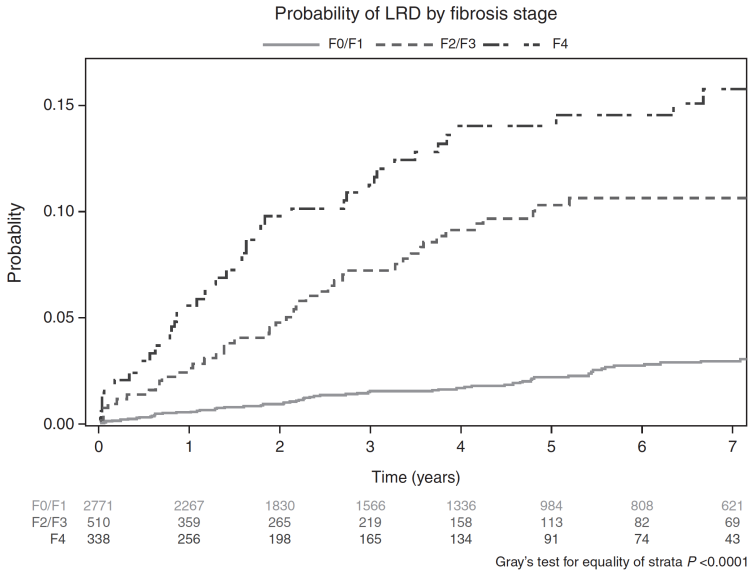
Published Online
July 10, 2015
http://dx.doi.org/10.1016/S2352-3018(15)00114-9

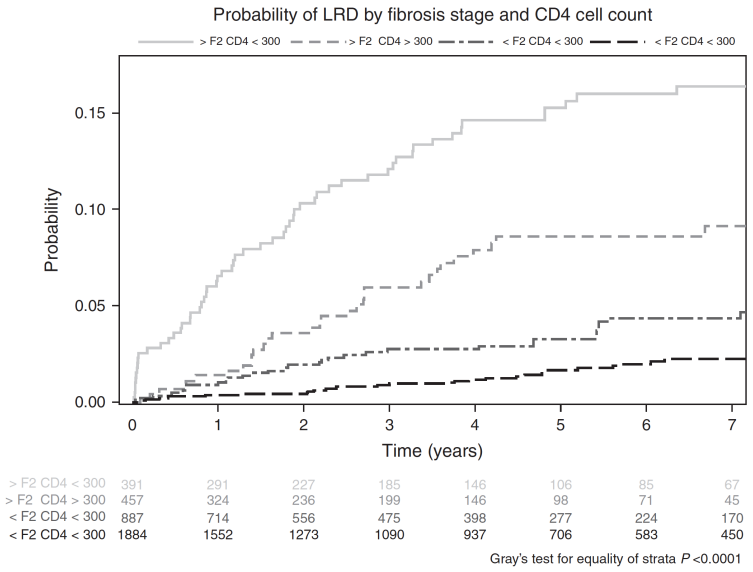
	All patients	HCV genotype 1a	HCV genotype 1b	HCV genotype 4
SVR12 (95% CI)	210/218* (96·3%, 92·9–98·4)	136/144 (94·4%, 84·5–99·4)	42/44 (95·5%, 84·5–99·4)	27/28 (96·4%, 81·7–99·9)
Lost to follow-up or other non-virological failure	1†	0	1	0
Virological breaththrough	0	0	0	0
Virological relapse	5	4	0	1
Reinfection	2	1	1	0

Data are n/N (%, 95% CI) or number of patients. Sustained virological response (SVR) defined as hepatitis C virus (HCV) RNA less than lower limit of quantitation (<15 IU/mL) at follow-up week 12. *Two patients with HCV genotype 6 infection were also included; both patients achieved SVR12. †Prohibited concomitant medication.

***Table 2*: Rates of sustained virological response after 12 weeks of follow-up (full analysis set)**

Treatment with DAAs in HIV+/HCV+ coinfected should be prioritized for those with at least F2 fibrosis





3,941 HCV antibody-positive EuroSIDA patients with follow-up after 1 January 2000 were included.

Liver-related deaths (LRD) accounted for 145 of 670 (21.6%) deaths in the study population. LRD rates peaked in those aged 35–45 years, and ***occurred almost exclusively in those with at least F2 fibrosis at baseline.***

In adjusted Cox models, risk factors for LRD included F4 (HR 6.3, 95%CI 4.1–9.6) or F2/F3 fibrosis (HR2.5, 95%CI 1.5–4.2 vs. F0/F1, respectively), CD4+ cell count (HR 0.83, 95%CI 0.73–0.95 per doubling) and hepatitis B surface Ag-positive (HR 2.2, 95% CI 1.3–3.5 vs. hepatitis B surface Ag-negative).

The 5-year probability of LRD was low in those with F0/F1 fibrosis (HR 2.2%, 95%CI 1.7–2.9), but ***substantial in those with F2/F3 and F4 fibrosis (HR 10.3%, 95% CI 7.6–13.5; and HR 14.0%, 95% CI 10.3–18.3, respectively)***.

Treatment with DAAs should be prioritized for those with at least F2 fibrosis. Early initiation of cART with the aim of avoiding low CD4+ cell counts should be considered essential to decrease the risk of LRD and the need for HCV treatment.

Grint D, et al. AIDS, 2015

Summary of Key Recent Clinical Trials in Treatment-Naive Pts

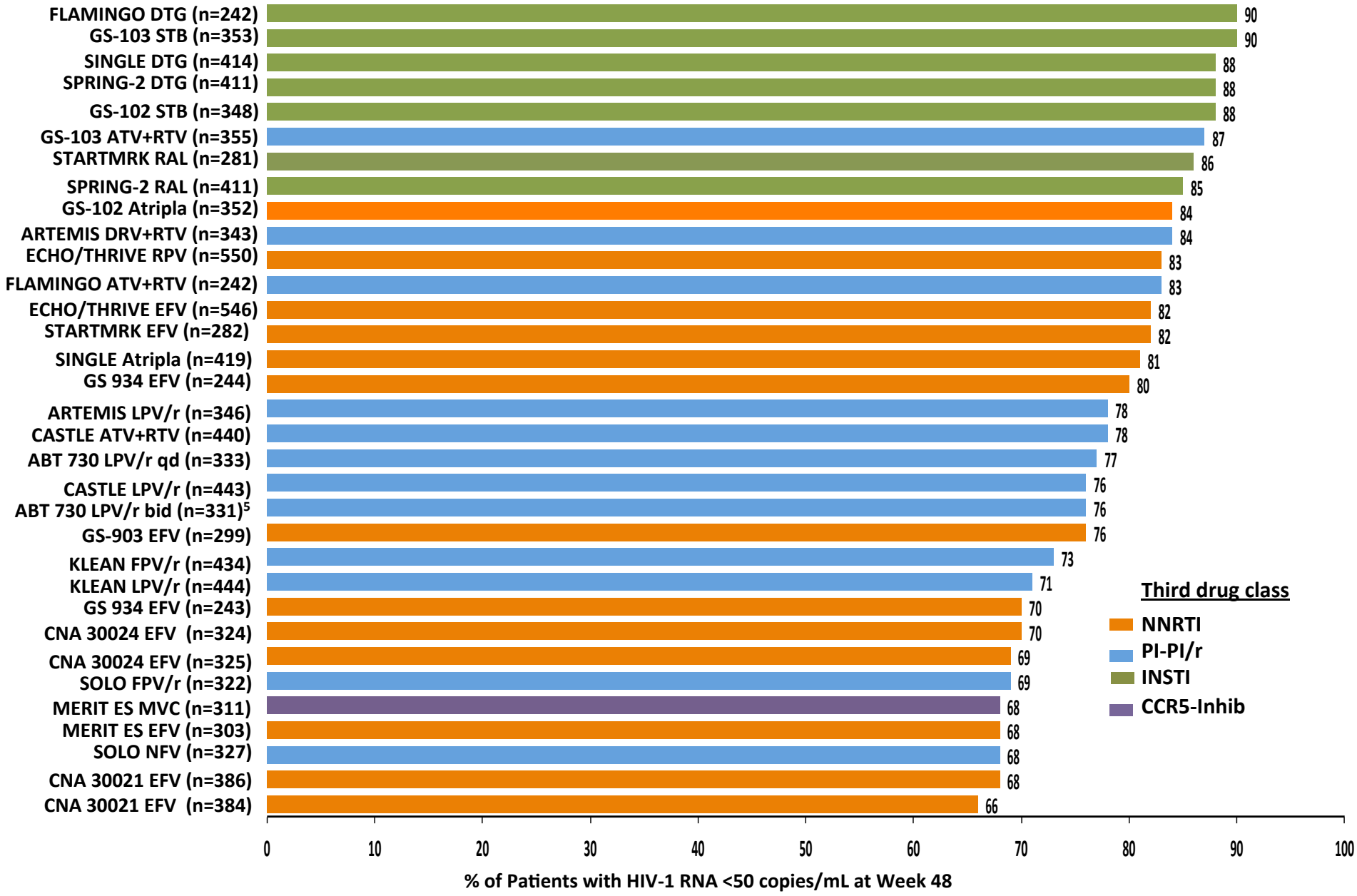
- EVG/COBI/TDF/FTC vs
  - EFV/TDF/FTC[1]
  - ATV/RTV + TDF/FTC[2-3]
- RPV/TDF/FTC vs
  - EFV + TDF/FTC (blinded)[4,5]
  - EFV/TDF/FTC (open label)[6]
- DTG vs
  - RAL[7]
  - EFV[8]
  - DRV/RTV[9]
- RAL vs ATV/RTV vs DRV/RTV[10]

- **Key results[1-10]**
  - High rate of virologic success in all arms
  - Superiority for INSTIs to EFV (DTG), DRV/r (DTG, RAL), ATV/r (RAL, EVG/c for women)
  - No comparative trial of RPV/TDF/FTC vs PI/r or INSTIs
  - Varying rates of resistance at failure; no resistance with boosted PIs and DTG
  - Lower rates of lipid perturbations with integrase inhibitors (not consistently for EVG/c) and RPV
  - More favorable tolerability profile with integrase inhibitors, RPV
  - Low drug interaction for integrase inhibitors (not for EVG/c)

1. Sax P, et al. Lancet. 2012;379:2439-2448. 2. DeJesus E, et al. Lancet. 2012;379:2429-2438. 3. Squires K, et al. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention. Vancouver, July 19-22, 2015. Abstract MOLBPE08. 4. Molina JM, et al. Lancet. 2011;378:238-246. 5. Cohen CJ, et al. Lancet 2011;378:229-237. 6. Cohen C, et al. AIDS 2014. Abstract WEPE064. 7. Raffi F, et al. Lancet. 2013;381:735-743. 8. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818. 9. Clotet B, et al. Lancet. 2014;383:2222-2231. 10. Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

Registrational Treatment-Naive Clinical Trials:
Cross-Study Comparison

HIV RNA <50 c/mL at Week 48



What to Start
Comparison of Updated 2013-2015 Guidelines

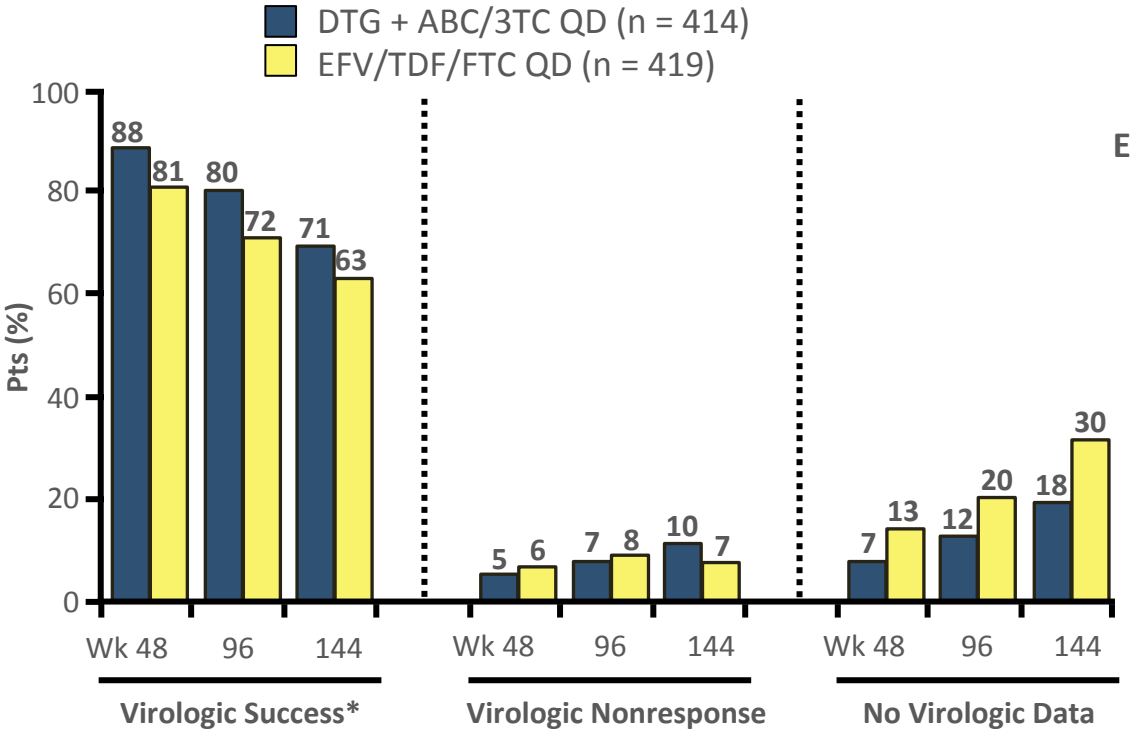
Regimen	CNA-SIMIT 2014[1]	DHHS 2015[2]	IAS 2014[3]	EACS 2014[4]	BHIVA 2015[5]	GESIDA 2015[6]	CNS-ANRS 2013[7]
EFV/TDF/FTC	Preferred	Alternative	Recommended	Recommended	Alternative	Alternative	Preferred
EFV + ABC/3TC	Preferred*	Other*	Recommended*	Recommended*	Alternative*	Other*	Preferred*
RPV/TDF/FTC	Preferred*	Alternative#	Recommended*	Recommended*	Preferred*	Alternative*	Preferred*
ATV/r + TDF/FTC	Preferred	Alternative	Recommended	Recommended	Preferred	Alternative	Preferred
ATV/r + ABV/3TC	Preferred*	Other*	Recommended*	Recommended*	Alternative*	Alternative*	Preferred*
DRV/r + TDF/FTC	Preferred	Recommended	Recommended	Recommended	Preferred	Alternative	Preferred
DRV/r + ABV/3TC	Preferred	Alternative	Alternative	Recommended	Alternative*	Other	Alternative
RAL + TDF/FTC	Preferred	Recommended	Recommended	Recommended	Preferred	Preferred	Alternative
RAL+ABV/3TC	Preferred	Other	Alternative	Recommended	Alternative	Alternative	Alternative
EVG/COBI/TDF/FTC	Preferred	Recommended	Recommended	Recommended	Preferred	Alternative	
DTG + TDF/FTC	Preferred	Recommended	Recommended		Preferred	Preferred	
DTG + ABV/3TC	Preferred	Recommended	Recommended		Preferred	Preferred	

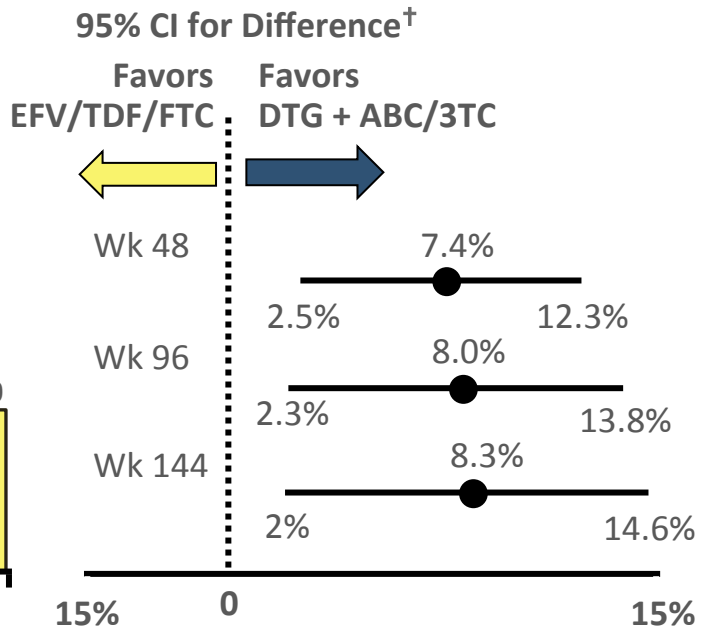
* Only if HIV-RNA <100.000 c/mL; # Only if HIV-RNA <100.000 c/mL and CD4 >200 cell/mm3.

1. Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1, 2014 Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1301_allegato.pdf;
2. DHHS Guidelines 2015 Available at http://aidsinfo.nih.gov/guidelines
3. ARV Treatment of Adult HIV Infection. 2012 Recommendation of the IAS-USA panel. JAMA 2014;312:410-425.
4. EACS Guidelines 2014. Available at http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_Treatment_of_HIV_Infected_Adults.pdf.
5. BHIVA guidelines for the treatment of HIV-positive adults with antiretroviral therapy 2015 (draft document).
6. GESIDA. Documento de consenso de Gesida/Plan Nacional sobre el SIDA respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana. Actualización enero 2015
7. CNS-ANRS. Prise en charge médicale des personnes vivant avec le HIV. Rapport 2013; Hoen B et al. Journal of the International AIDS Society 2014, 17:19034

SINGLE: DTG + ABC/3TC Superior to EFV/TDF/FTC in Tx-Naive Pts To Wk 144

- Emergent resistance in those with VF: 0/39 (DTG) vs 7/33 (EFV)

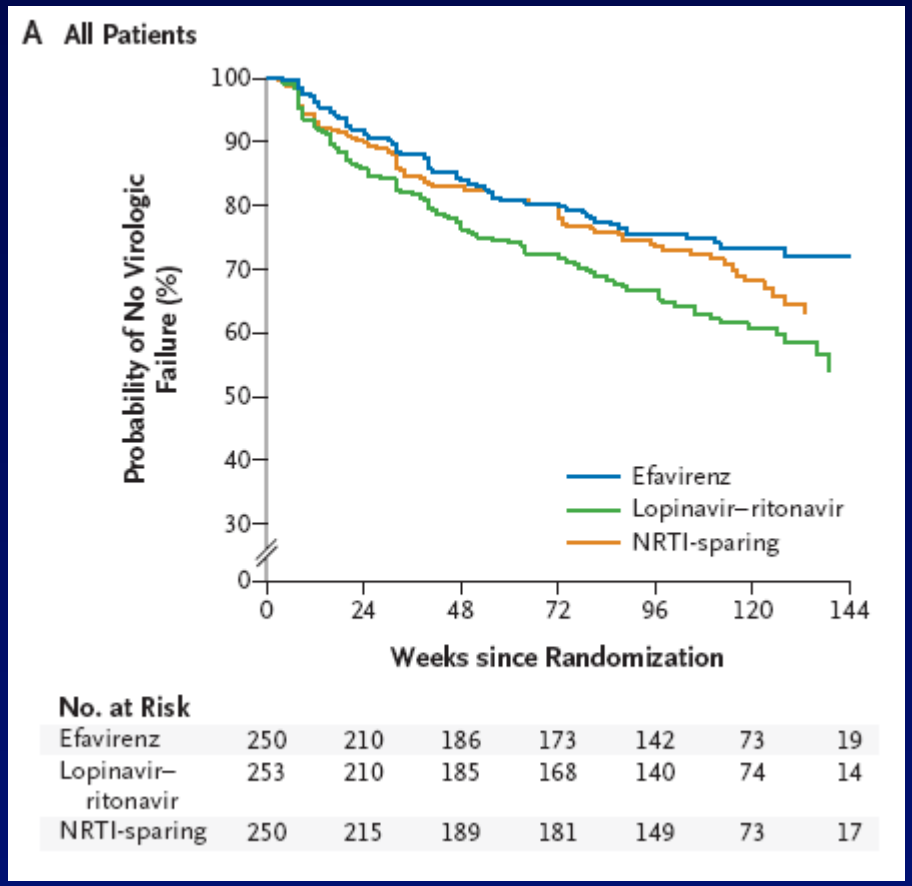




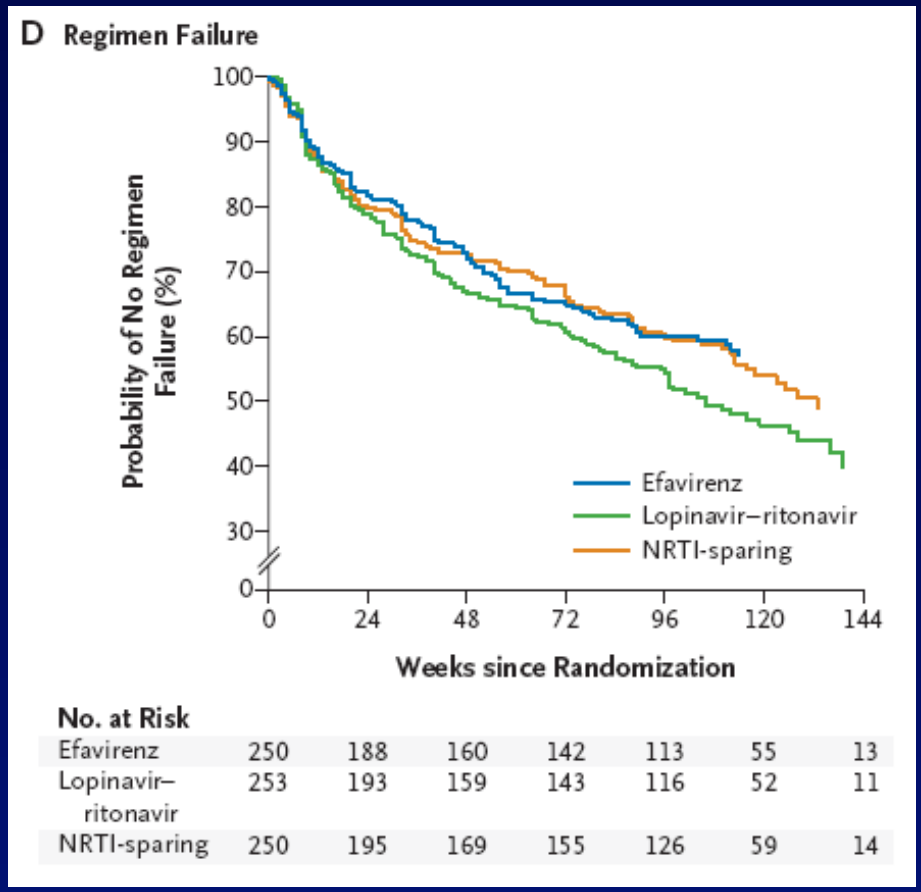
*HIV-1 RNA < 50 copies/mL as defined by FDA Snapshot algorithm.
†-10% noninferiority margin.
Pts with HBV infection were excluded from this study.

Pappa K, et al. ICAAC 2014. Abstract H-647a.

ACTG 5142 – Time-to-virological failure & time-to-regimen failure



No. at Risk							
Efavirenz	250	210	186	173	142	73	19
Lopinavir–ritonavir	253	210	185	168	140	74	14
NRTI-sparing	250	215	189	181	149	73	17

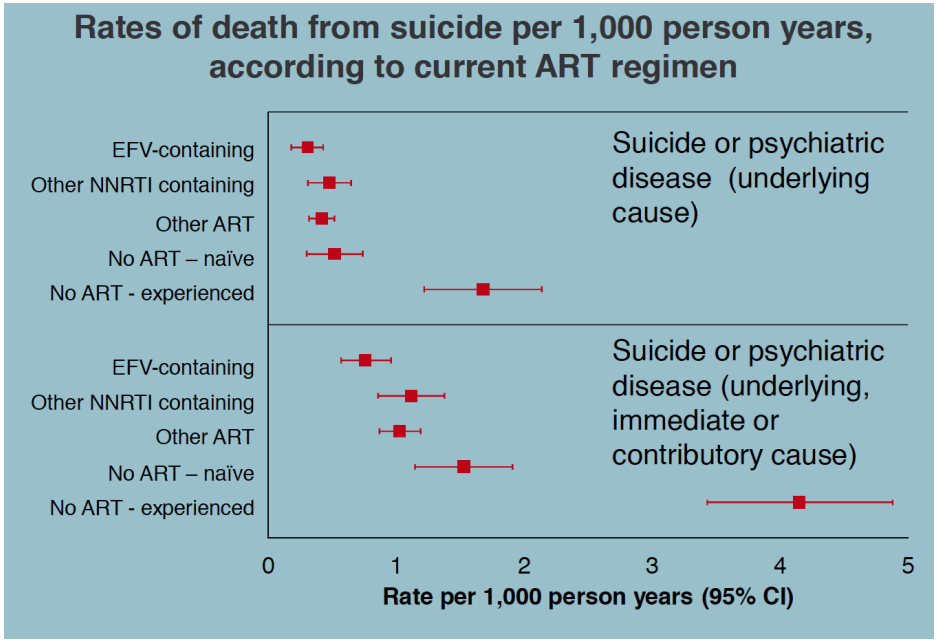


No. at Risk							
Efavirenz	250	188	160	142	113	55	13
Lopinavir–ritonavir	253	193	159	143	116	52	11
NRTI-sparing	250	195	169	155	126	59	14

Riddler SA, NEJM 2008

Lack of Association Between Use of Efavirenz and Death from Suicide[1]

- Analysis of the D:A:D study to investigate whether the association between use of EFV and death from suicide observed in the randomized clinical trial setting[2] is replicated in an observational setting
- N=49,717 with 371,333 person-years of follow-up. 193 deaths with underlying cause of suicide or psychiatric disease



Incidence Rate Ratios (IRR) for association between ART regimen and death from suicide/psychiatric disease

	Adjusted* IRR		
	IRR	95% CI	p-value†
Suicide or Psychiatric disease (underlying cause)			
EFV-containing	0.56	0.29, 1.07	<0.0001
Other NNRTI-containing	0.94	0.50, 1.77	
Other ART	0.76	0.43, 1.36	
No ART – naïve	1.00	-	
No ART – experienced	3.38	1.91, 5.97	

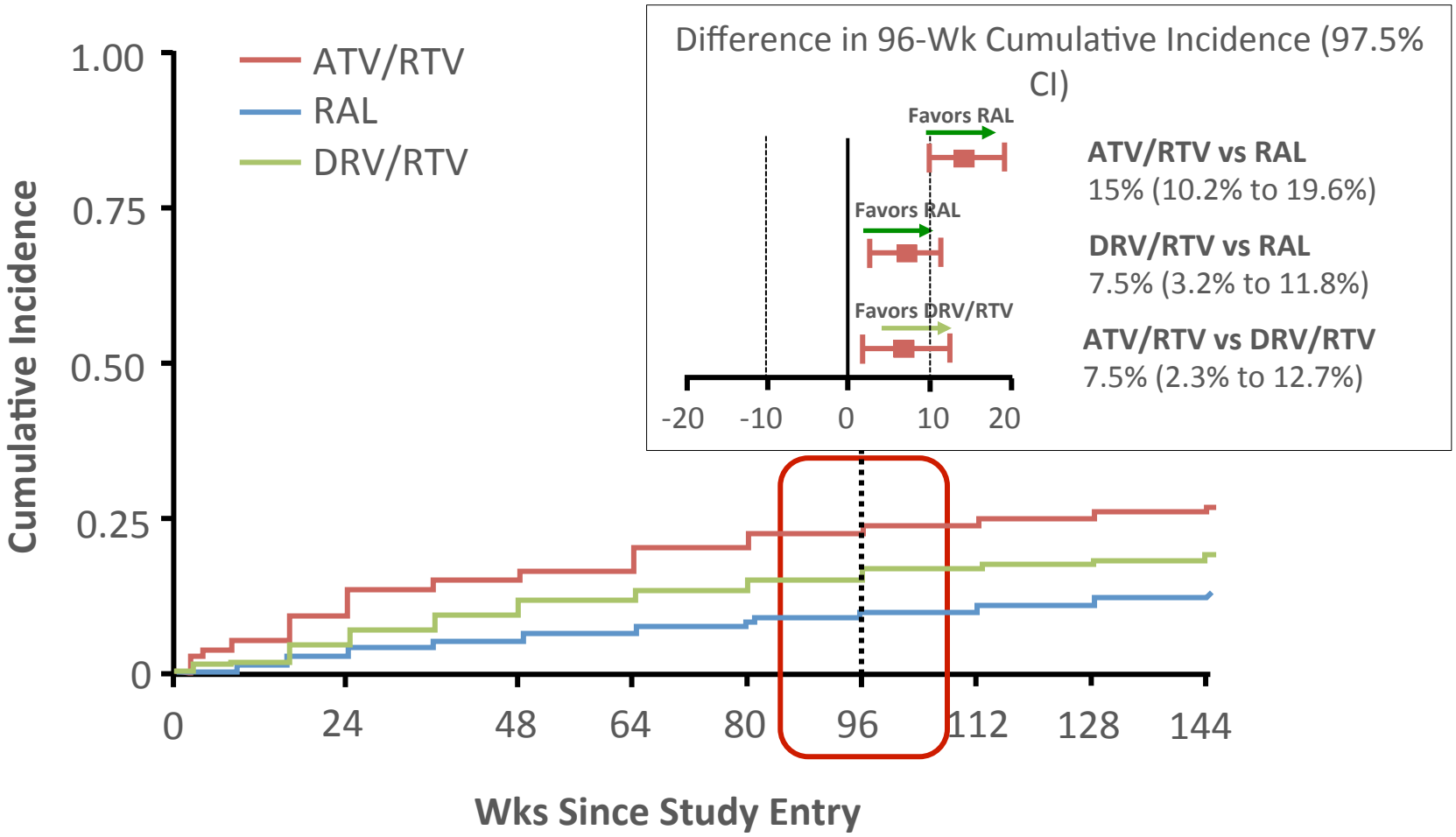
*adjusted for: nadir CD4, current CD4, age, gender, time since HIV diagnosis, cohort, previous clinical event, risk for HIV acquisition

† p-value relates to the global test investigating the different levels of the ART variable

In this observational setting, risk of death from suicide and related causes for individuals receiving EFV-based ART was similar to that in individuals receiving other ART regimens

1. Smith C, et al. Glasgow 2014. Poster #O315
2. Mollan KR, et al. Ann Intern Med. 2014;161:1-10

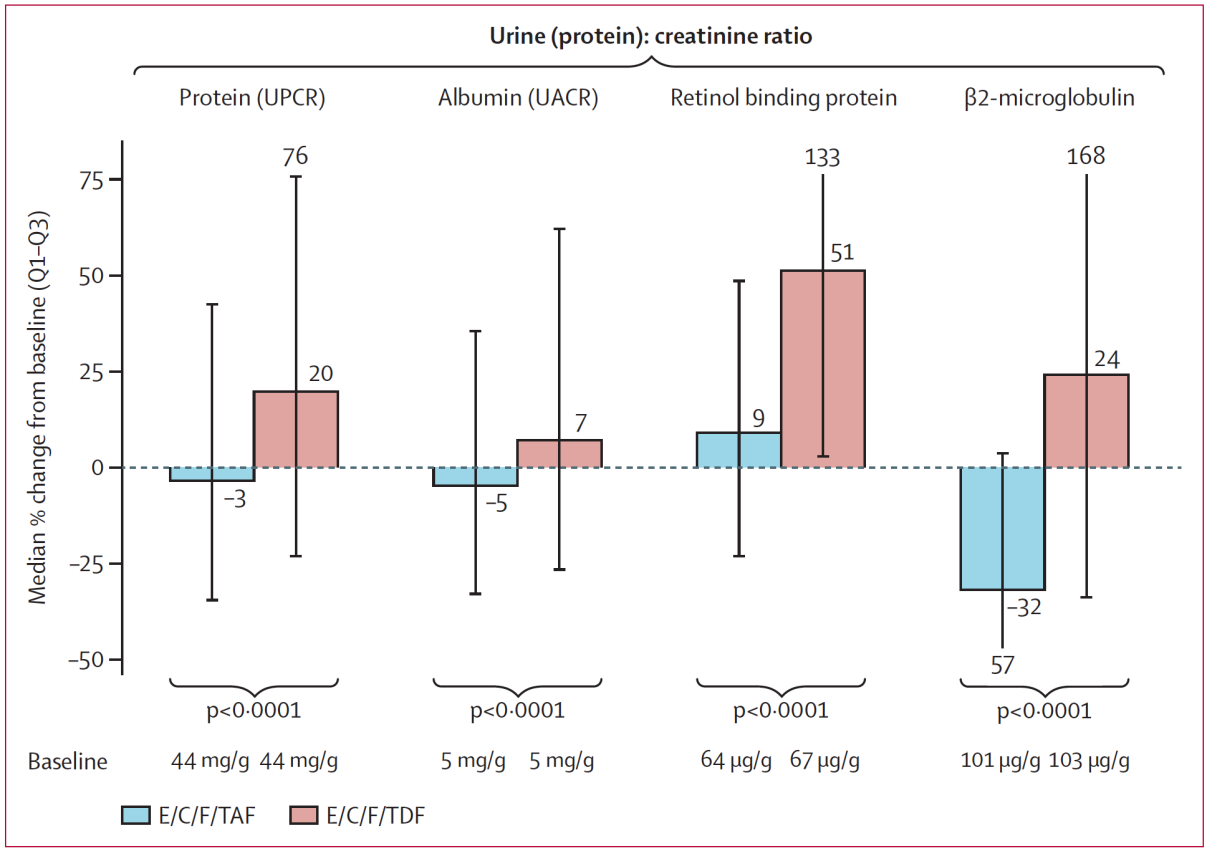
ACTG 5257: Cumulative Incidence of Virologic or Tolerability Failure at Wk 96



Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

GS 104 & 111 pooled analysis

Changes in quantitative proteinuria at week 48



At 48 weeks, quantitative proteinuria (**total urinary protein, albumin, retinol binding protein and β2-microglobulin to urine creatinine ratios**) increased from baseline in the E/C/F/TDF.

Reductions or significantly smaller increases in these urinary proteins were noted in the E/C/F/TAF group .

Other measures of proximal renal tubular function (**fractional excretion of phosphate and uric acid**) showed significantly less change in patients receiving E/C/F/TAF compared with the E/C/F/TDF.

Sax PE, et al. Lancet, 2015

ORIGINAL ARTICLE

Substitution of Nevirapine, Efavirenz, or Abacavir for Protease Inhibitors in Patients with Human Immunodeficiency Virus Infection

Esteban Martínez, M.D., Juan A. Arnaiz, M.D., Daniel Podzamczer, M.D., David Dalmau, M.D., Esteban Ribera, M.D., Pere Domingo, M.D., Hernando Knobel, M.D., Melcior Riera, M.D., Enric Pedrol, M.D., Lluis Force, M.D., Josep M. Llibre, M.D., Ferran Segura, M.D., Cristóbal Richart, M.D., Cristina Cortés, M.D., Manuel Javaloyas, M.D., Miquel Aranda, M.D., Ana Cruceta, M.D., Elisa de Lazzari, B.Sc., and José M. Gatell, M.D., for the Nevirapine, Efavirenz, and Abacavir (NEFA) Study Team*

From the Hospital Clínic, Barcelona (E.M., J.A.A., A.C., E.L., J.M.G.); Hospital de Bellvitge, L'Hospitalet (D.P.); Hospital de Mútua de Terrassa, Terrassa (D.D.); Hospital de Vall d'Hebrón, Barcelona (E.R.); Hospital de la Santa Creu i Sant Pau, Barcelona (P.D.); Hospital del Mar, Barcelona (H.K.); Hospital Son Dureta, Palma de Mallorca (M.R.); Hospital General de Granollers, Granollers (E.P.); Hospital de Mataró, Mataró (L.F.); Hospital Sant Jaume, Calella (J.M.L.); Hospital Parc Taulí, Sabadell (F.S.); Hospital Joan XXIII–Universitat Rovira i Virgili, Tarragona (C.R.); Hospital Creu Roja, L'Hospitalet (C.C.); Hospital de Viladecans, Viladecans (M.J.); and Hospital de Terrassa, Terrassa (M.A.) — all in Spain. Address reprint requests to Dr. Martinez at the Infectious Diseases Unit, Hospital Clinic–Institut d'Investigacions Biomediques August Pi i Sunyer, University of Barcelona, Villarroel 170, 08036 Barcelona, Spain, or at esteban@ fundsoriano.es.

*Members of the NEFA Study Team are listed in the Appendix.

N Engl J Med 2003;349:1036-46.

ABSTRACT

BACKGROUND

We assessed the strategy of substituting nevirapine, efavirenz, or abacavir for a protease inhibitor in patients infected with human immunodeficiency virus type 1 (HIV-1) in whom virologic suppression had been achieved.

METHODS

We randomly assigned 460 adults who were taking two nucleoside reverse-transcriptase inhibitors and at least one protease inhibitor and whose plasma HIV-1 RNA levels had been less than 200 copies per milliliter for at least the previous six months to switch from the protease inhibitor to nevirapine (155 patients), efavirenz (156), or abacavir (149). The primary end point was death, progression to the acquired immunodeficiency syndrome, or an increase in HIV-1 RNA levels to 200 copies or more per milliliter.

RESULTS

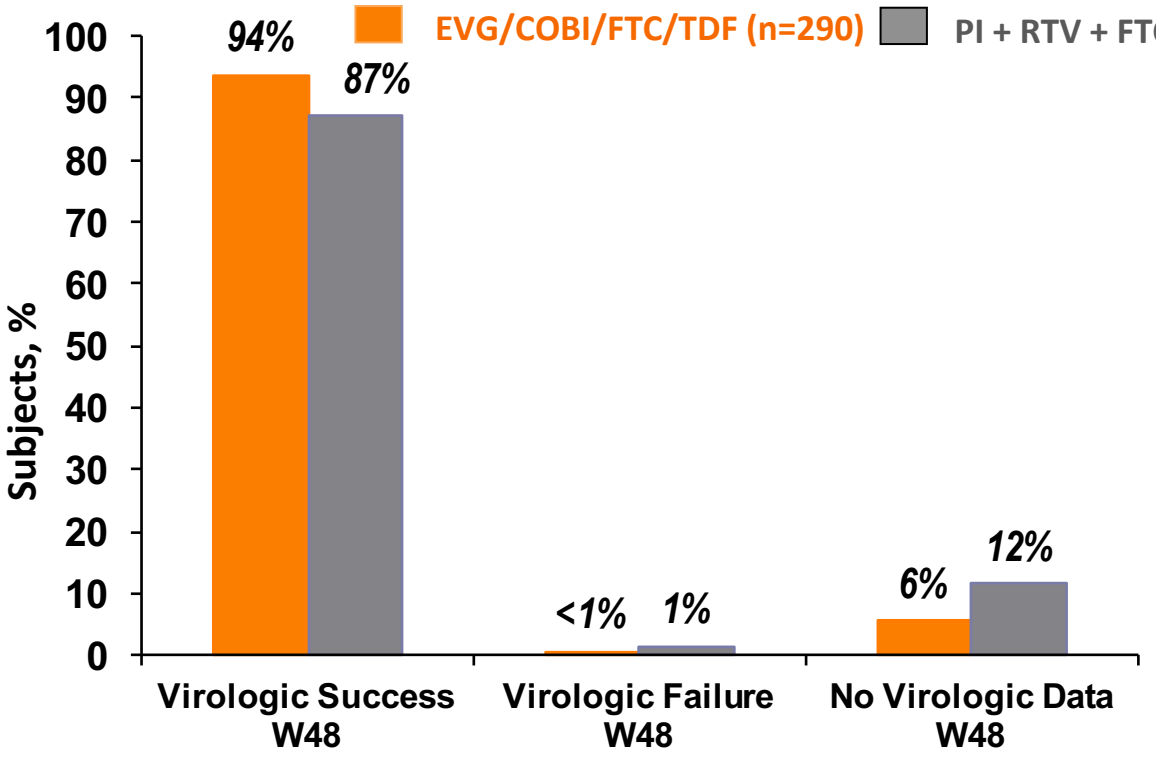
At 12 months, the Kaplan–Meier estimates of the likelihood of reaching the end point were 10 percent in the nevirapine group, 6 percent in the efavirenz group, and 13 percent in the abacavir group (P=0.10 according to an intention-to-treat analysis). HIV-1 RNA could be amplified in 21 of the 29 patients in whom virologic failure developed during treatment with study medication (72 percent), and resistance mutations to the study medication and to at least one of the nucleoside reverse-transcriptase inhibitors in the regimen that failed were detected in all but 1 of the 21 patients. Twenty-three of the 29 patients with virologic failure during treatment with study medication had received prior suboptimal therapy with nucleoside reverse-transcriptase inhibitors. Fewer patients in the abacavir group (6 percent) than in the nevirapine group (17 percent) or the efavirenz group (17 percent) discontinued the study medication because of adverse events (P=0.01). The proportion of patients with fasting lipid levels warranting therapeutic intervention decreased significantly in the abacavir group, but the prevalence of clinical lipodystrophy did not change significantly in the three groups.

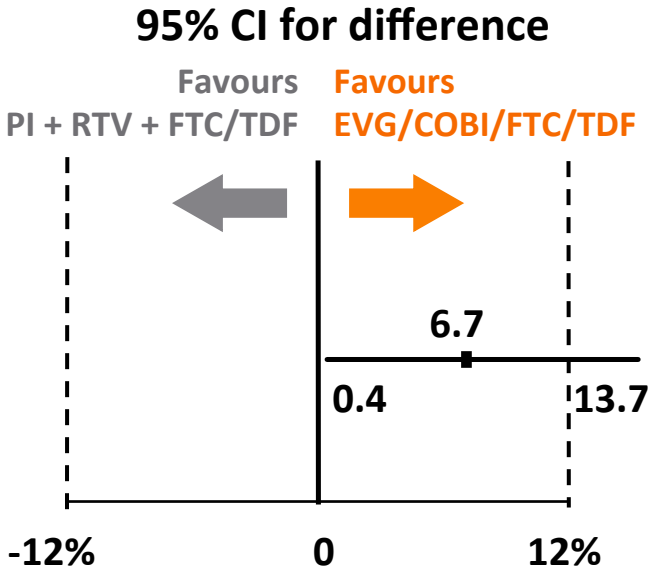
CONCLUSIONS

When therapy was switched from a protease inhibitor to nevirapine, efavirenz, or abacavir in patients with virologic suppression, there was a trend toward a higher rate of virologic failure among those given abacavir.

STRATEGY – PI

Primary Endpoint: HIV-1 RNA <50 c/mL: Week 48





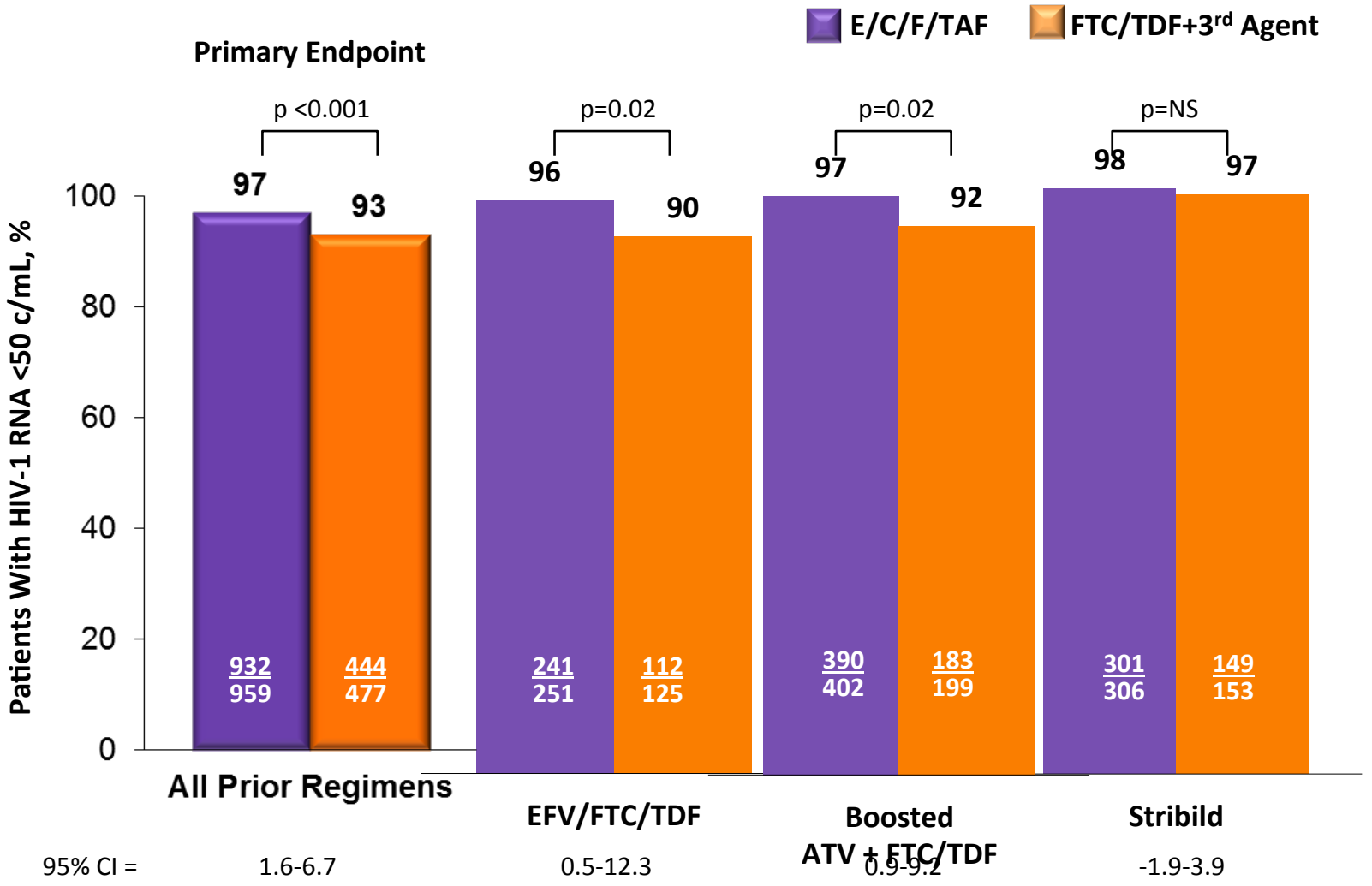
Prespecified sequential testing
Statistical superiority (*P*=0.025)

CD4 Cell Count (cells/mm³)	Baseline (mean)	ΔWeek 48 (mean)	*P*-value (Δ W48 - BL)
EVG/COBI/FTC/TDF	603	+40	<0.001
PI + RTV + FTC/TDF	625	+32	=0.025

Arribas JR, et al. CROI 2014; Boston, MA. #551LB; Arribas JR, et al. Lancet Infect Dis. 2014 Jul;14(7):581-9.

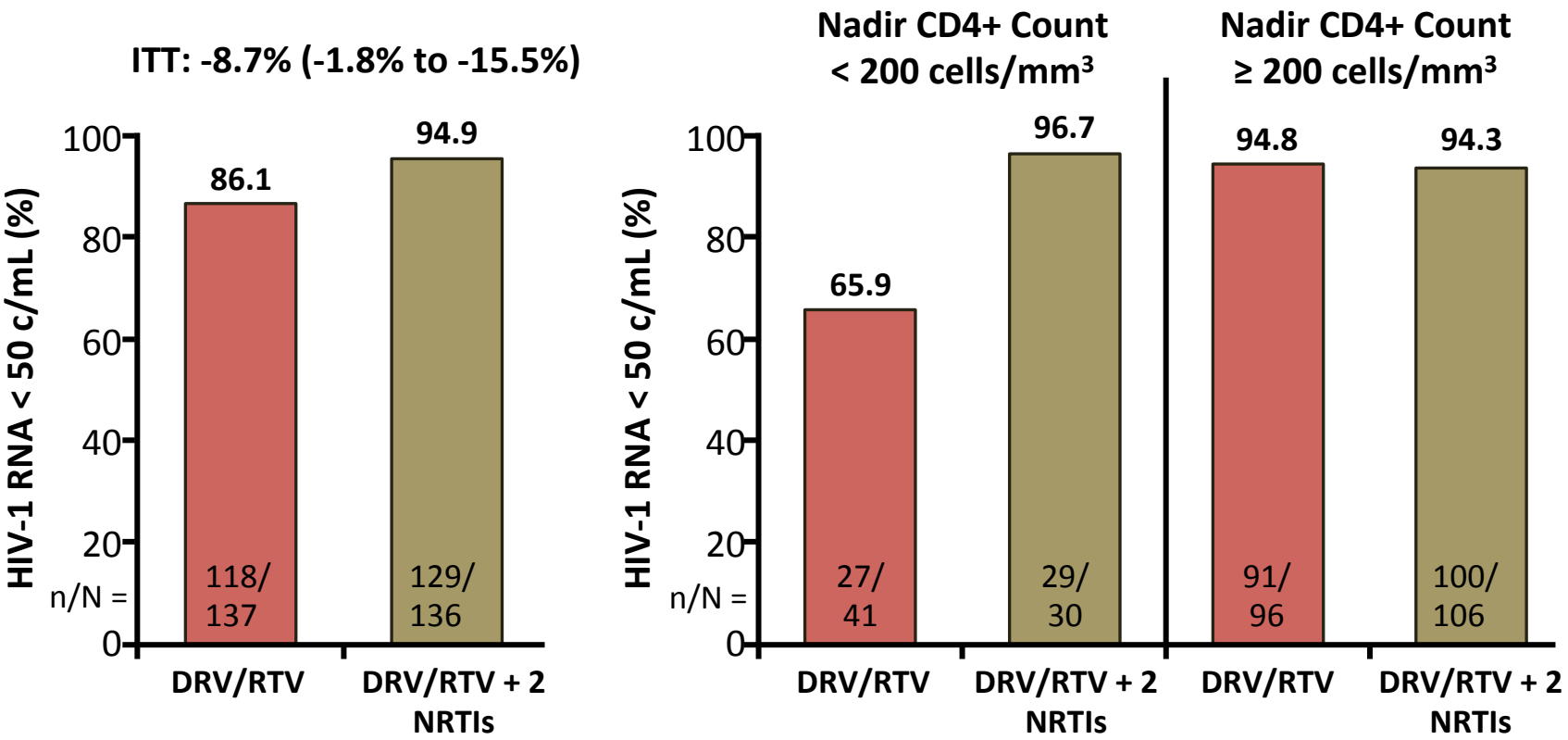
Study 109: Suppressed Adults Switched from a TDF-containing regimen to E/C/F/TAF

Virologic Outcome: By Prior FTC/TDF-Based Regimens



Mills A, et al. IAS 2015, Vancouver, Canada. Oral # TUAB0102

PROTEA: Virologic Response at Wk 48



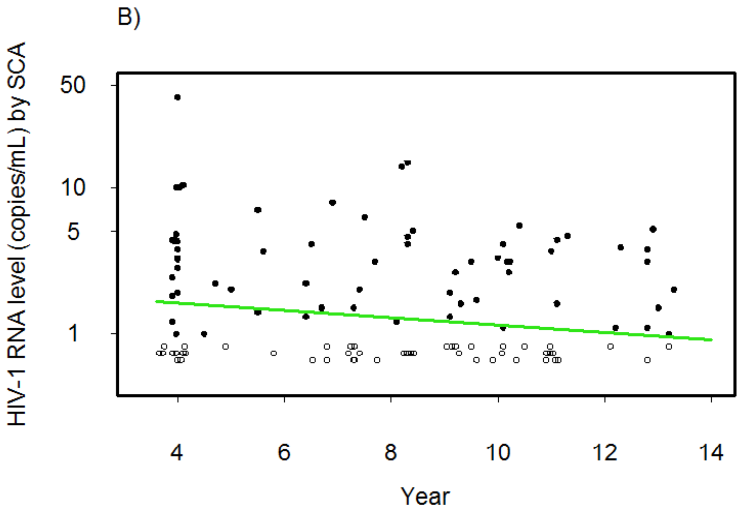
- No difference in efficacy between treatment arms in "switch included" analysis that classified pts with viral suppression at Wk 48 after reintensification or second switch as virologic responders.

Antinori A, et al. Glasgow HIV 2014. Abstract O423A. Clarke A, et al. Glasgow HIV 2014. Abstract O423B. Antinori A, et al. AIDS 2015;29(14):1811-1820.

Continued decay of plasma HIV-1 RNA after 4 years of cART

Continued decay of plasma HIV-1 RNA was observed, averaging 6% decline per year and with an estimated half-life of 11.5 years. In contrast to prior reports, persistent viremia continues to slowly decline during years 4-12 of suppressive ART.

Residual viremia ≥1 copy/mL after 4 years of ART was predicted by higher pre-ART HIV-1 RNA, higher on-treatment CD8 cell count, and lower on-treatment CD4/CD8 ratio, but not by initial ART regimen.



Predictor	N	Unadjusted		Adjusted for pre-ART HIV-1 RNA	
		OR [95% CI]	P-value	OR [95% CI]	P-value
Pre-ART HIV-1 RNA (log$_{10}$ copies/ml)	668	**1.79 [1.32, 2.42]**	**<0.001**		
Pre-ART CD4+ T-cell count (per 100 cells/mm^3)	668	0.91 [0.83, 1.00]	0.053	0.98 [0.89, 1.08]	0.63
Pre-ART CD8+ T-cell count (per 100 cells/mm^3)	668	1.01 [0.98, 1.05]	0.45	1.02 [0.99, 1.06]	0.21
Pre-ART CD4/CD8 ratio (per 0.5 higher)	668	0.71 [0.37, 1.36]	0.30	0.83 [0.56, 1.22]	0.34
Age at Parent study entry (per 10 years)	668	1.09 [0.92, 1.29]	0.35	1.07 [0.90, 1.28]	0.41
On-treatment CD4+ T-cell count (per 100 cells/mm^3)	664	0.99 [0.92, 1.07]	0.88	1.02 [0.95, 1.10]	0.53
On-treatment CD8+ T-cell count (per 100 cells/mm^3)	664	**1.07 [1.02, 1.12]**	**0.008**	**1.06 [1.01, 1.11]**	**0.014**
On-treatment CD4/CD8 ratio (per 0.5 higher)	664	**0.72 [0.58, 0.90]**	**0.004**	**0.78 [0.63, 0.98]**	**0.031**
Sex: Female (vs. Male)	668	0.70 [0.44, 1.11]	0.13	0.69 [0.44, 1.10]	0.12
Initial ART regimen:	668				0.19
PIs+NRTIs (vs NNRTIs+NRTIs)		1.16 [0.79, 1.71]	0.45	1.30 [0.88, 1.92]	0.91
Other (vs. NNRTIs+NRTIs)		1.06 [0.60, 1.87]	0.83	1.03 [0.58, 1.85]	
Race/Ethnicity	668				0.68
Hispanic (vs. white non-Hispanic)		0.89 [0.57, 1.39]	0.60	0.91 [0.58, 1.42]	0.41
Black non-Hispanic (vs. white)		0.79 [0.52, 1.20]	0.26	0.83 [0.54, 1.28]	0.78
Other (vs. white)		1.17 [0.31, 4.39]	0.82	1.21 [0.31, 4.84]	
IV Drug Use: Previously (vs. Never)	668	1.08 [0.56, 2.07]	0.82	1.13 [0.59, 2.18]	0.71

N is the number of observations in the model (2 values per participant); OR: Odds Ratio

On-treatment: average of values at Weeks 192 and 208

Riddler SA, et al. J Infect Dis, 2015

Seminario Nadir 2015 - Iniziativa resa possibile grazie al supporto di ViiV Healthcare

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