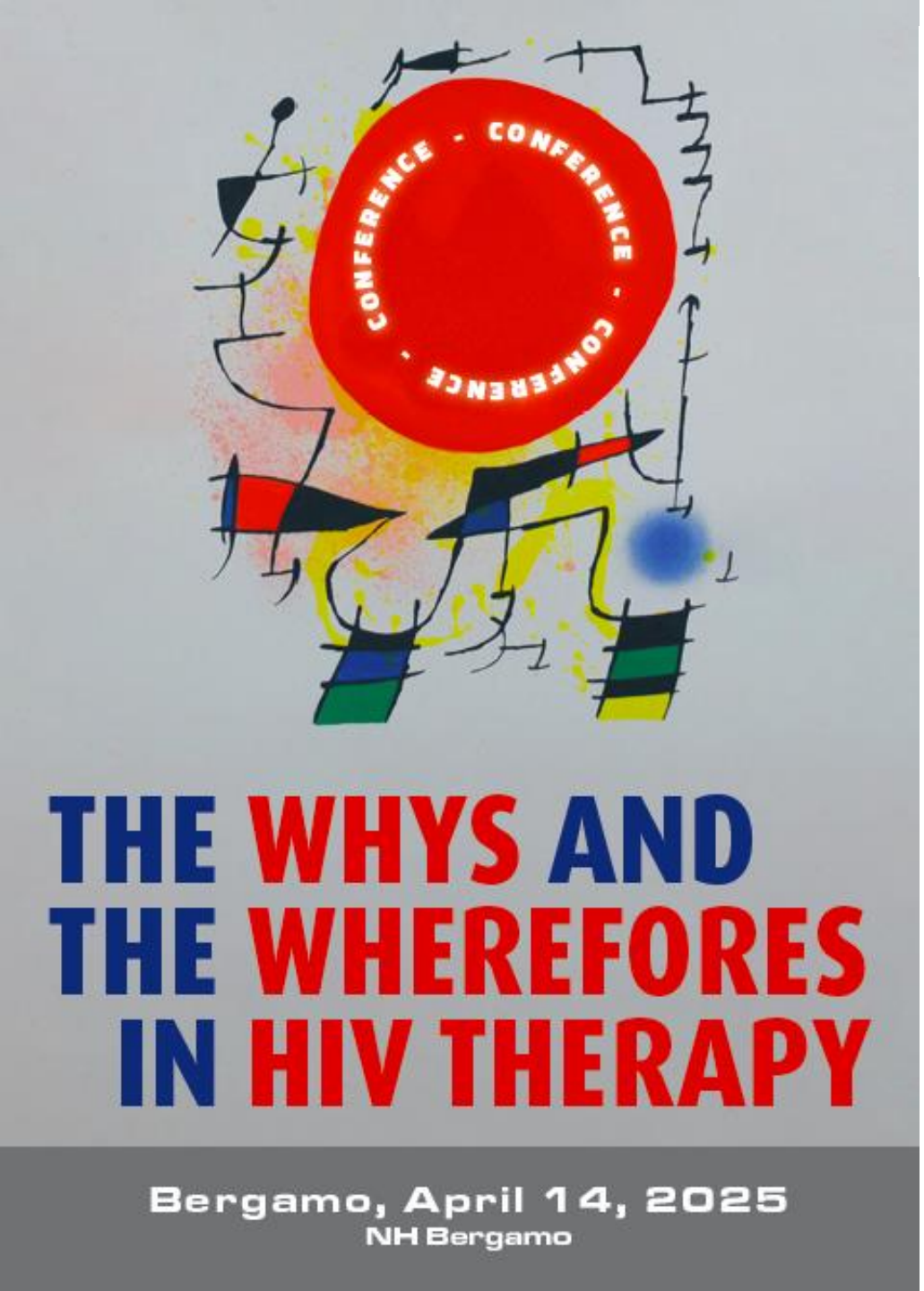

Benefits achieved by the intensification strategy in the HIV therapy

Annamaria Cattelan

UOC Malattie Infettive e Tropicali

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What is Intensification of Antiretroviral Therapy?

- Addition of a new antiretroviral agent to enhance viral suppression and/or immunological recovery to improve patient's outcomes

Andrea, 35-yr-old Italian male

He was admitted to our Infectious Diseases Unit on January 18th, 2021, for fever, persistent diarrhoea, vomiting, nausea and 12 kg loss over the last month.

[Social information]

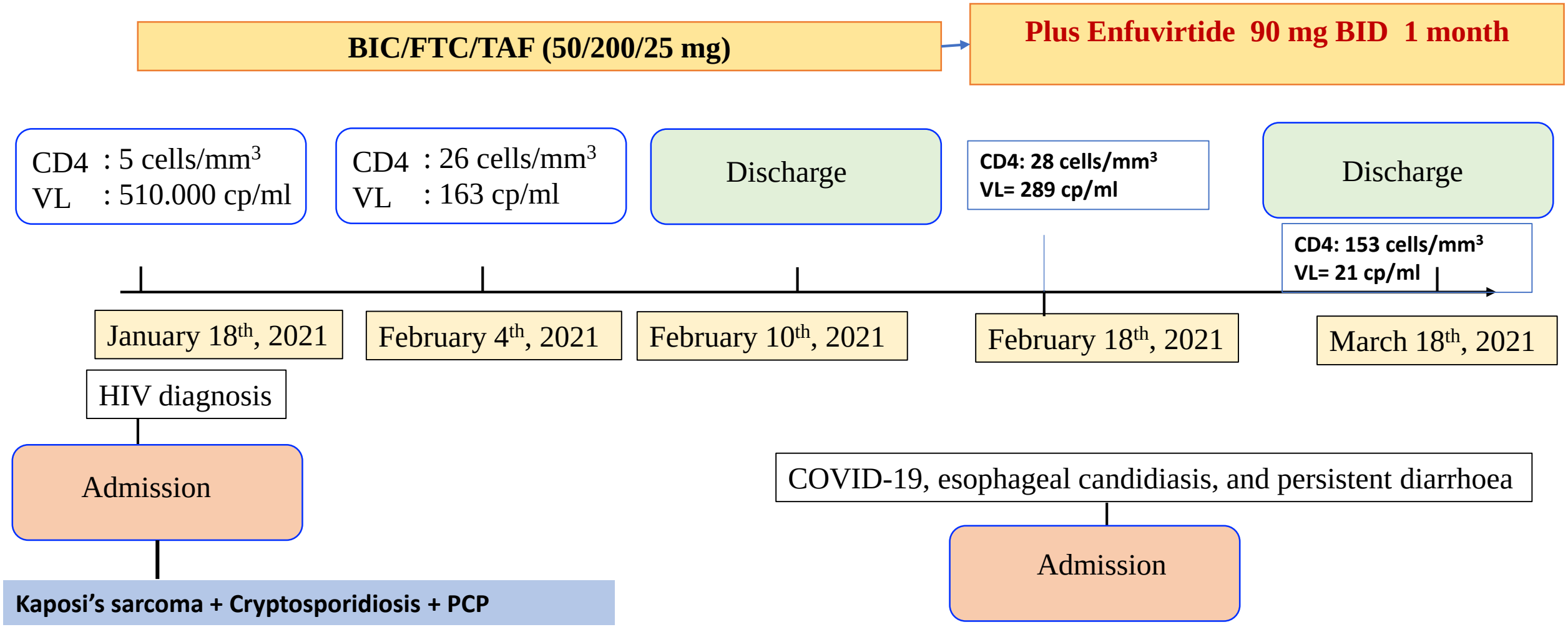
- MSM, smoker, recreational use of cannabis/cocaine and alcohol

High education level (he worked in the Chancellor's office)

[Past medical history]

- Nothing remarkable

Antiretrovirals and viro-immunological profile



What is Intensification of Antiretroviral Therapy?

- Addition of a new antiretroviral agent to enhance viral suppression and/or immunological recovery to improve patient's outcomes

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Antiretroviral Guidelines:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed [insert date] [insert page number, table number, etc., if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the ClinicalInfo website (https://clinicalinfo.hiv.gov).

Poor CD4 Cell Recovery and Persistent Inflammation Despite Viral Suppression

Updated: May 26, 2021
Reviewed: May 26, 2021

Key Considerations and Recommendations

- Persistently low CD4 T lymphocyte (CD4) cell counts and immune activation are each associated with increased AIDS- and non-AIDS-related morbidity and mortality among individuals with antiretroviral therapy (ART)-mediated viral suppression.
- Adding antiretroviral (ARV) drugs to a suppressive ARV regimen (ART intensification) does not improve CD4 cell recovery or reduce immune activation and, therefore, **is not recommended (AI).**
- In individuals with viral suppression, switching ARV drug classes does not consistently improve CD4 cell recovery or reduce all relevant markers of immune activation and **is not recommended (BIII).**
- Interleukin-2 **is not recommended (AI)** to increase CD4 cell counts and/or decrease immune activation, because clinical trial data demonstrated no clinical benefit.
- Other interventions designed to increase CD4 cell counts and/or decrease immune activation **are not recommended** outside of a clinical trial, because no current interventions have been proven to decrease morbidity or mortality during ART-mediated viral suppression **(AII).**
- Efforts to decrease morbidity and mortality during ART-mediated viral suppression should focus on addressing modifiable risk factors for chronic disease (e.g., encouraging smoking cessation, a healthy diet, and regular exercise; treating hypertension and hyperlipidemia).
- Monitoring markers of immune activation and inflammation is not recommended, because no intervention targeting immune pathways has proven to improve the health of individuals with HIV, and many blood markers that predict morbidity and mortality fluctuate within individuals **(AII).**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Scenarios for ART intensification

- ✓ **Persistent low-level viremia**
- ✓ **Immune activation or slow CD4 recovery**
- ✓ **Persistent inflammation**
- ✓ **Drug resistance**

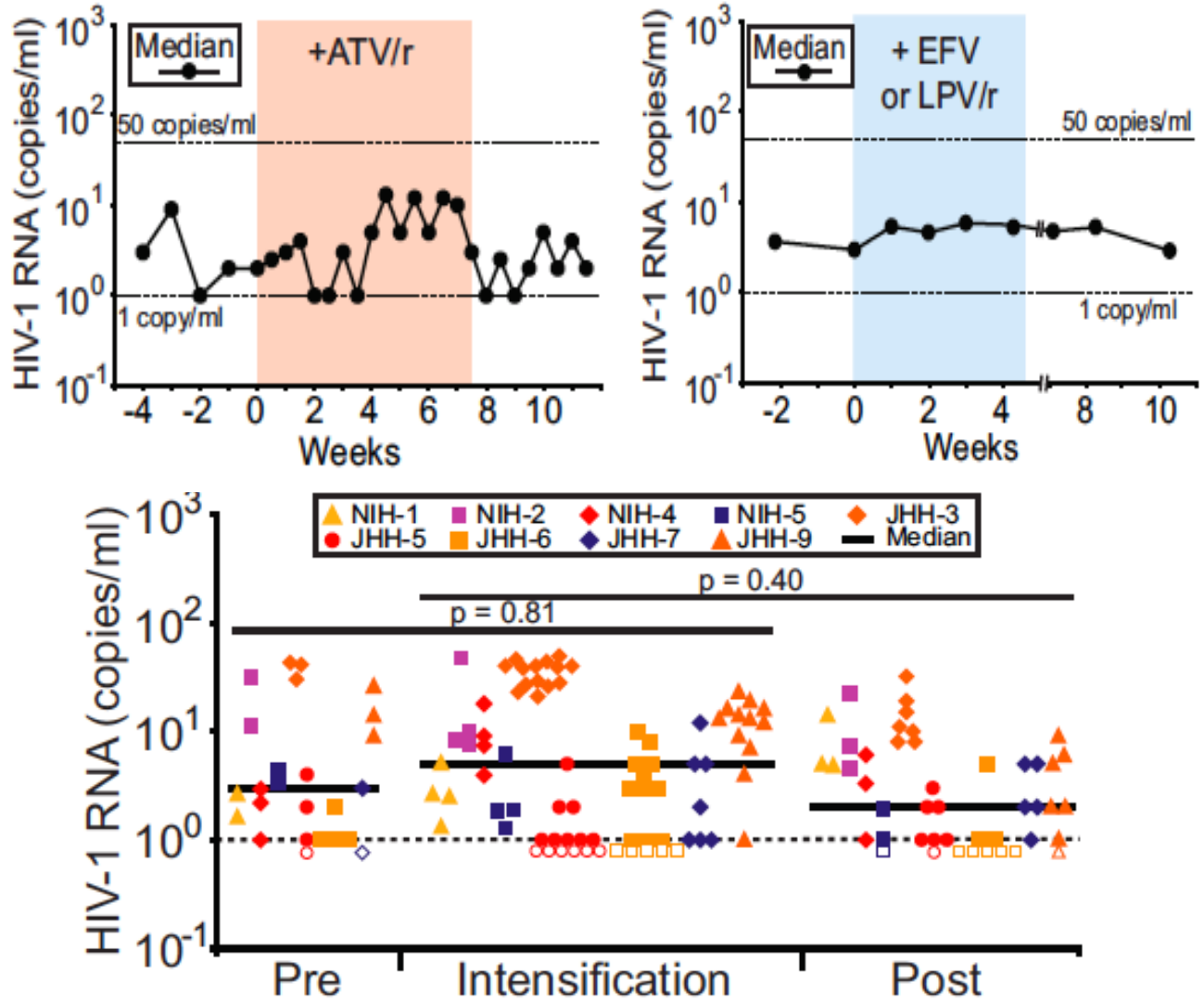
Intensification: common approaches

- ✓**Adding integrase inhibitors (e.g., raltegravir, dolutegravir)**
- ✓**Adding CCR5 antagonists (maraviroc)**
- ✓**New strategies including new non-direct antiviral agents, such as Broadly neutralizing antibodies (bNAbs)**

…….One suspects that pending addition of another antiretroviral drug class, a new round of intensification studies will commence.
(Timothy J Henrich, Lancet HIV 2018)

Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy

In HIV-1-infected individuals on currently recommended antiretroviral therapy (ART), viremia is reduced to <50 copies of HIV-1 RNA per milliliter, but low-level residual viremia appears to persist over the lifetimes of most infected individuals. There is controversy over whether the residual viremia results from ongoing cycles of viral replication. To address this question, we conducted 2 prospective studies to assess the effect of ART intensification with an additional potent drug on residual viremia in 9 HIV-1-infected individuals on successful ART. By using an HIV-1 RNA assay with single-copy sensitivity, we found that levels of viremia were not reduced by ART intensification with any of 3 different antiretroviral drugs (efavirenz, lopinavir/ritonavir, or atazanavir/ritonavir). The lack of response was not associated with the presence of drug-resistant virus or suboptimal drug concentrations. Our results suggest that residual viremia is not the product of ongoing, complete cycles of viral replication, but rather of virus output from stable reservoirs of infection.

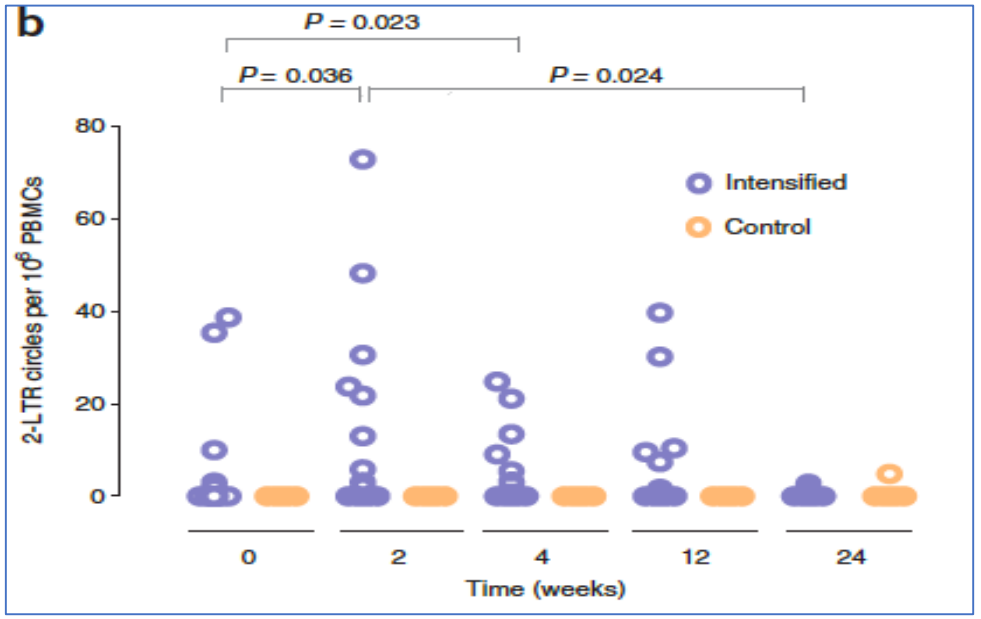


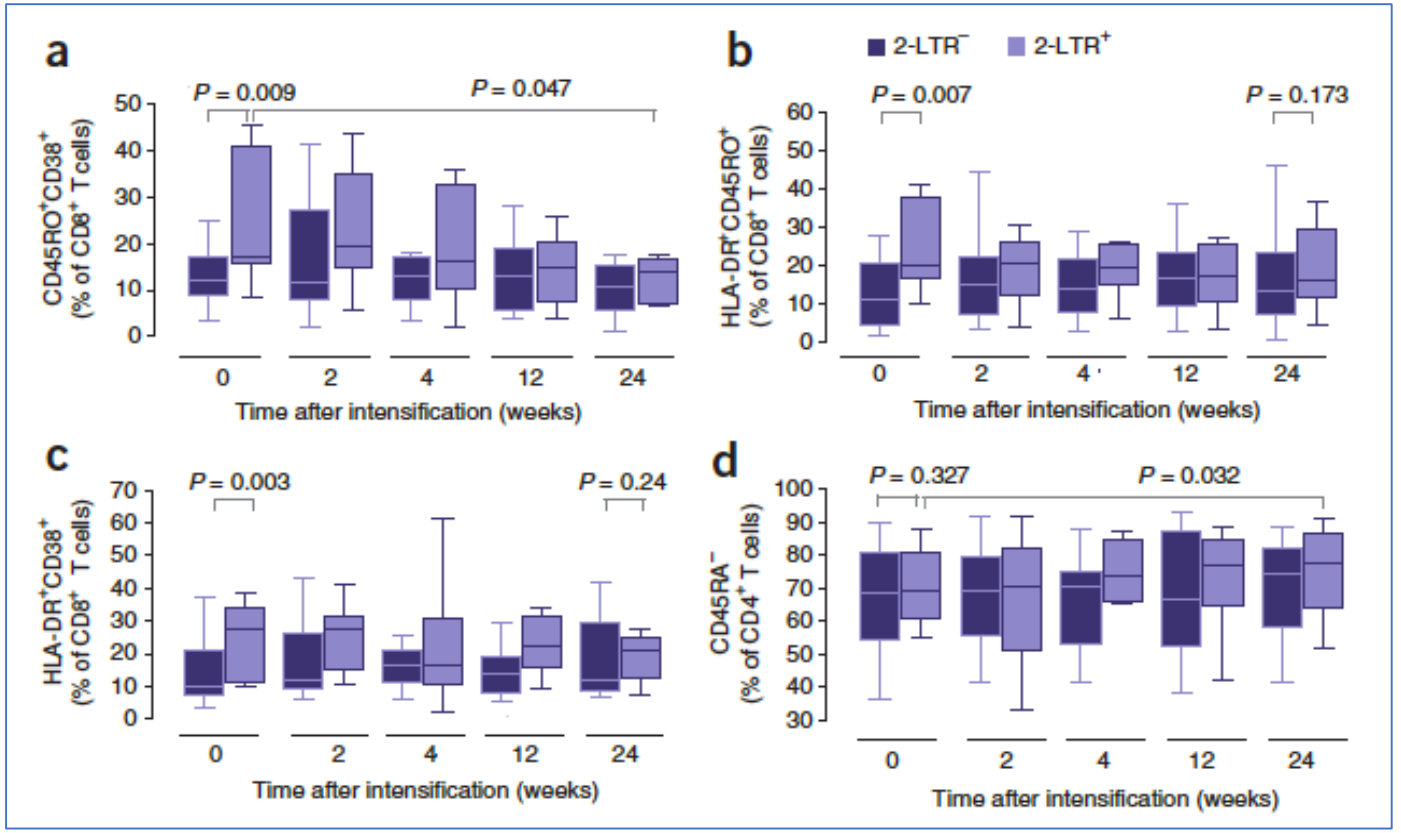
PNAS 2009; 106: 9403–9408

HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

nature medicine

Study design: open label study i which 69 HIV+ subjects on suppressive HAART for at least one year were randomly assigned 45 subjects to a treatment intensification with raltegravir (45 pts) for 48 weeks and 24 subjects served as a control arm





Raltegravir intensification of a three-drug suppressive HAART regimen resulted in a specificand transient increase in episomal DNAs in a large percentage of HAART-suppressed subjects. Furthermore, in subjects with these episomal DNAs, immune activation was higher at baseline and was subsequently normalized after raltegravir intensification.

Nat Med, 2010; 4: 460-66

The Effect of Raltegravir Intensification on Low-level Residual Viremia in HIV-Infected Patients on Antiretroviral Therapy: A Randomized Controlled Trial

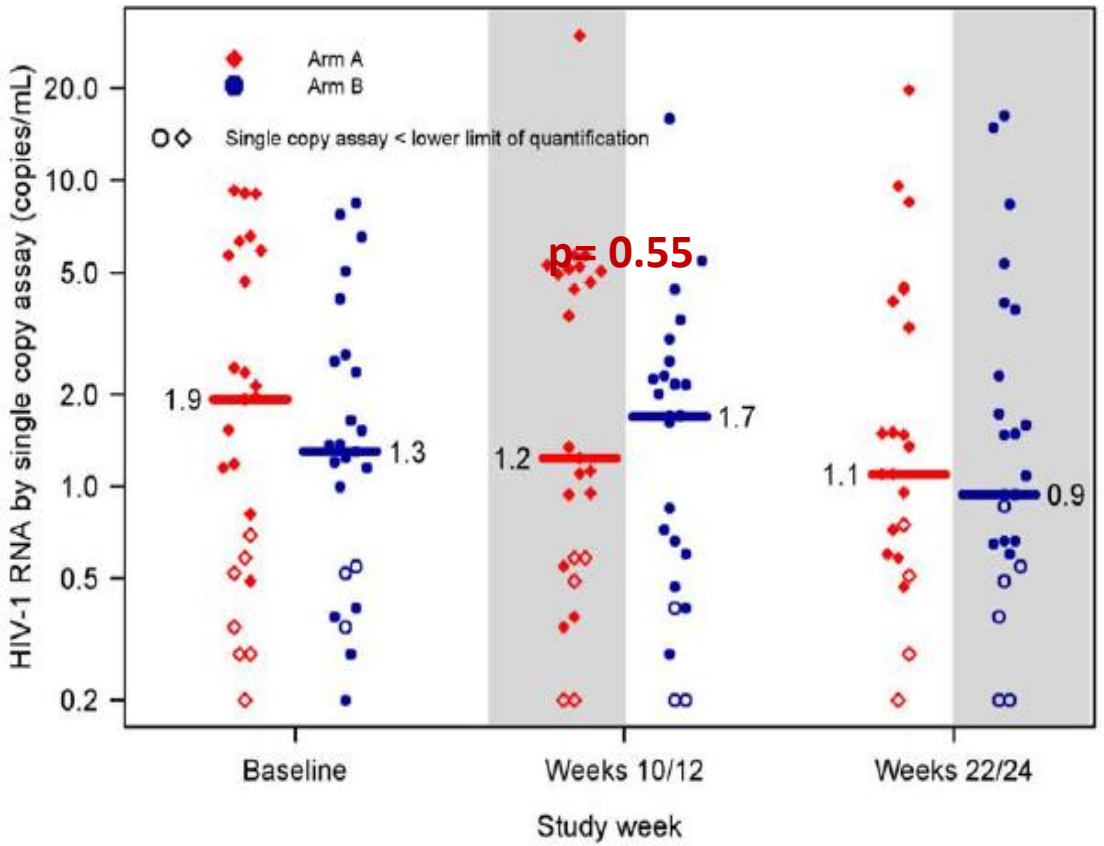
ACTG 5244 Trial

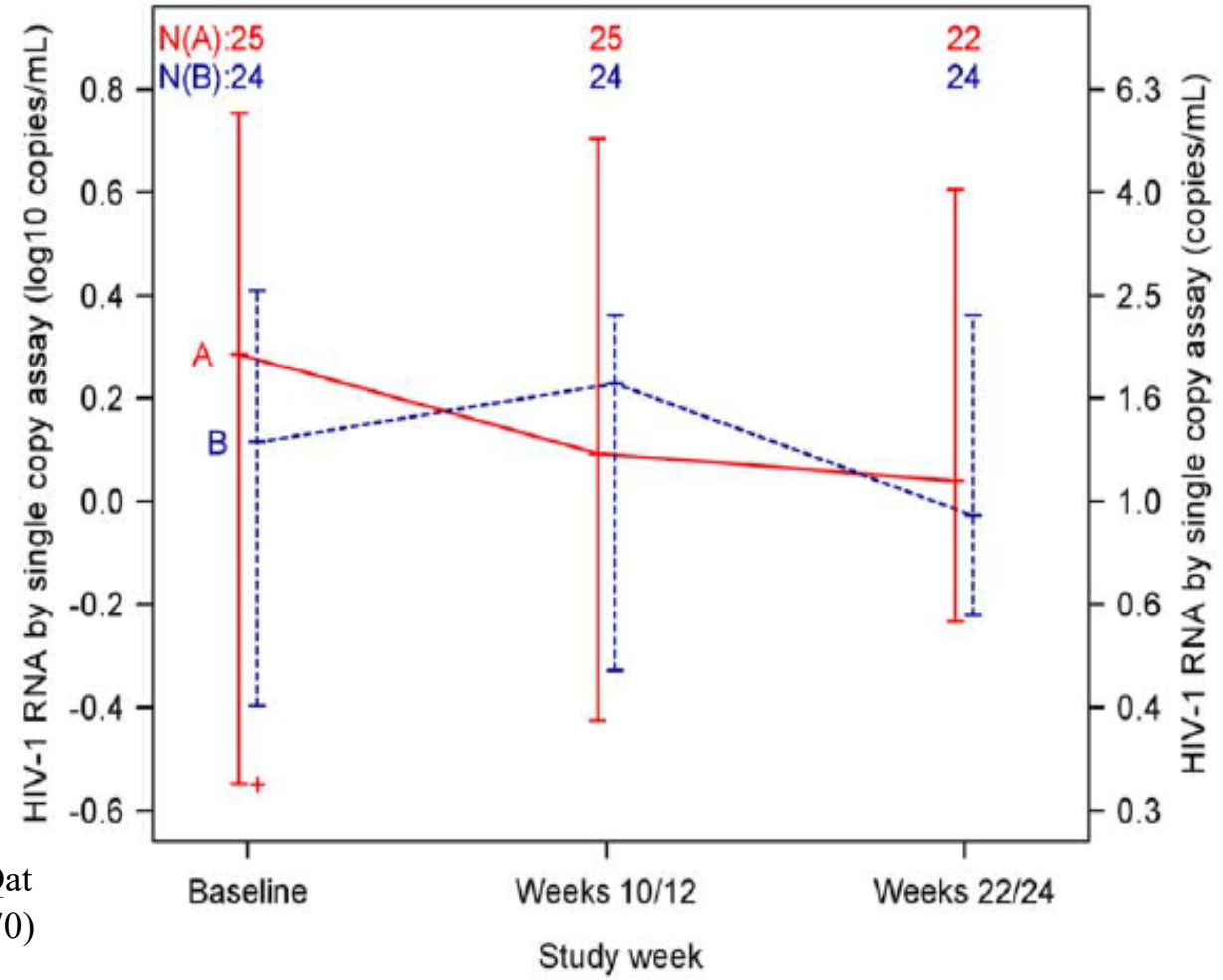
Study design: Patients receiving ART who had plasma HIV-1 RNA levels below 50 copies/mL but detectable viremia by single copy assay (SCA) were randomized to add either raltegravir or placebo to their ART regimen for 12 weeks

Characteristic	Overall ($n=53$)	Raltegravir-First (Group A) ($n=27$)	Placebo-First (Group B) ($n=26$)
Age, median (years)	49	51	47
Male sex (%)	48 (91%)	24 (89%)	24 (92%)
Race/ethnicity			
White non-Hispanic	36 (68%)	20 (74%)	16 (62%)
Black non-Hispanic	9 (17%)	5 (19%)	4 (15%)
Hispanic	7 (13%)	2 (7%)	5 (19%)
Not-reported	1 (2%)	0 (0%)	1 (4%)
Background entry regimen			
PI-containing	18 (34%)	9 (33%)	9 (35%)
NNRTI-containing	35 (66%)	18 (67%)	17 (65%)
Baseline CD4 count (cells/mm^3), median (Q1, Q3)	589 (452, 751)	538 (401, 717)	613 (454, 833)
Years since first undetectable HIV-1 RNA value, median (Q1, Q3)	5.5 (3.5, 7.0)	4.8 (3.2, 7.9)	5.7 (3.7, 7.0)
Screening HIV-1 RNA by SCA (copies/mL), median (Q1, Q3)	1.7 (0.6, 2.9)	1.2 (0.2, 3.1)	1.9 (0.8, 2.9)

PlosOne 2010; 7:e1000321

No reduction in low-level residual viremia after raltegravir intensification





The proportion of patients who had ≥ HIV-1 RNA levels below the LLQat week 10/12 did not differ between he two groups (20% versus13%, p =0.70)

No change in CD4 cell count and in markers of CD4 or CD8 cell activation in blood were found

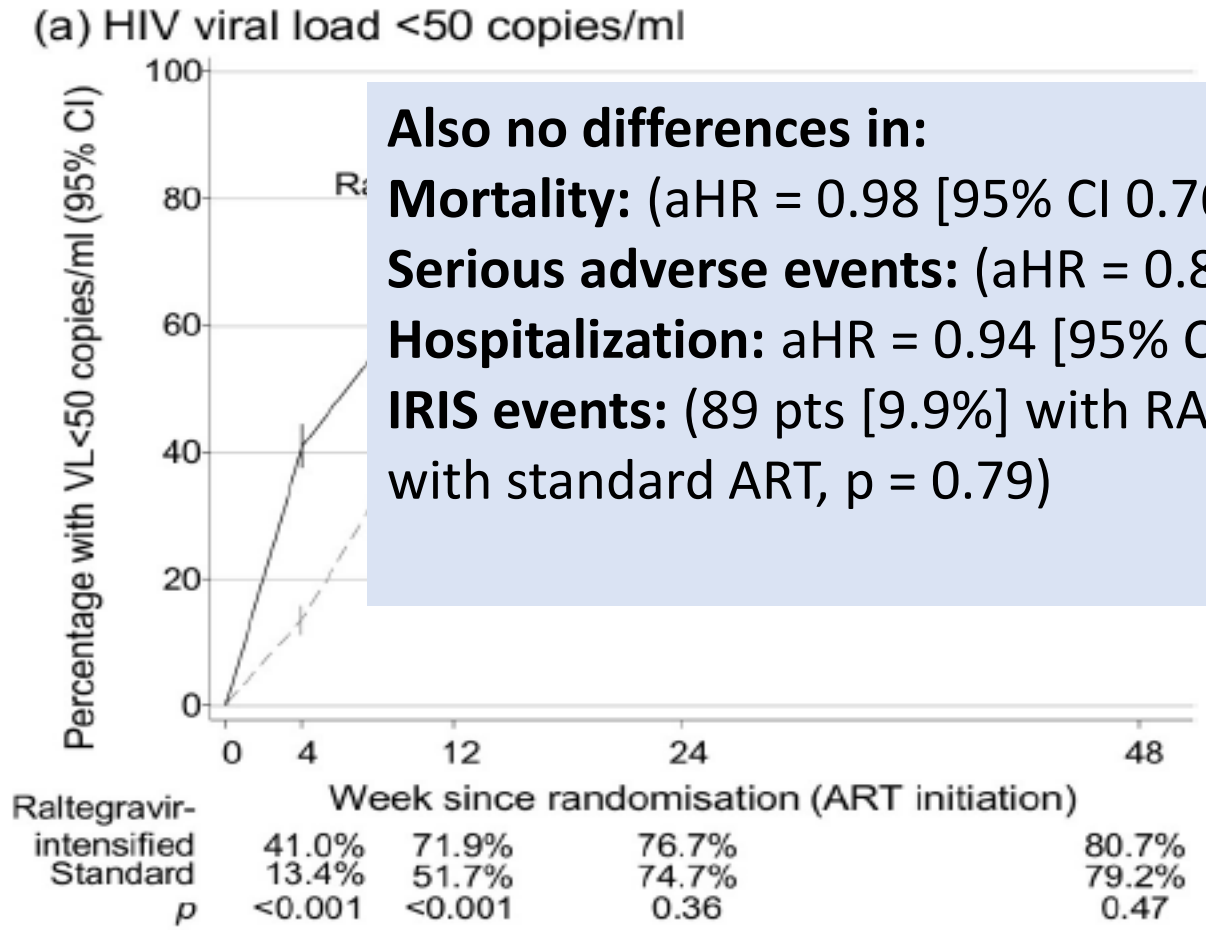
PlosOne 2010; 7:e1000321

Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: A randomised controlled trial

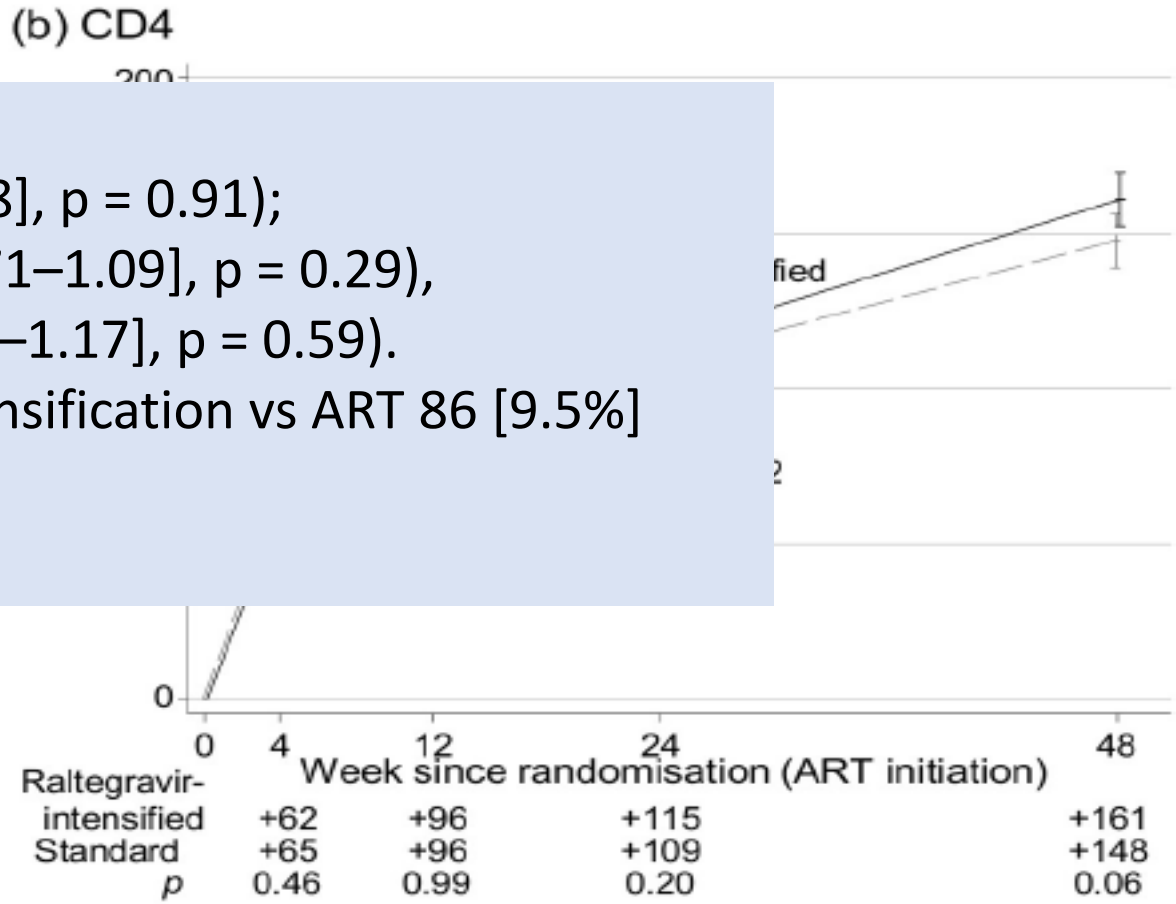
THE REALITY TRIAL

PLOS MEDICINE

Study design: 1805 advanced naive patients (CD4< 100) who were randomized to receive ART with raltegravir intensification for 12 weeks or standard of care



Also no differences in:
Mortality: (aHR = 0.98 [95% CI 0.76–1.28], p = 0.91);
Serious adverse events: (aHR = 0.88 [0.71–1.09], p = 0.29),
Hospitalization: aHR = 0.94 [95% CI 0.76–1.17], p = 0.59).
IRIS events: (89 pts [9.9%] with RAL intensification vs ART 86 [9.5%] with standard ART, p = 0.79)



PLoS Med 2018; 15(12):e1002706.

Intensification of Antiretroviral Therapy through Addition of Enfuvirtide in Naive HIV-1-Infected Patients with Severe Immunosuppression Does Not Improve Immunological Response: Results of a Randomized Multicenter Trial (ANRS 130 Apollo)

The APOLLO TRIAL

Study design: randomized study in in 195 naive HIV-1-infected patients, either asymptomatic with CD4 counts of<100/mm3 or stage B/C disease with CD4 <200/mm3. Patients received TDF/FTC with LPV/r or EFV and were randomized to receive ENF for 24 weeks (ENF arm) or not (control arm).

Characteristic	Enfuvirtide group (n = 100)	Control group (n = 94)	Total (n = 194)
No. (%) male	74 (74)	77 (82)	151 (78)
Mean (SD) age (yr)	44 (9)	43 (10)	44 (10)
No. (%) of patients by mode of infection			
Heterosexual contact	55 (55)	51 (54)	106 (55)
Men having sex with men	33 (33)	30 (32)	63 (32)
Injecting drug user	2 (2)	1 (1)	3 (2)
Transfusion	0 (0)	1 (1)	1 (1)
Unknown	10 (10)	11 (12)	21 (11)
No. (%) of patients by clinical stage			
A	10 (10)	11 (12)	21 (11)
B	16 (16)	16 (17)	32 (16)
C	74 (74)	67 (71)	141 (73)
No. (%) of patients with active AIDS event at wk 0	55 (55)	53 (56)	108 (56)
No. (%) of patients with delay from HIV diagnosis to wk 0 of ≤6 mo	84 (84)	75 (80)	159 (82)
Baseline CD4 count (no. of cell/mm^3)			
Mean (SD)	49 (50)	54 (62)	51 (56)
Median (IQR)	35 (14, 69)	29 (11, 88)	30 (12, 72)
Baseline HIV-1 RNA load ($\log_{10}$ no. of copies/ml)			
Mean (SD)	5.3 (0.6)	5.4 (0.6)	5.4 (0.6)
Median (IQR)	5.4 (5–5.8)	5.4 (5–5.8)	5.4 (5–5.8)
No. (%) of patients receiving standard treatment of:			
Lopinavir-ritonavir	78 (78)	79 (84)	157 (81)
Efavirenz	22 (22)	15 (16)	37 (19)

AAC 2013; 57: 758-65

Intensification of Antiretroviral Therapy through Addition of Enfuvirtide in Naive HIV-1-Infected Patients with Severe Immunosuppression Does Not Improve Immunological Response: Results of a Randomized Multicenter Trial (ANRS 130 Apollo)

The APOLLO TRIAL

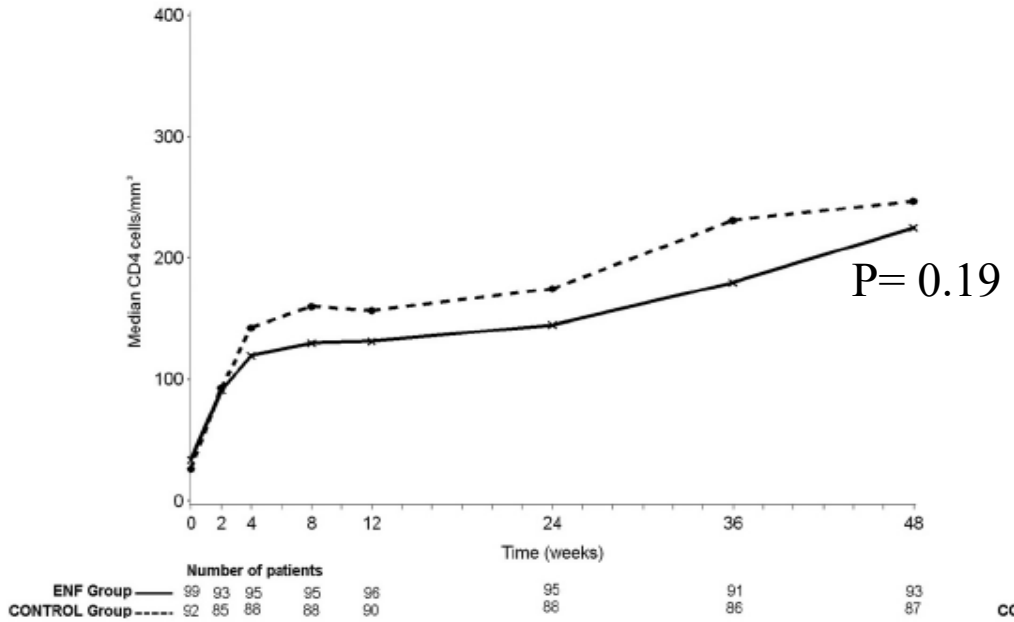


FIG 2 Median CD4 cell count from week 0 to week 48, ANRS 130 Apollo trial (ENF, enfuvirtide; data points are medians, and errors bars are omitted for clarity).

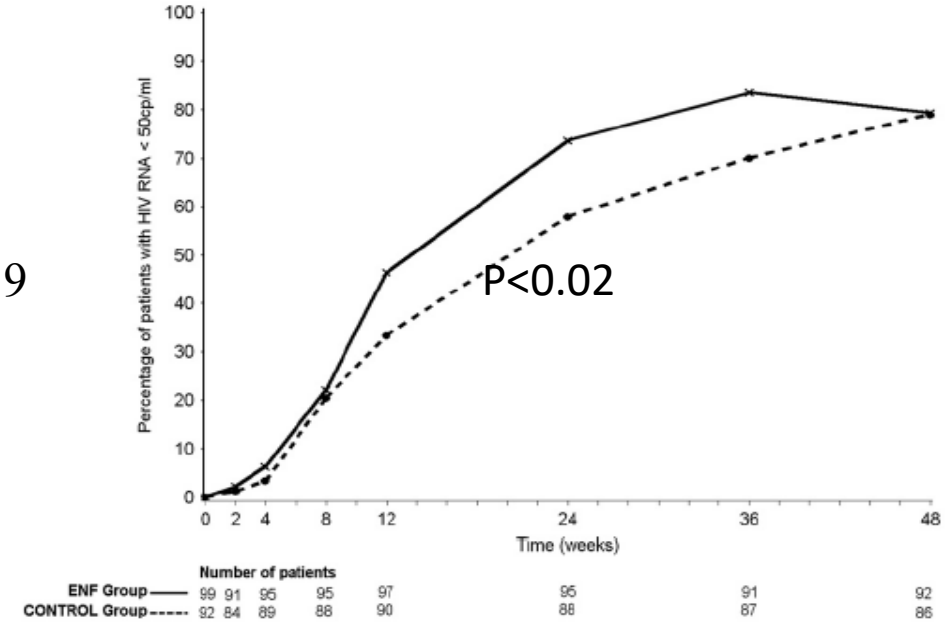


FIG 3 Proportion of patients with HIV-1 RNA loads of <50 copies/ml, ANRS 130 Apollo trial (ENF, enfuvirtide; data points are medians, and errors bars are omitted for clarity).

The proportions of patients with CD4 counts of>200/mm3 at week 24 were 34% and 38% in the ENF and control arms, respectively (P=0.53).The proportions of patients with HIV-1 RNA loads of<50 copies/ml were 74% and 58% at week 24 in the ENF and control arms, respectively (P<0.02), and the proportion reached 79% in both arms at week 48. 20% and 12 patients (13%) in the ENF and control arms, respectively, experienced at least one AIDS event during follow-up (P= 0.17).

AAC 2013; 57: 758-65

Failure of combined antiretroviral therapy intensification with maraviroc and raltegravir in chronically HIV-1 infected patients to reduce the viral reservoir: the *IntensHIV* randomized trial

The IntensHIV Trial

22 patients were randomly assigned for 48 weeks to continue their current first line regimen (>12 wks of HIV-RNA < 20) of Truvada® plus Kaletra® or intensify it with Maraviroc and Raltegravir for 24 wks

The primary objective was to obtain a 50% decrease in proviral HIV-1 DNA levels in lymphoid cells with intensification

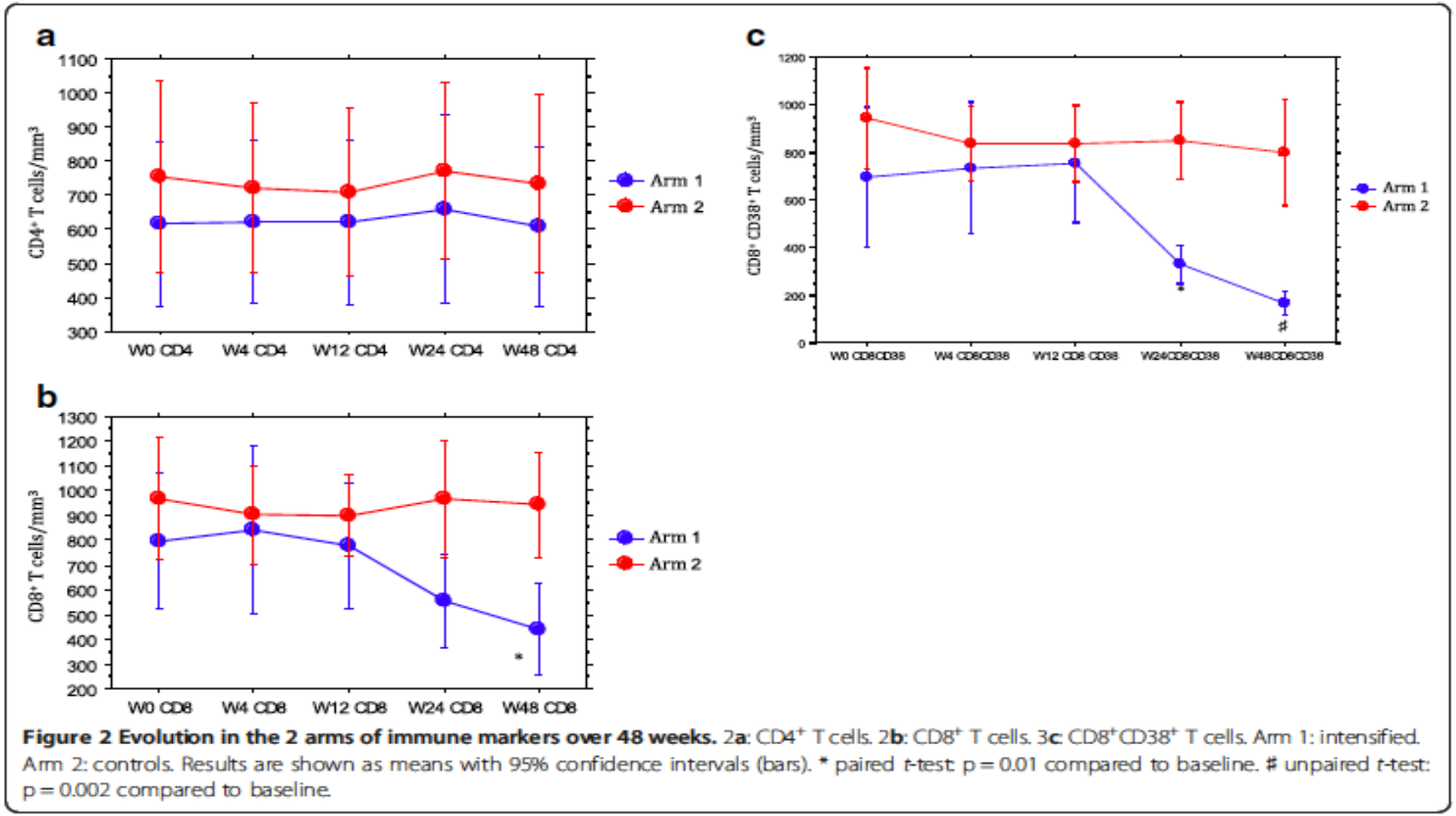


Figure 2 Evolution in the 2 arms of immune markers over 48 weeks. 2**a**: $CD4^+$ T cells. 2**b**: $CD8^+$ T cells. 3**c**: $CD8^+CD38^+$ T cells. Arm 1: intensified. Arm 2: controls. Results are shown as means with 95% confidence intervals (bars). * paired *t*-test: $p = 0.01$ compared to baseline. # unpaired *t*-test: $p = 0.002$ compared to baseline.

AIDS Research and Therapy 2014, 11:33

Failure of combined antiretroviral therapy intensification with maraviroc and raltegravir in chronically HIV-1 infected patients to reduce the viral reservoir: the *IntensHIV* randomized trial

The IntensHIV Trial

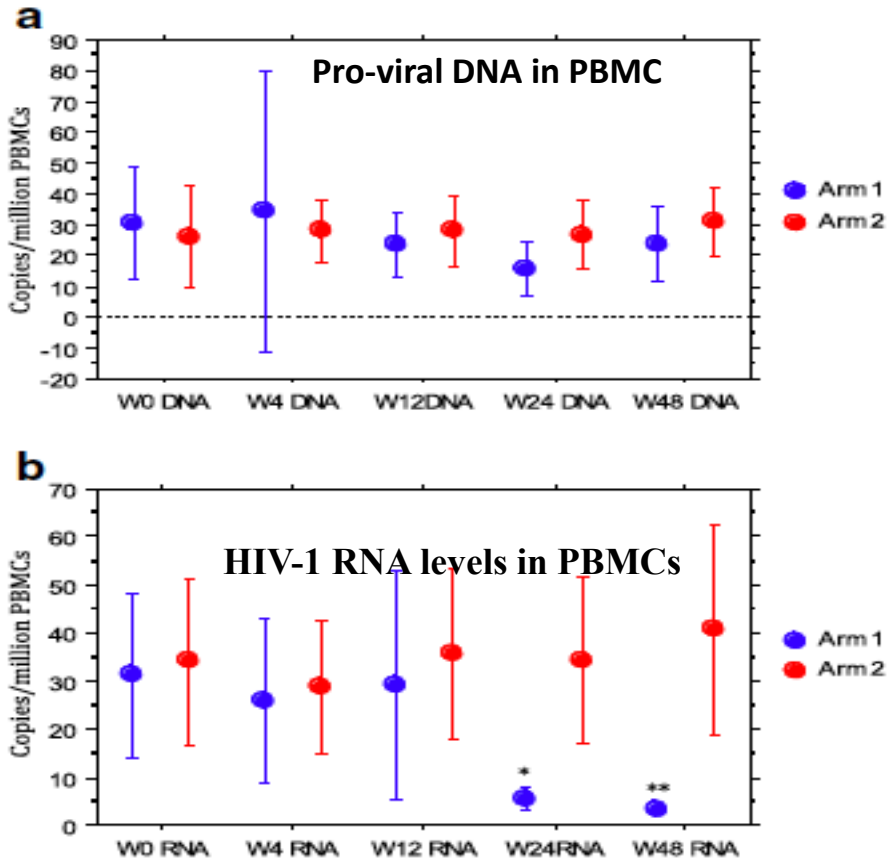
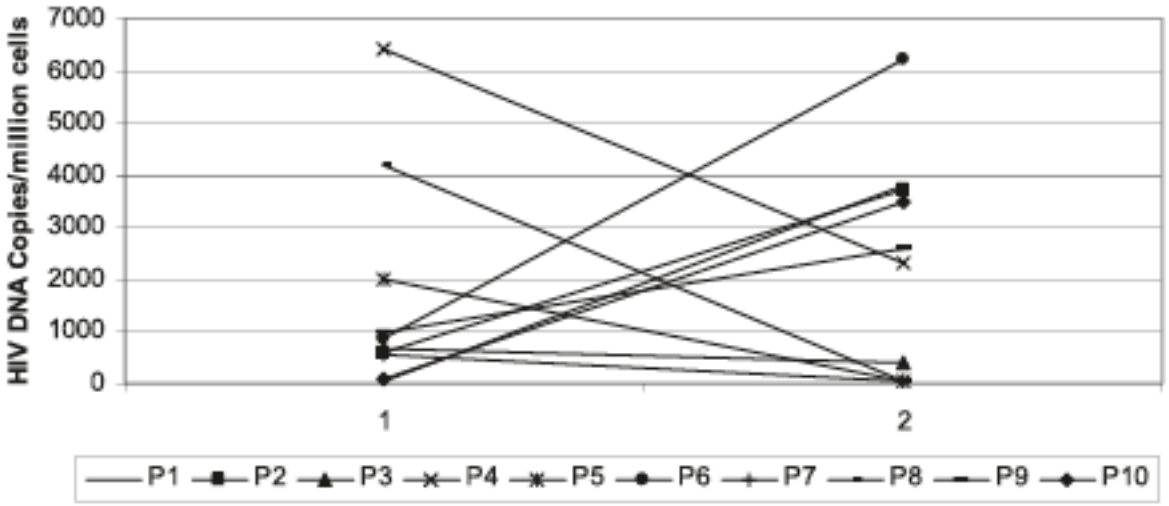


Figure 3 Evolution in the 2 arms of PBMCs viral markers over 48 weeks in the 2 arms. 3**a**: proviral HIV-1 DNA in PBMC. 3**b**: HIV-1 ARN in PBMCs. Arm 1: intensified. Arm 2: controls. Results are shown as means with 95% confidence intervals (bars). *non-parametric paired test: p = 0.07 compared to baseline; **p = 0.06 compared to baseline.

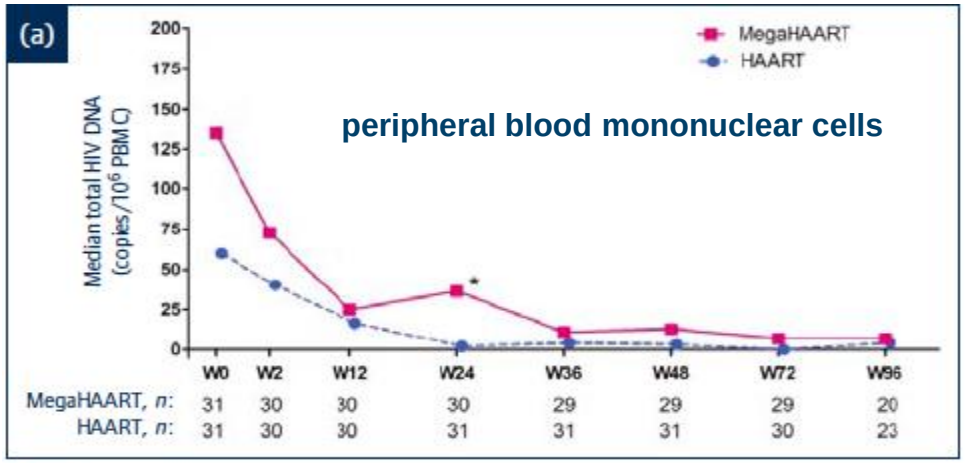


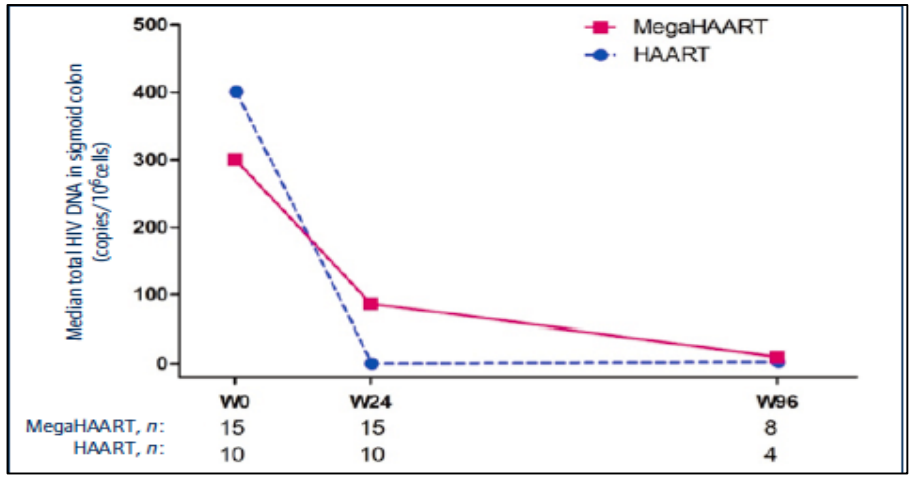
Evolution of HIV-1 DNA in lymphoid cells taken from sigmoid colon in the intensified group (copies/106 cells): no trend was observed

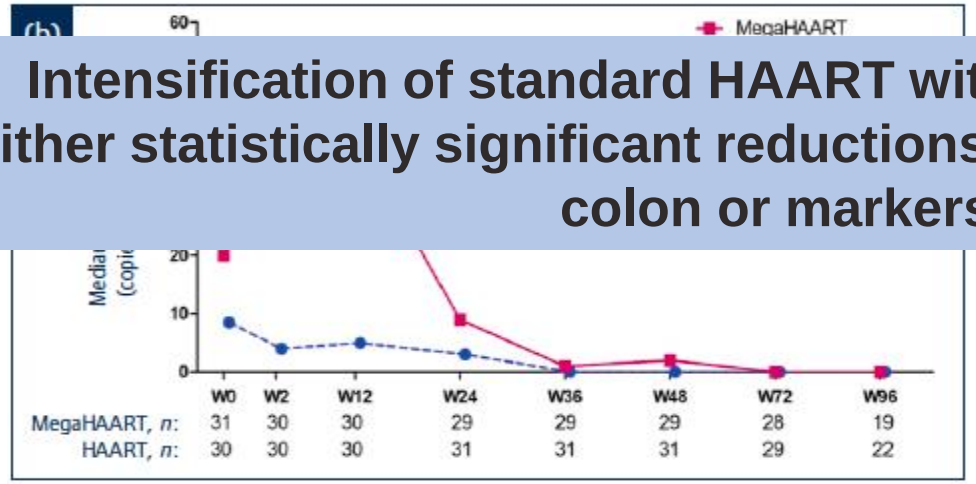
AIDS Research and Therapy 2014, 11:33

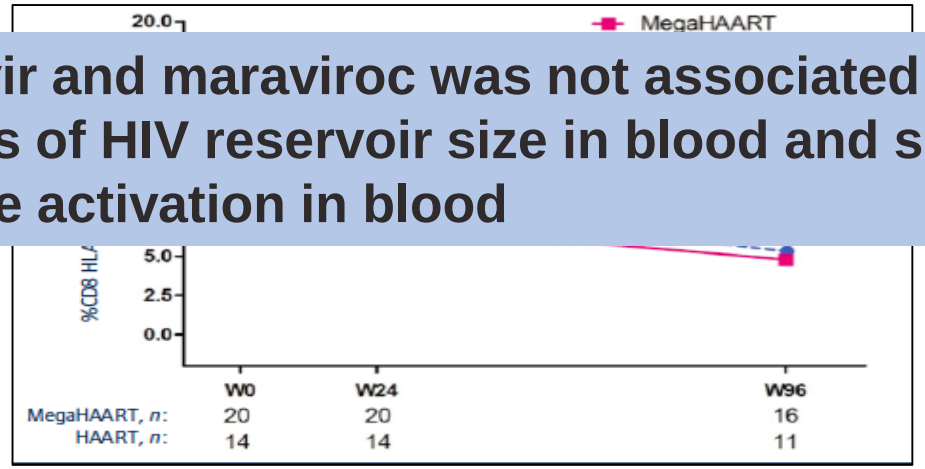
Markers of HIV reservoir size and immune activation after treatment in acute HIV infection with and without raltegravir and maraviroc intensification

Study design: 62 Individuals with acute HIV infection were randomised to HAART (EFV/FTC/TDF, n =31) or megaHAART, a standard regimen intensified by RAL/MRV (n =31), during the first 24 weeks of therapy









Intensification of standard HAART with raltegravir and maraviroc was not associated with either statistically significant reductions of markers of HIV reservoir size in blood and sigmoid colon or markers of immune activation in blood

Journal of Virus Eradication 2015; 1: 116–122

Maraviroc in addition to cART during primary HIV infection: Results from MAIN randomized clinical trial and 96-weeks follow-up

The MAIN Trial

Study design: open trial of 29 patients with PHI. Subjects were randomly assigned to receive cART-only (cART), cART + 8 weeks of MVC (ST-MVC) or cART + 48 weeks of MVC (LT-MVC),

Seven patients (24%) had a predicted CXCR4 co-receptor usage. At week 48, 27 patients (93.1%) reached HIV-RNA <50cps/mL. Median CD4 T-cell count increase was 313 cells/ L ($p < 0.001$).At multivariate linear regression analysis, LT-MVC arm had the greatest CD4 T-cell increase, while patients in ST-MVC arm had the least gain in CD4 T-cells ($p = 0.007$). At week 96, multivariate analysis showed no associations between former treatment arm and CD4 T-cell gain.

BL characteristics	Univariate (n=29)		Multivariate (n=29)	
	W48 CD4 T-cellmean change (%) (±SE)	P	W48 CD4 T-cellmean change (%) (±SE)	P
Treatment arm		0.696		**0.007**
cART (n=10)	Ref		Ref	
ST-MVC (n=9)	−6.6 (135.8)	0.961	−238.5 (102.8)	**0.020**
LT-MVC (n=10)	95.1 (132.2)	0.472	90.6 (89.6)	0.312
Age	7.3 (6.3)	0.248		
Risk factor		0.781		
MSM	Ref			
Heterosexuals	−86.8 (123.9)	0.483		
Other	−35.2 (148.4)	0.813		
Predicted co-receptor usage				
CCR5	132.4 (127.5)	0.299		
CXCR4	Ref			
Fiebig				
<V	163.3 (107.6)	0.129	78.6 (89.7)	0.381
V	Ref		Ref	
CD4, per 100 cell/μL increase	−76.1 (18.7)	**<0.001**	−68.0 (17.3)	**<0.001**
CD4%, per 1% increase	−2.3 (4.3)	0.584		
CD8, per 100 cell/μL increase	−5.4 (4.0)	0.179	−3.6 (3.3)	0.273
CD8%, per 1% increase	−0.7 (3.0)	0.818		
CD4:CD8, per 1 increase	−15.1 (76.8)	0.844		
HIV-RNA, per log10cp/mL increase	108.8 (51.7)	**0.035**	92.2 (41.1)	**0.025**

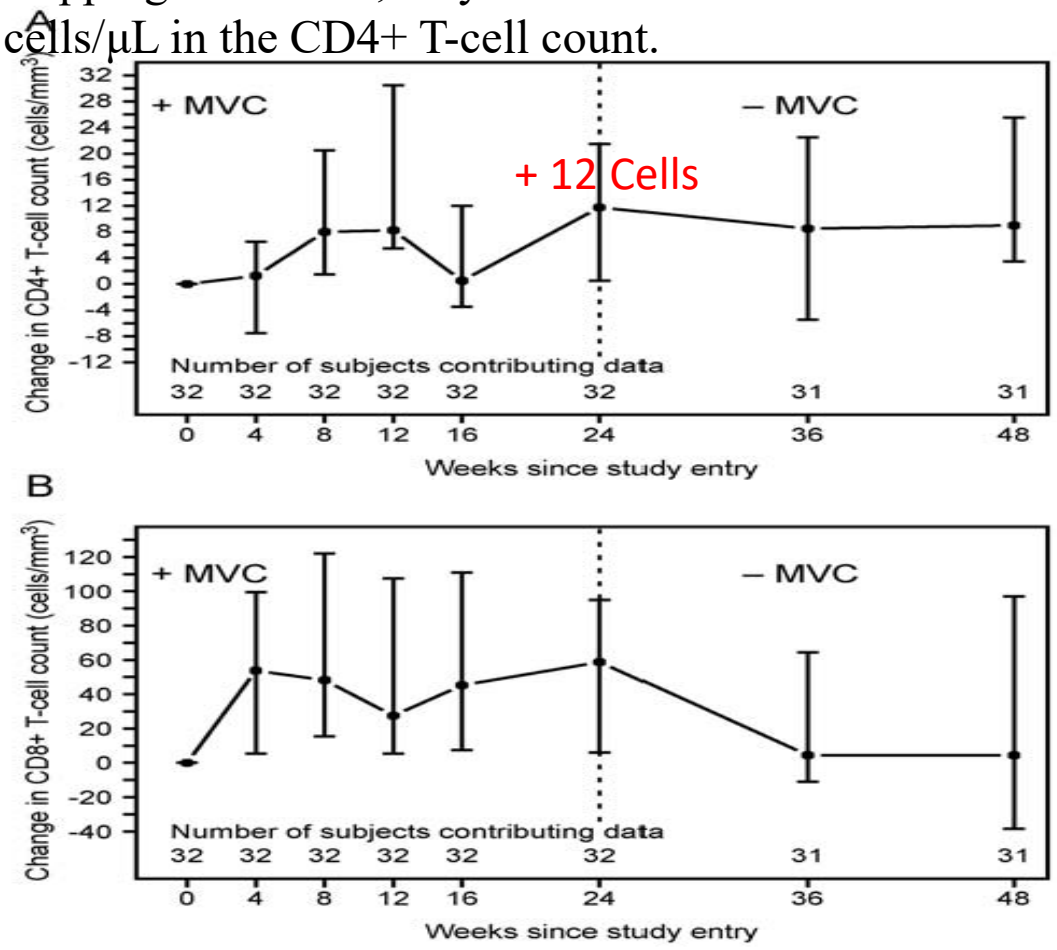
BL characteristics	Univariate (n=23)		Multivariate (n=23)	
	W96 CD4 T-cellmean change (%) (±SE)	P	W96 CD4 T-cellmean change (%) (±SE)	P
Treatment arm		0.497		0.521
cART (n=9)	Ref		Ref	
ST-MVC (n=6)	153.1 (156.1)	0.327	−136.4 (125.3)	0.276
LT-MVC (n=8)	−24.4 (144.0)	0.865	−30.8 (134.3)	0.818
Age	13.7 (6.9)	**0.046**	4.7 (7.4)	0.524
Risk factor		0.982		
MSM	Ref			
Heterosexuals	−7.1 (140.1)	0.959		
Other	27.4 (180.4)	0.879		
Predicted coreceptor usage				
CCR5	102.9 (143.3)	0.473		
CXCR4	Ref			
Fiebig				
<V	126.1 (124.6)	0.312		
V	Ref			
CD4, per 100 cell/μL increase	−90.0 (18.6)	**<0.001**	−0.8 (0.2)	**<0.001**
CD4%, per 1% increase	−4.4 (5.6)	0.432		
CD8, per 100 cell/μL increase	−6.9 (4.2)	0.101	−0.1 (0.1)	0.404
CD8%, per 1% increase	−2.9 (3.7)	0.427		
CD4:CD8, per 1 increase	18.8 (169.9)	0.912		
HIV-RNA, per log10cp/mL increase	126.7 (55.3)	**0.022**	80.1 (51.4)	0.119

Journal of Clinical Virology 85 (2016) 86–89

A Pilot Trial of Adding Maraviroc to Suppressive Antiretroviral Therapy for Suboptimal CD4$^+$ T-Cell Recovery Despite Sustained Virologic Suppression: ACTG A5256

ACTG 5256

Study design: single-arm pilot trial involving 34 subjects with suppressed plasma levels of HIV-1 RNA for at least 48 weeks and stable suboptimal CD4+ T-cell recovery (<250); subjects added Maraviroc to their existing ART for 24 weeks. After stopping maraviroc, they were followed for an additional 24 weeks. Primary objective: an increase of at least 20 cells/μL in the CD4+ T-cell count.



Biomarker	Baseline Level (n = 32)	Change in Level, Median (90% CI), by Interval	
		From Baseline to Wk 22/24 (n = 32)	From Wk 22/24 to Wk 46/48 (n = 31)
IL-6 (pg/mL)	8	0.7 (–.9 to +1.6)	–0.5 (–2.1 to +.6)
MCP-1 (pg/mL)	447.2	+44.6 (–39.6 to +103.1)	+7.7 (–18.5 to +43.2)
MCP-2 (pg/mL)	16.8	–1.4 (–2.4 to +2.2)	+0.2 (–2.3 to +1.8)
sTNF-RII (ng/mL)	1	+0.2 (+.1 to +.3)	0 (0 to +.1)
hs-CRP (mg/dL)	0.1	0 (0 to +.1)	0 (0–0)
sICAM-1 (ng/mL)	470.1	–25.7 (–59.3 to +23.5)	–32.4 (–46.3 to +6.8)
CD40L (pg/mL)	113.4	–0.4 (–45.6 to +43.1)	+34.9 (0 to +66.7)
sCD14 (μg/mL)	2.1	0 (–.1 to +.2)	–0.2 (–.4 to +.1)
MMP-9 (ng/mL)	171.1	–12.5 (–48.1 to +4)	+12.8 (–14.9 to +29.5)
P-selectin (ng/mL)	189.8	–11.7 (–66.2 to +30.5)	–17.3 (–62.1 to +5.2)
D-dimer (μg/mL)	0.3	+0.09 (+.06 to +.13)	–0.02 (–.03 to +.01)

The Journal of Infectious Diseases 2012;206:534–42

Effect of the CCR5 antagonist maraviroc on the occurrence of immune reconstitution inflammatory syndrome in HIV (CADIRIS): a double-blind, randomised, placebo-controlled trial

CADIRIS Trial

Study design: double-blind, randomised, placebo-controlled trial of 276 pts who were naive to ART, had CD4 count lower than 100 cells per µL and HIV RNA greater than 1000 copies per mL.

They were randomized to receive either maraviroc (600 mg twice daily) or placebo in addition to an ART regimen that included tenofovir, emtricitabine, and efavirenz for 48 weeks.

Primary objective: reduction in the risk of IRIS

	Maraviroc (N=140)	Placebo (N=136)
Women	51 (36%)	47 (35%)
Age (years)	36·7 (8·1)	37·5 (9·3)
Participants with history of AIDS-defining conditions[24]	80 (57%)	83 (61%)
Mexico	50/62 (81%)	48/62 (77%)
South Africa	30/78 (39%)	35/74 (47%)
Mycobacterium tuberculosis in any site	29 (21%)	35 (26%)
M tuberculosis, disseminated or extrapulmonary	14 (10%)	20 (15%)
CD4 cells per µL	36·0 (15·5–57·0)	32·0 (19·0–60·5)
Mexico	32·0 (13·0–53·0)	27·0 (16·0–52·0)
South Africa	38·0 (20·0–61·0)	38·0 (22·0–68·0)
CD4 cells, proportion of leucocytes	4·4% (2·3–6·6)	4·0% (2·5–7·0)
Mexico	3·6% (1·8–6·0)	4·0% (1·9–7·0)
South Africa	4·9% (2·7–7·1)	4·2% (2·7–7·1)
CD8 cells per µL	468·0 (355·0–738·0)	492·0 (335·0–746·0)
Mexico	507·5 (396·0–804·0)	458·0 (330·0–753·0)
South Africa	447·5 (305·0–650·0)	516·0 (341·0–722·0)
CD8 cells, proportion of leucocytes	61·9% (54·1–70·4)	63·1% (53·4–71·3)
Mexico	63·9% (55·1–71·2)	63·4% (55·6–73·3)
South Africa	60·5% (53·5–69·9)	62·9% (52·1–70·0)
Plasma HIV-1 RNA (log_{10} copies per mL)	5·3 (0·6)	5·4 (0·6)
Haemoglobin (g/dL)	12·2 (1·8)	12·1 (1·8)

Data are n (%), mean (SD), or median (IQR).

Lancet HIV 2014; 1: e60–67

Comparison of event rates of primary and secondary outcome

	Maraviroc	Placebo	p value*
Participants with IRIS events†	33 (24%)‡	31 (23%)‡	0·74
Participants with severe IRIS events‡	7 (5%)	9 (7%)	0·59
Participants with non-cutaneous IRIS events‡	16 (12%)	16 (12%)	0·98
Participants with tuberculosis related IRIS§	10 (7%)	13 (10%)	0·50
Unmasking	2 (2%)	4 (3%)	0·39
Paradoxical	8 (6%)	9 (7%)	0·80
Participants with non-AIDS related clinical events by 48 weeks¶	12 (9%)	7 (5%)	0·26
Deaths by 48 weeks‖	6 (5%)	4 (3%)	0·56

Comparison of immunological and virological outcomes by treatment group

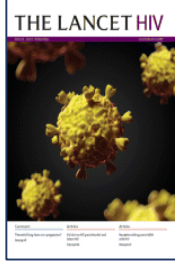
	Maraviroc	Placebo	p value*
CD4 cells per µL			
Baseline (n=140, 136)	36 (16–57)	32 (19–61)	0·88
Week 12 (n=128, 127)	148 (105–211)	137 (82–180)	0·04
Week 24 (n=127, 124)	165 (113–225)	142 (113–198)	0·09
Week 48 (n=122, 120)	209 (151–274)	191 (147–257)	0·24
CD8 cells per µL			
Baseline (n=140, 136)	468 (355–738)	492 (335–746)	0·99
Week 12 (n=128, 127)	936 (601–1365)	729 (520–965)	0·0006
Week 24 (n=127, 124)	831 (562–1175)	640 (486–952)	0·002
Week 48 (n=122, 119)	841 (612–1213)	695 (506–919)	0·0009

Maraviroc does not confer a meaningful protection from the occurrence of IRIS.
In patients with advanced AIDS, the addition of maraviroc as immunomodulator seems to have no effect on CD4 cell recovery or the occurrence of opportunistic infections during the first year of therapy

Lancet HIV 2014; 1: e60–67

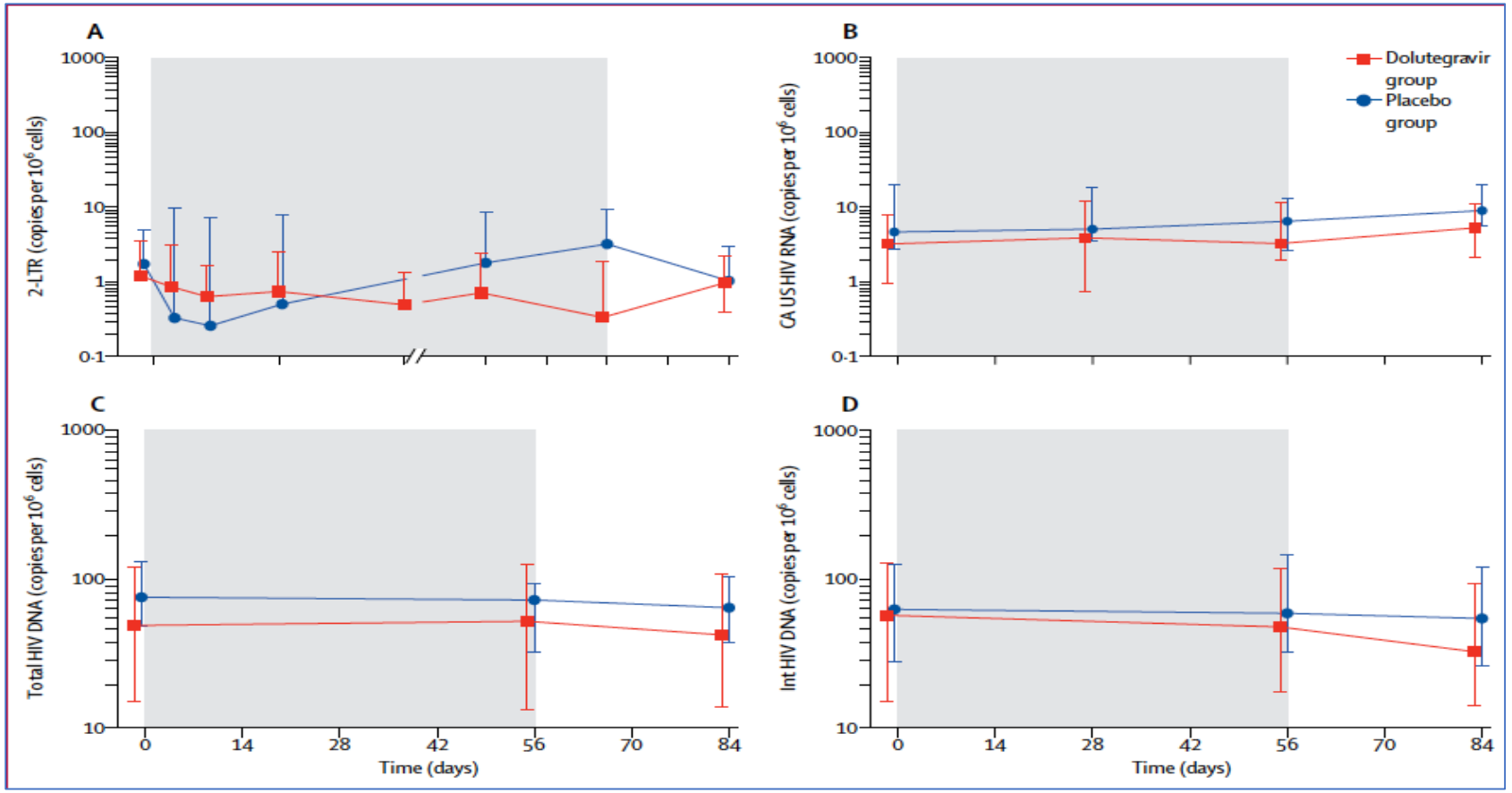
Could Maraviroc or/and Integrase inhibitors play a role in intensification of ARV in the coming years?

The effect of antiretroviral intensification with dolutegravir on residual virus replication in HIV-infected individuals: a randomised, placebo-controlled, double-blind trial



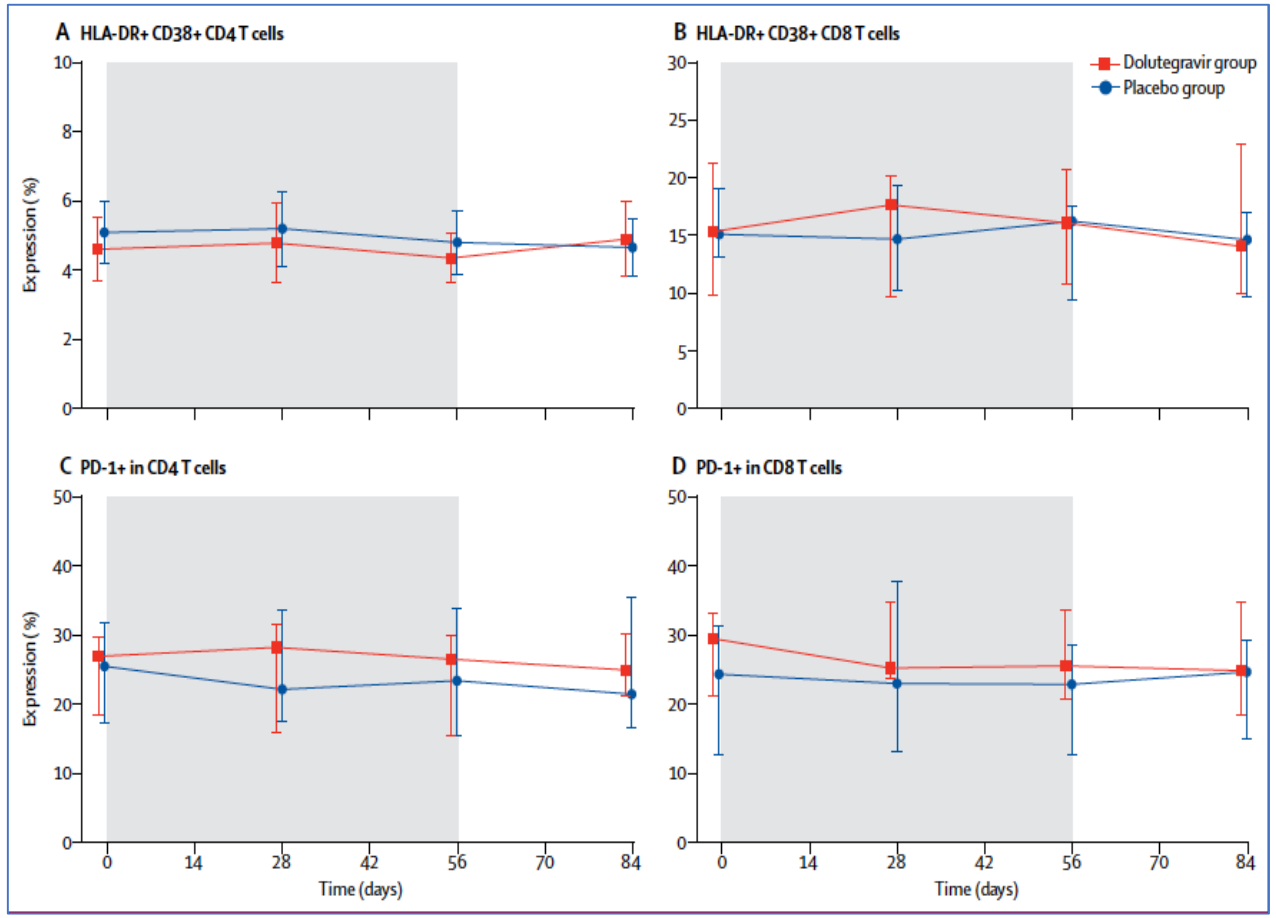
Study design: randomised, placebo-controlled, double-blind trial of 46 HIV-i adults receiving ART (at least three agents) for at least 3 years. Eligible participants had HIV-RNA <50 copies per mLfor >3 years and <20 copies per mL at screening and two CD4 counts >350 cells per µL in the previous 24 months including screening. Participants were randomly assigned (1:1) to receive 50 mg oral dolutegravir or placebo once a day for 56 days in addition to background ARV.

Median 2-LTR circles fold-change from baseline to day 7 was –0.17 (IQR –090 to 090) in the DTG group and –0.26 (–1.00 to 1.17) in the placebo group (p=017). Virological analyses of cell-associated HIV RNA, total HIV DNA, integrated HIV DNA, and plasma HIV RNA showed no significant difference in the change from baseline to any timepoint between the dolutegravir and placebo group.

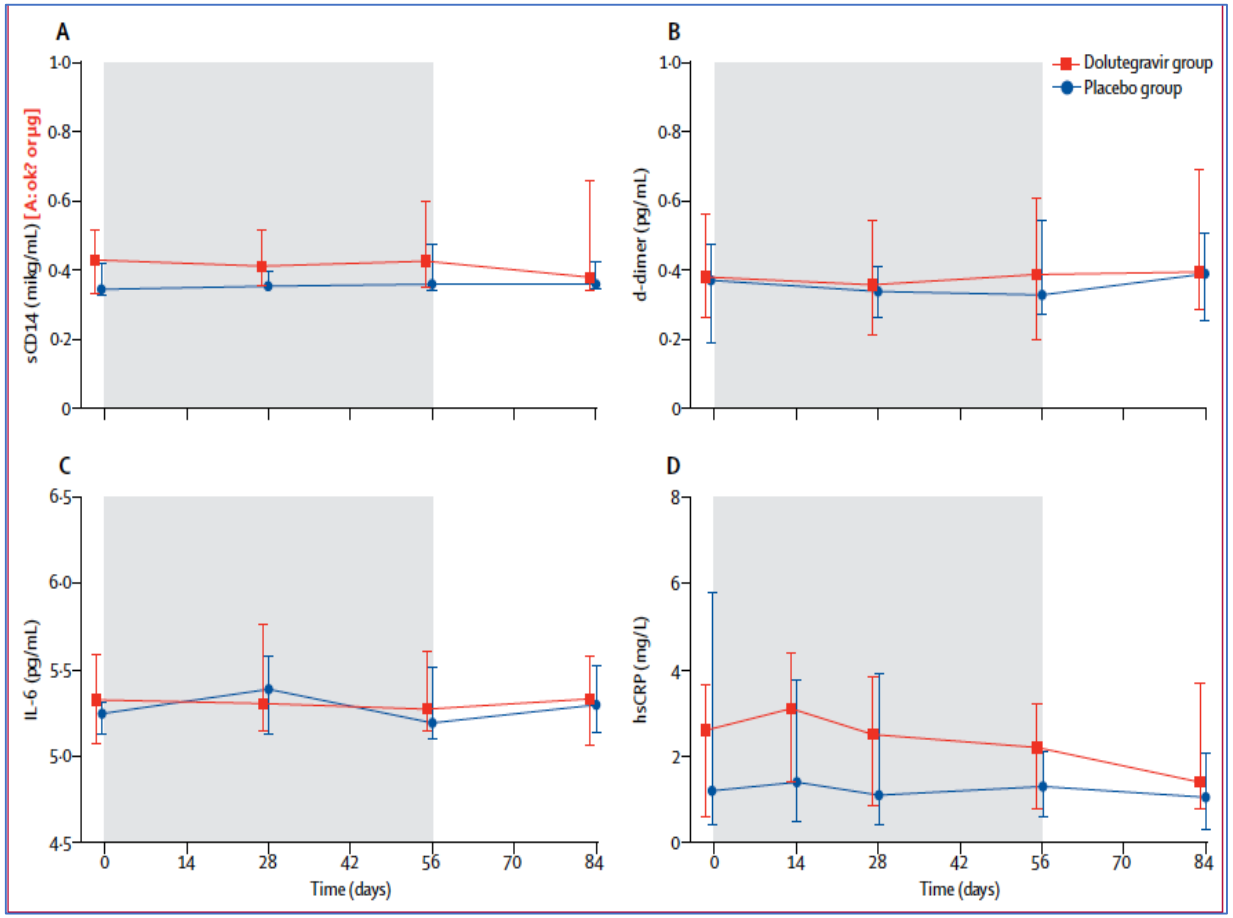


Lancet HIV 2018; published online April 9

T-cell activation and exhaustion during ART intensification



Soluble biomarkers of inflammation and coagulation during ART intensification



These results show that adding dolutegravir to suppressive ART did not affect residual virus replication in blood in HIV-infected individuals on ART.

Lancet HIV 2018; published online April 9

frontiers

Enhanced immune reconstitution with albuvirtide in HIV-infected immunological non-responders

Treatment efficacy parameter	Intensive group (n=25)	Control group (n=25)	P-value
$CD4^+$T absolute counts cells/μL			
Baseline*	287 (99)	280(105)	0.813
Week 12*	356 (133)	282 (110)	0.037
Change in $CD4^+$T cells at week 12 from baseline#	45 (24, 122)	-5(-23, 13)	<0.001
$CD8^+$T absolute counts cells /μL			
Baseline#	576 (412, 907)	650 (572, 910)	0.2
Week 12#	690 (567, 919)	608 (411, 1095)	0.528
Change in $CD8^+$T cells at week 12 from baseline#	82 (18, 158)	-41 (-137, 207)	0.043
CD4/CD8 ratio			
Baseline#	0.45 (0.31, 0.65)	0.44 (0.28, 0.55)	0.357
Week 12#	0.44 (0.32, 0.63)	0.44 (0.30, 0.53)	0.541
Change in CD4/CD8 ratio at week 12 from baseline#	0.01 (-0.04, 0.07)	0.01 (-0.02,0.09)	0.455
Proportion of participants with $CD4^+$T cell count increase ≥100 cells/μL or ≥30% from baseline at week 12	10 (40.0)	2 (8.0)	0.018

Front Cell Infect Microbiol. 2024 Jun 21:14:139

What is one of the main questions we often ask ourselves?

Is switching to DTG/3TC non inferior to switching to BIC/FTC/TAF

AIDS 2024

PASO-DOBLE study: Design

Phase IV, open-label, multicentre, randomised clinical trial[1]

30 sites across Spain

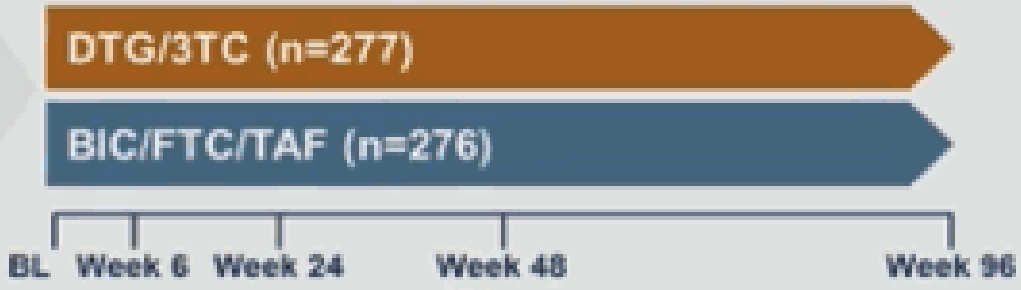
Collaborative study between **Fundación SEIMC-GeSIDA** and ViiV Healthcare

Screening

- HIV-1 RNA <50 c/mL for ≥24 weeks
- Current ART containing >1 pill/day, cobi booster, EFV or TDF
- No prior VF or known/suspected resistance
- No prior DTG or BIC
- No chronic hepatitis B

Randomised 1:1

Stratified by BL TAF use and sex at birth



Primary endpoint: Participants with plasma HIV-1 RNA ≥50 c/mL (FDA Snapshot; non-inferiority margin 4%)
Key secondary endpoint: Weight change (study was powered to assess differences)

Other secondary endpoints include efficacy, safety, tolerability, immune recovery, metabolic parameters, kidney function, blood pressure, body composition and bone mineral density, PROs, and genotypic resistance analysis in case of virological failure

Four sub-studies: Omics | Senescence | Fat biopsies | Liver steatosis

1. PASO DOBLE. Available at: https://clinicaltrials.gov/ct2/show/NCT04884139.

PASO-DOBLE study: Baseline characteristics

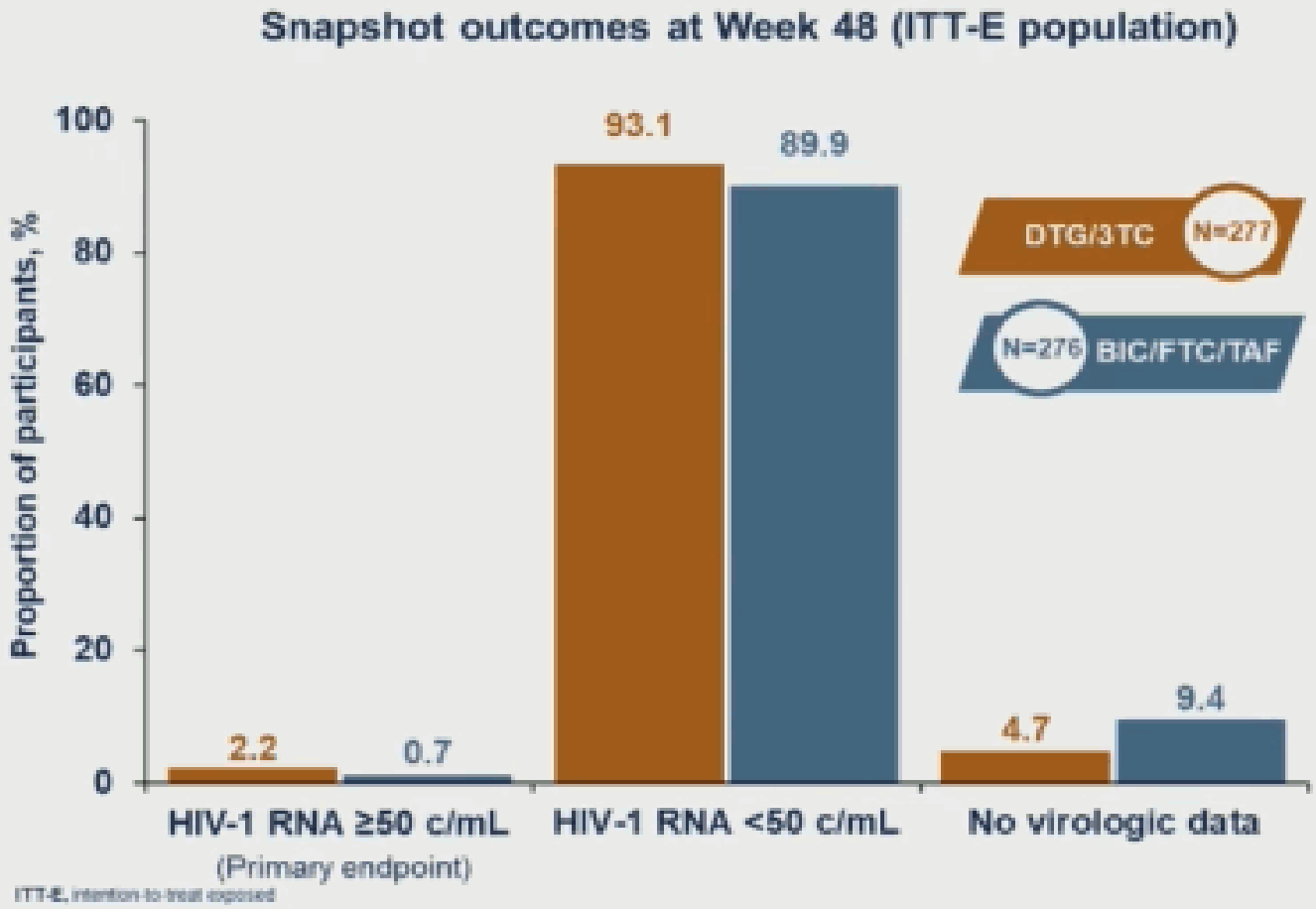
	DTG/3TC (n=277)	BIC/FTC/TAF (n=276)
Age, years	50 (41-57)	51 (39-58)
Female sex at birth	74 (26.7%)	73 (26.4%)
Ethnicity		
Caucasian	201 (72.6%)	201 (72.8%)
Latinx	66 (23.8%)	67 (24.3%)
Black	4 (1.4%)	5 (1.8%)
Other/unknown	6 (2.2%)	3 (1.1%)
Total time on ART, years	11.7 (7.2-19.3)	11.1 (7.0-19.2)
Time with HIV RNA <50 cp/mL, months	103.4 (43.0-170.2)	97.7 (41.5-163.3)
Duration of prior ART regimen, months	66.2 (43.5-97.0)	62.8 (41.1-88.7)
CD4 cells/mm^3	712 (516-918)	684 (473-859)
CD4 <350 cells/mm^3	26 (9.4%)	24 (8.7%)
CD4 nadir cells/mm^3	293 (144-472)	302 (159-476)
BMI, kg/m^2	25.1 (22.3-28.49)	24.8 (22.2-28.2)
Overweight/obese (BMI >25 kg/m^2)	143 (51.8%)	134 (48.6%)

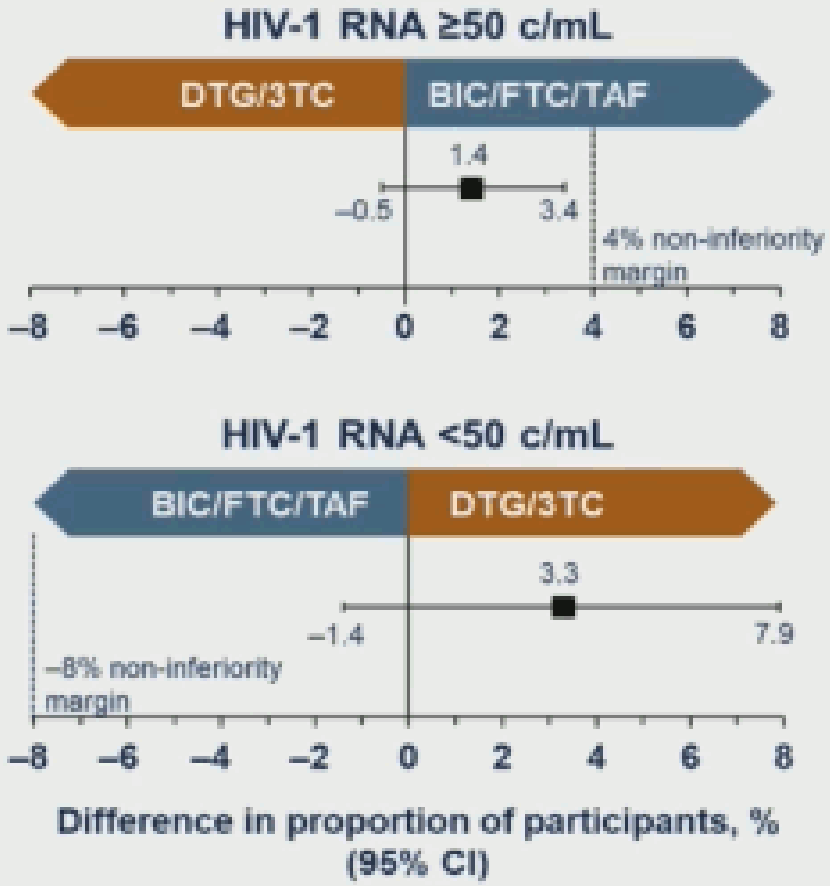
PASO-DOBLE study: Pre-switch ART

	DTG/3TC (n=277)	BIC/FTC/TAF (n=276)
NRTI 1 in previous ART regimen		
TAF	77 (27.8%)	78 (28.3%)
ABC	59 (21.3%)	52 (18.8%)
TDF	92 (33.2%)	103 (37.3%)
No NRTI 1	49 (17.7%)	43 (15.6%)
NRTI 2 in previous ART regimen		
3TC	70 (25.3%)	64 (23.2%)
FTC	182 (65.7%)	190 (68.8%)
No NRTI 2	25 (9.0%)	22 (8.0%)
Core drug in previous ART regimen		
NNRTI only	138 (49.8%)	141 (51.1%)
INSTI only	44 (15.9%)	49 (17.8%)
PI only	93 (33.6%)	82 (29.7%)
>1 core drugs	2 (0.7%)	4 (1.4%)

AIDS 2024

PASO-DOBLE study: Virologic efficacy



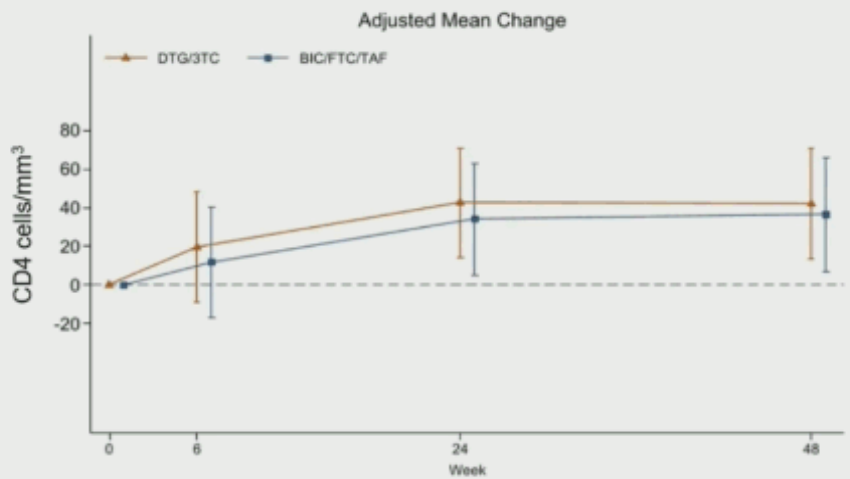


PASO-DOBLE study: Virological failure and emergent resistance

	DTG/3TC N=277	BIC/FTC/TAF N=276
Confirmed virologic failure* through Week 48	0	1
Emergent resistance	0	0

*Confirmed virologic failure was defined as HIV-1 RNA ≥50 cp/mL followed by a second consecutive HIV-1 RNA assessment ≥200 cp/mL

PASO-DOBLE study: CD4 cell/mm³ changes



Adjusted by baseline value, sex, presence of TAF in previous ART, age and ethnicity

AIDS 2024

PASO-DOBLE study: Adverse events

Participants with AEs, n (%)	DTG/3TC n=277	BIC/FTC/TAF n=276	p-value
Any AE *	207 (74.7)	216 (78.3)	0.327
Grade 3–4 AEs	3 (1.1)	10 (3.6)	0.049
Serious AE	12 (4.3)	13 (4.7)	0.831
Drug-related AEs	19 (6.9)	27 (9.8)	0.213
AEs leading to withdrawal #	1 (0.4)	2 (0.7)	0.561

DTG/3TC: General discomfort and arthromyalgia (n=1)
BIC/FTC/TAF: Insomnia (n=1), sleep disturbances (n=1)

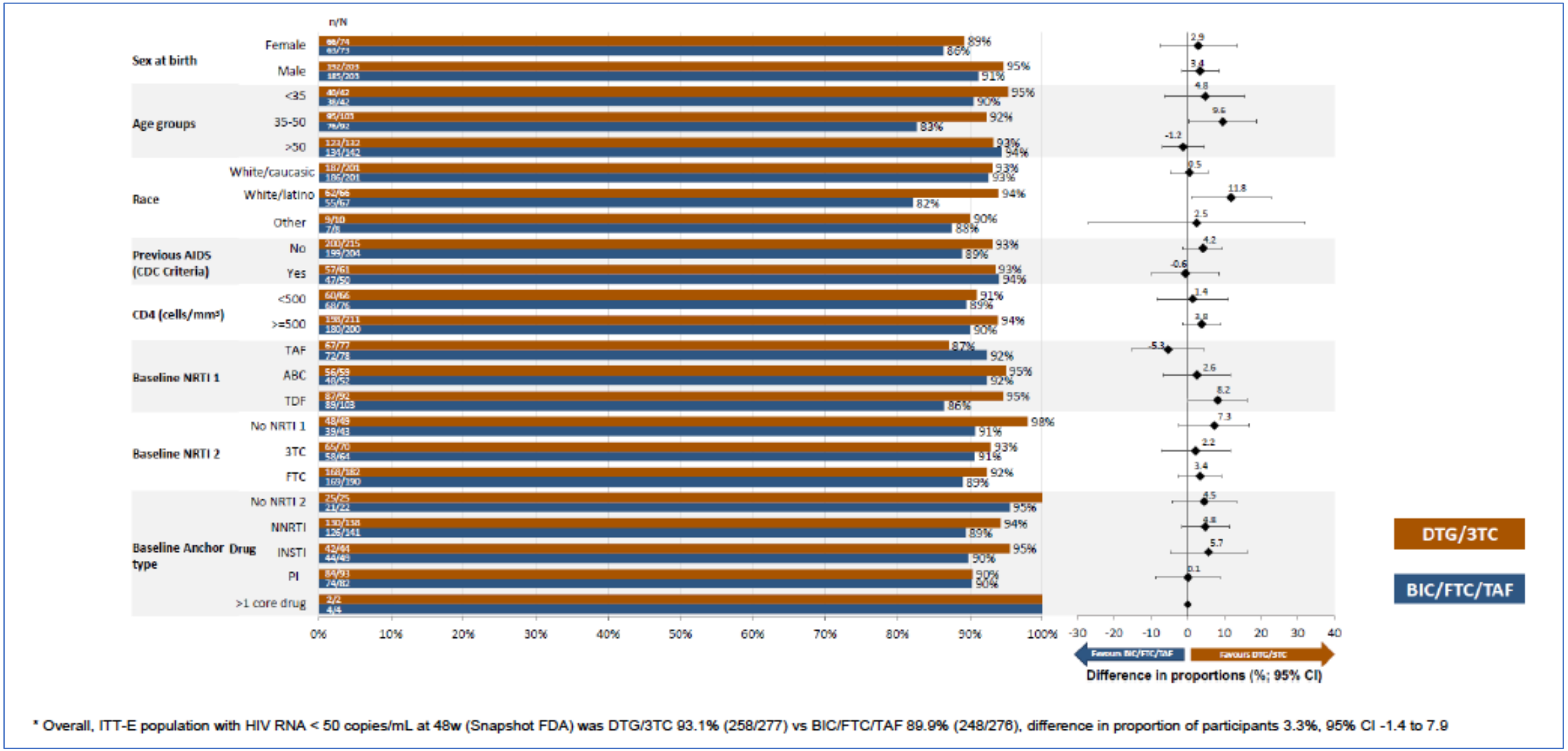
* Most common AEs (>10% in either arm) per system organ class for DTG/3TC and BIC/FTC/TAF arms were:

- infections (36.8% and 45.3%)
- musculoskeletal (19.5% and 18.5%)
- gastrointestinal (17.3% an 10.5%),
- metabolism (13.7% and 9.4%), and
- psychiatric (9.7% and 13.4%)

Switch to DTG/3TC vs BIC/FTC/TAF (PASO-DOBLE Study): Efficacy and Weight Changes by Predefined Subgroups

Tiraboschi et al. CROI 2025; San Francisco, CA. Poster 661

Proportion of PWH With HIV RNA Levels <50 Copies/mL by Subgroups in the ITT-E Population at 48 Weeks



* Overall, ITT-E population with HIV RNA < 50 copies/mL at 48w (Snapshot FDA) was DTG/3TC 93.1% (258/277) vs BIC/FTC/TAF 89.9% (248/276), difference in proportion of participants 3.3%, 95% CI -1.4 to 7.9

553 PWH:DTG/3TC (n=277)AND BIC/FTC/TAF (n=276)

•Significant differences in viral suppression favored DTG/3TC vs BIC/FTC/TAF in the following subgroups: age 35-50 years (9.6%, 95% CI 0.3 to 18.9), Latin-American ethnicity (11.8%, 95%CI 1.0 to 22.7), and TDF at baseline (8.2%, 95%CI 0.1 to 16.2)

Tiraboschi et al. CROI 2025; San Francisco, CA. Poster 661

Neurocognitive impairment (NCI)

The prevalence of NCI was 42.6% [1].

- NCI may be accompanied by depressive symptoms [2], and each of these can adversely affect daily functioning [3].
- NCI in treated PWH may be due to different factors:
  - irreversible injury that occurred prior to ART
  - persistent HIV replication in the central nervous system (CNS) [4],
  - persistent CNS inflammation [5]
  - ART toxicity [6]

Controversy exists regarding the importance of CNS-penetrating ART in treating NCI in PWH, as observational studies yield mixed results—some link better CNS penetration to improved NC performance, while others find no association or worse outcomes.

1.Neurology 2020; 95:e2610–21; 2. Curr HIV/AIDS Rep 2019; 16:82–95; 3. J Neurovirol 2018; 24:141–5. 4. Arch Neurol 2002; 59:923–8. 5. AIDS Res Ther 2010; 7:15; 6. J Neurovirol 2012

Clinical Infectious Diseases

MAJOR ARTICLE

Antiretroviral Therapy Intensification for Neurocognitive Impairment in Human Immunodeficiency Virus

A5324 Study Team

Study design: a randomized, double-blind, placebo-controlled, 96-week trial of ART intensification with dolutegravir (DTG) + MVC, DTG + Placebo, or Dual - Placebo in 191 PWH with plasma HIV RNA <50 copies/mL on ART and NCI. The primary outcome was the change on the normalized total z score (ie, the mean of individual NC test z scores) at week 48.

Characteristic	Total (N = 191)	Dual Placebo (n = 63)	DTG + Placebo (n = 67)	DTG + MVC (n = 61)
Age, y[a]	52 (8)	52 (7)	52 (9)	52 (8)
Sex at birth, female[b]	56 (29%)	15 (24%)	23 (34%)	18 (30%)
Race, Black or African American[b]	97 (51%)	30 (48%)	30 (45%)	37 (61%)
Ethnicity, Hispanic[b]	42 (22%)	15 (24%)	17 (25%)	10 (16%)
Primary language, English[b]	127 (66%)	40 (63%)	44 (66%)	43 (70%)
History of injection Drug use[b]	14 (7%)	2 (3%)	8 (12%)	4 (7%)
HIV RNA, <50 copies/mL[b]	184 (96%)	62 (98%)	64 (96%)	58 (95%)
CD4+ T-cell count, per μL[a]	703 (300)	681 (294)	703 (278)	726 (331)
Nadir CD4+ T-cell count ≤100/μL[2]	57 (30%)	19 (30%)	20 (30%)	18 (30%)
CD4+/CD8+ T-cell ratio[a]	1.00 (0.51)	0.95 (0.46)	1.00 (0.48)	1.05 (0.59)
Body mass index, kg/m^2[a]	29.0 (6.7)	29.5 (6.6)	29.0 (6.8)	28.6 (6.8)
Efavirenz use[b]	60 (32%)	24 (38%)	18 (27%)	18 (30%)
Number of comorbid conditions[a]	4.49 (4.68)	4.32 (3.81)	4.35 (5.03)	4.84 (5.15)
Polypharmacy, >5 concomitant drugs[b]	73 (38%)	21 (33%)	26 (39%)	26 (43%)
Average *z* score[a]	−1.00 (0.73)	−0.96 (0.79)	−0.97 (0.70)	−1.09 (0.70)
Symptomatic HIV-associated neurocognitive disorder diagnosis (mild neurocognitive disorder or HIV-associated dementia)[b]	124 (65%)	42 (67%)	44 (66%)	38 (62%)

CID 2023:77 (15 September)

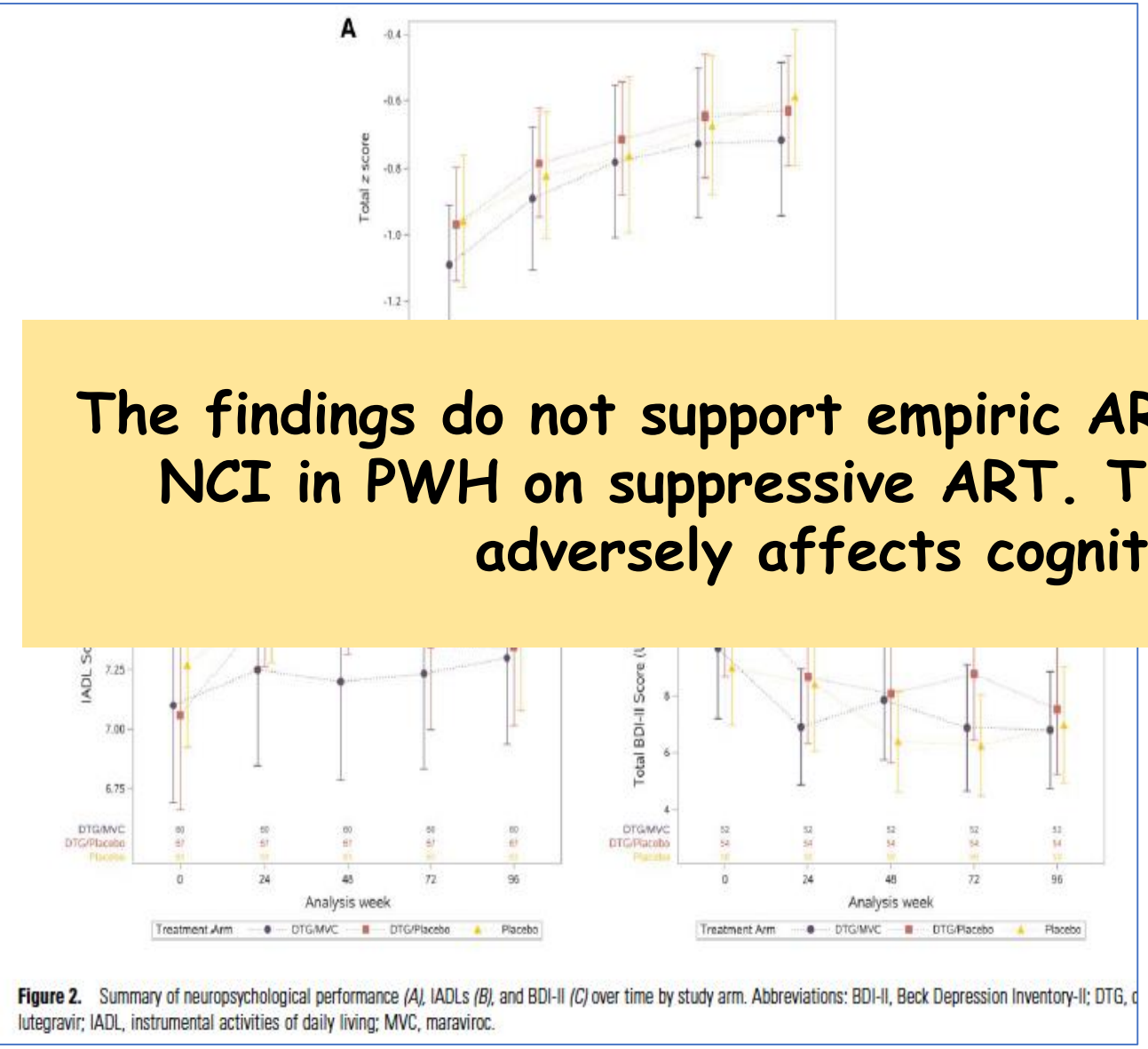


Figure 2. Summary of neuropsychological performance *(A)*, IADLs *(B)*, and BDI-II *(C)* over time by study arm. Abbreviations: BDI-II, Beck Depression Inventory-II; DTG, d lutegravir; IADL, instrumental activities of daily living; MVC, maraviroc.

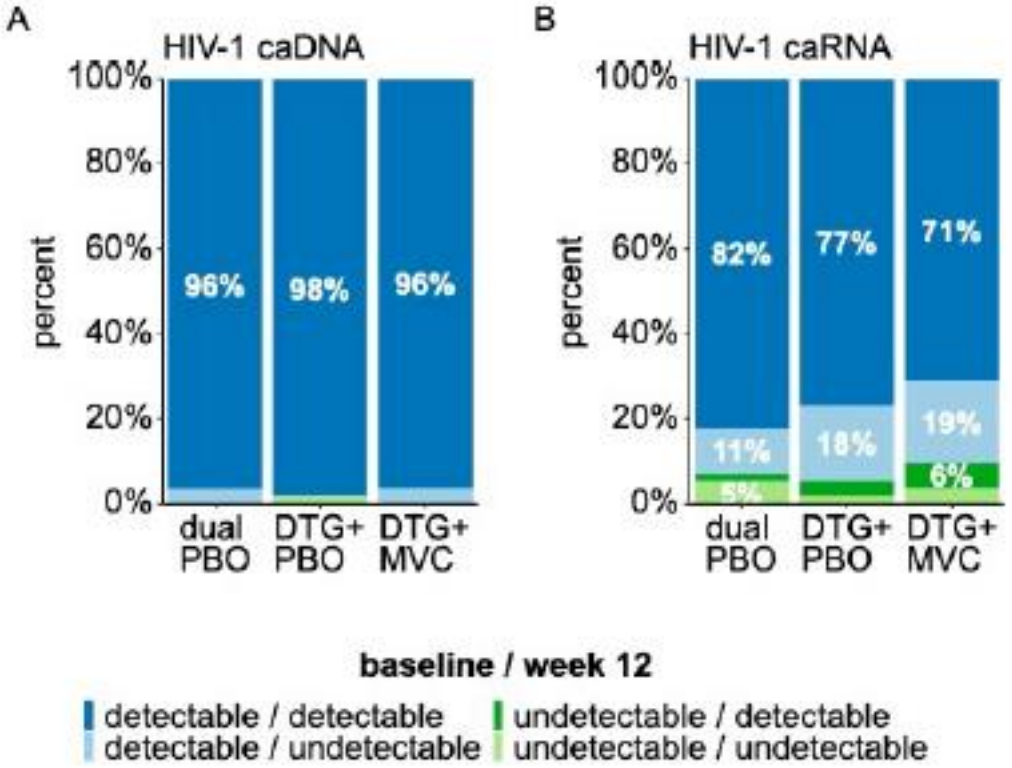
Cognitive Domain	Total (N = 190)	Arm A (Dual-Placebo) (n = 63)	Arm B (DTG + Placebo) (n = 67)	Arm C (DTG + MVC) (n = 60)
Attention/working memory	0.32 (0.21 to 0.43)	0.24 (0.04 to 0.43)	0.44 (0.28 to 0.60)	0.28 (0.07 to 0.50)
Executive function	0.25 (0.15 to 0.35)	0.26 (0.05 to 0.46)	0.24 (0.07 to 0.41)	0.25 (0.09 to 0.42)
Fine motor skills	0.25 (0.16 to 0.35)	0.38 (0.22 to 0.54)	0.19 (0.03 to 0.35)	0.18 (0.00 to 0.37)

The findings do not support empiric ART intensification as a treatment for NCI in PWH on suppressive ART. They also do not support that DTG adversely affects cognition, mood, or weight.

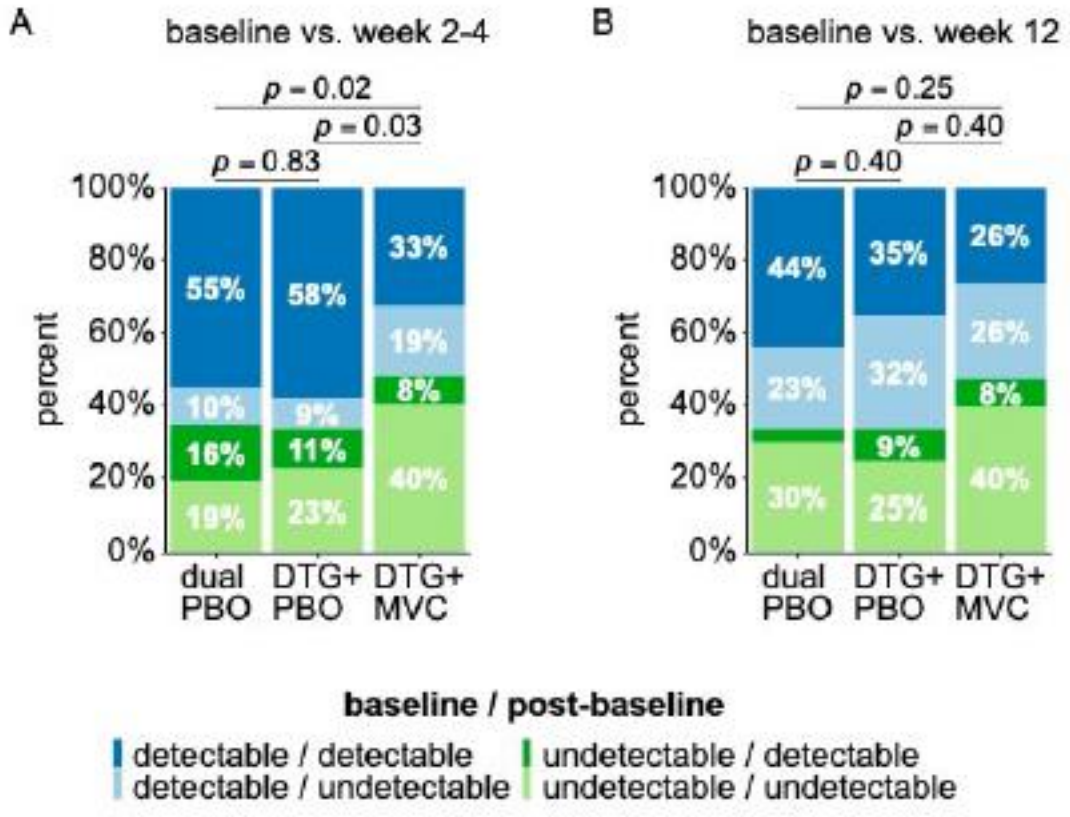
Biomarkers (TNF-α receptor II, soluble vascular cell adhesion molecule-1, soluble CD14, macrophage inflammatory protein (MIP)-1β (R&D Systems), and neurofilament light chain (NfL), measured both in plasma (at baseline, 12 weeks, and 48 weeks; n = 162) and CSF (at baseline and 48 weeks; n = 34) did not change by treatment arm

CID 2023:77 (15 September)

ACTG 5324: Impact of ARV Intensification with MVC and DTG on HIV-1 Virologic Markers

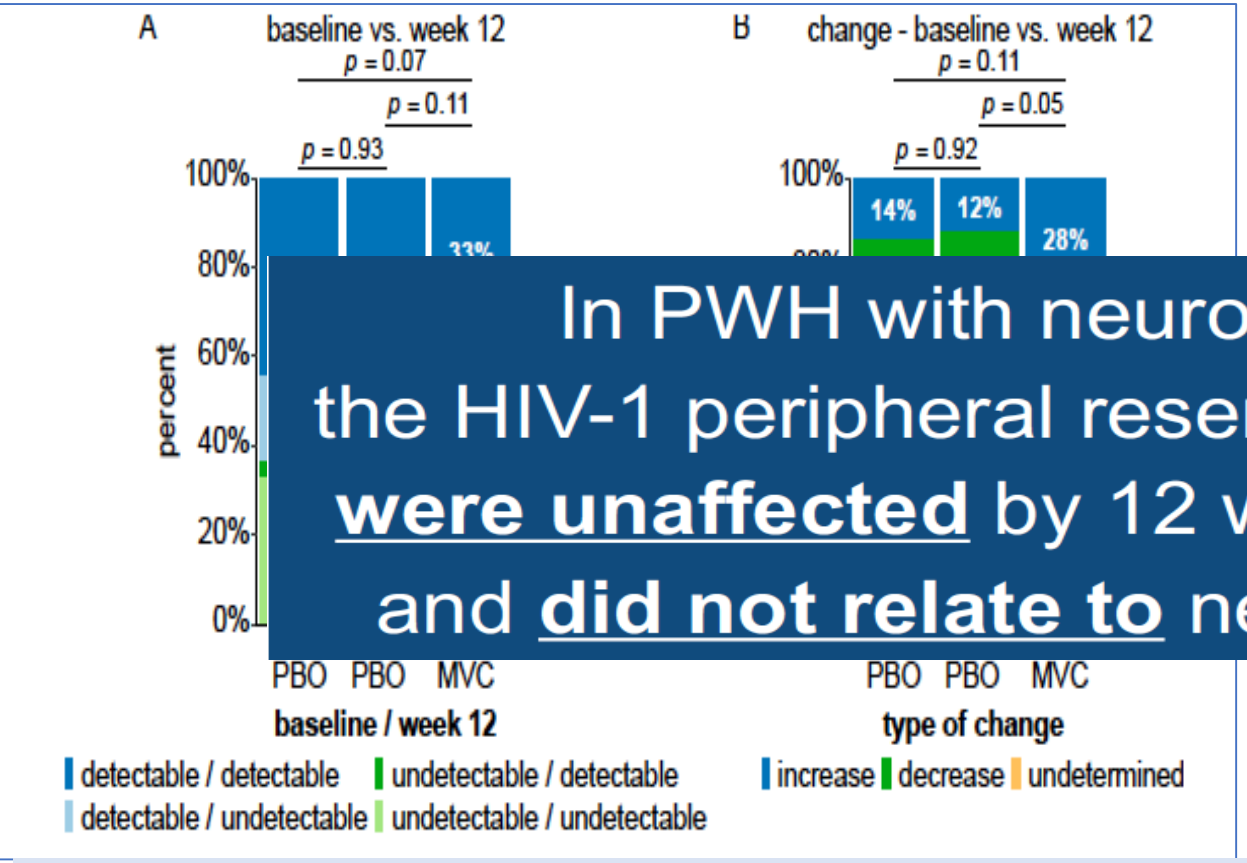


Detection and levels of HIV-1 caDNA and caRNA did not change significantly during first 12 weeks of intensification.



Detection of HIV-1 ca2LTR differed significantly in the DTG+MVC arm at week 2-4, with a higher proportion undetectable at week 2-4, but the difference was diminished by week 12.

Jonathan C Reed, et al. CROI 2025; Abs 672



In PWH with neurocognitive impairment, the HIV-1 peripheral reservoir and residual replication **were unaffected** by 12 weeks of ART intensification and **did not relate to** neurocognitive performance

HIV-1 marker[2]	Correlation with total Z-score[3]	P-Value[3]
		0.79
		0.34
		0.91
		0.75
		0.81
		0.16
		0.05
		0.25

HIV-1 markers and the normalized average neurocognitive performance (Z-score) are not strongly correlated.

Detection of HIV-1 plasma RNA did not differ between arms and a greater proportion of participants experienced an increase in HIV-1 plasma RNA in the DTG+MVC arm.

Jonathan C Reed, et al. CROI 2025; Abs 672

Antibody-based treatment

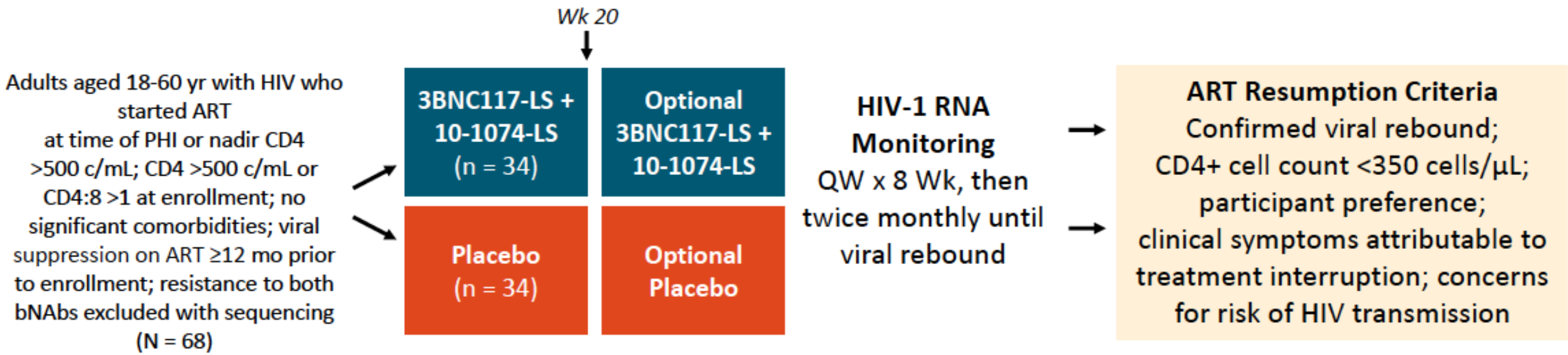
Half the men in an HIV cure study stayed off treatment for nearly a year after a two-antibody shot

Similar results from a South African study in young women, CROI hears

Gus Cairns | 12 March 2025 | Estimated reading time 8 minutes

RIO: Effect of bNAbs on HIV Control During ART Interruption

- International, placebo-controlled, double-blind, randomized phase II study

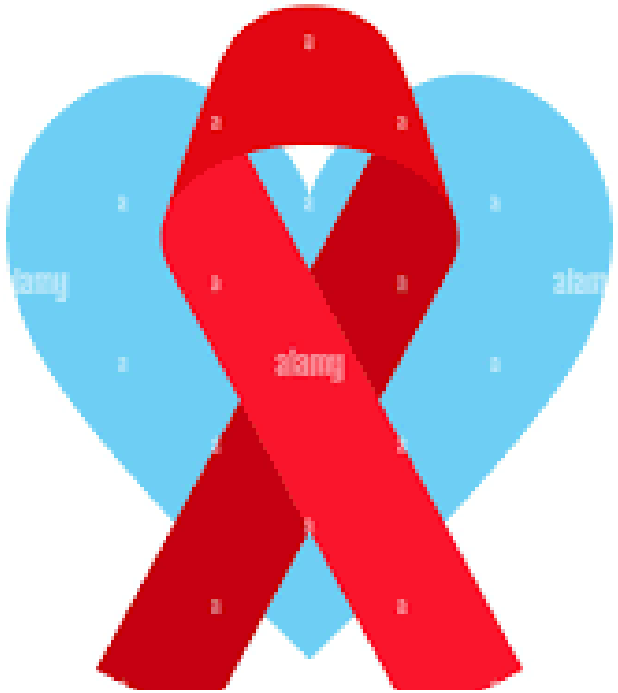


- **Primary endpoint:** Time to viral rebound (HIV-1 RNA >1000 c/mL for 6 wk, HIV-1 RNA >100,000 c/mL x 2, other instances reviewed by independent panel) by Wk 20 after ART interruption
- **Key secondary endpoints:** safety, long-term viral suppression

Fidler. CROI 2025. Abstr 107

Take home messages

- Overall, the addition of antiretroviral drugs in both treatment-naive and virologically suppressed patients does not affect residual viremia and does not enhance CD4 cell recovery.
- The BIC/FTC/TAF intensification regimen did not show improved virological success compared to the DTG/3TC regimen.
- The negative findings reported in the ACTG 5324 study do not support the use of ART intensification for treating NCI in people with HIV who are already on stable, suppressive ART.
- Exploring new trajectories in HIV care can extend beyond traditional intensification approaches to address emerging clinical needs.



grazie per l'attenzione