Clinical Data from the GP120 Inhibitor Temsavir and Its Relevance to Immune Reconstitution and HIV Associated Inflammation

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- I have received research grants or honoraria for lectures or advisory boards from Gilead Sciences, ViiV Healthcare, MSD, Janssen, Novartis, AbbVie and Roche

1. Low CD4 T cell counts is bad
2. Immune reconstitution from low CD4 T cell counts is challenging
3. Is inhibiting GP120 advantageous for immune reconstitution?

Low CD4+ Cell Count Predicts Mortality Risk

- A study of 13,011 North American and European PLWH who started ART between 1996 and 1999 with most achieving virologic suppression[a] 10 years after ART start, found that **low CD4+ cell count 10 years after ART was associated with increased mortality risk**
  - Baseline CD4+ cell count was not significantly associated with 10-year mortality risk
- **Both AIDS and non-AIDS mortality risk increased**

CD4+ cell count period	CD4+, cells/mm^3	Mortality risk, HR, 95% CI
CD4+ cell count at 10 years on ART	≥750	1 (ref)
	500-749	1.04, 0.80-1.37
	350-499	1.47, 1.12-1.93
	200-349	1.92, 1.45-2.54
	100-199	3.33, 2.42-4.60
	0-99	6.85, 4.89-9.60
Baseline CD4+ cell count	≥350	1 (ref)
	200-349	0.96, 0.77-1.19
	100-199	0.94, 0.74-1.20
	50-99	0.88, 0.67-1.16
	0-49	0.69, 0.52-0.90

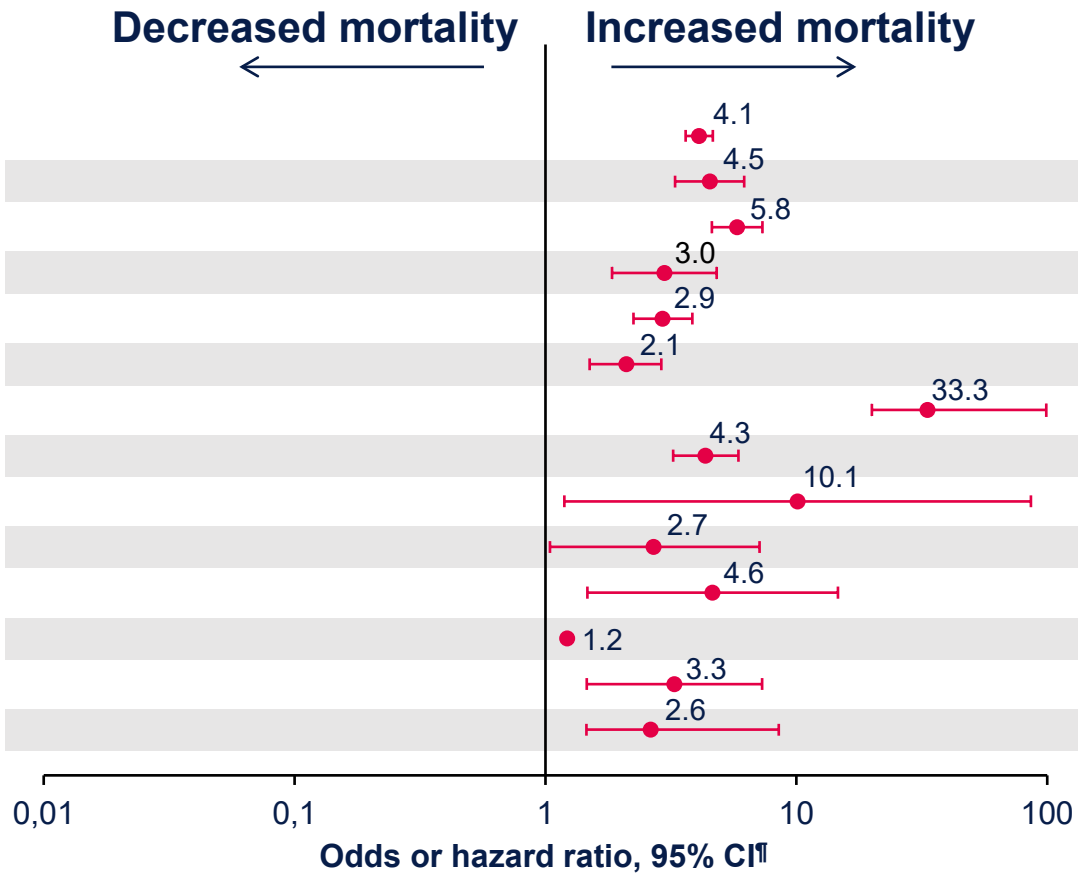
HR, hazard ratio; ref, reference.

After 10 years of ART, low CD4+ cell count was predictive of increased mortality risk in a cohort of PLWH even though the majority achieved virologic suppression

[a]88% achieved HIV-1 RNA <200 c/mL.

Trickey et al. *PLoS One*. 2016;11:e0160460.

Low CD4+ cell count and elevated mortality risk



Mortality, comparison (CD4+ cells/mm^3)	
Non-specific, 0-49 vs ≥500[1*]	Non-specific mortality
Non-specific, not achieving CD4+ ≥200[2†]	
Non-specific, ≤200 vs >200[3]	
Non-specific, <200 vs ≥200[4]	
Non-specific, <50 cells/mm^3 increased mortality[5‡]	
Non-specific, <100 vs ≥350[6]	
Non-specific, 0-49 vs ≥350[7§]	
AIDS-related, <200 vs ≥500[8]	
COVID-19, nadir CD4+ <200[9§]	
CMV end organ disease, <30 vs 30–59[10§]	
TB, <50 vs >200[11]	
TB, 50 CD4+ cells/mm^3 decrease[12]	
Pulmonary **TB**, ≤200[13‖]	
Pulmonary **TB**, quartile decrease in CD4+ count[14]	

Low CD4+ cell count was associated with increased non-specific mortality risk and mortality risk from specific causes including COVID-19, tuberculosis and AIDS-related mortality

*Risk ratio; †Not obtaining CD4+ ≥200 cells/mm3 within 24 months vs obtaining ≥200 cells/mm3 in <6 months ‡6-month mortality; §Odds ratio; ‖At time of TB treatment start; ¶Data plotted as hazard ratios unless stated otherwise **CI,** confidence interval; **CMV,** cytomegalovirus; **TB,** tuberculosis

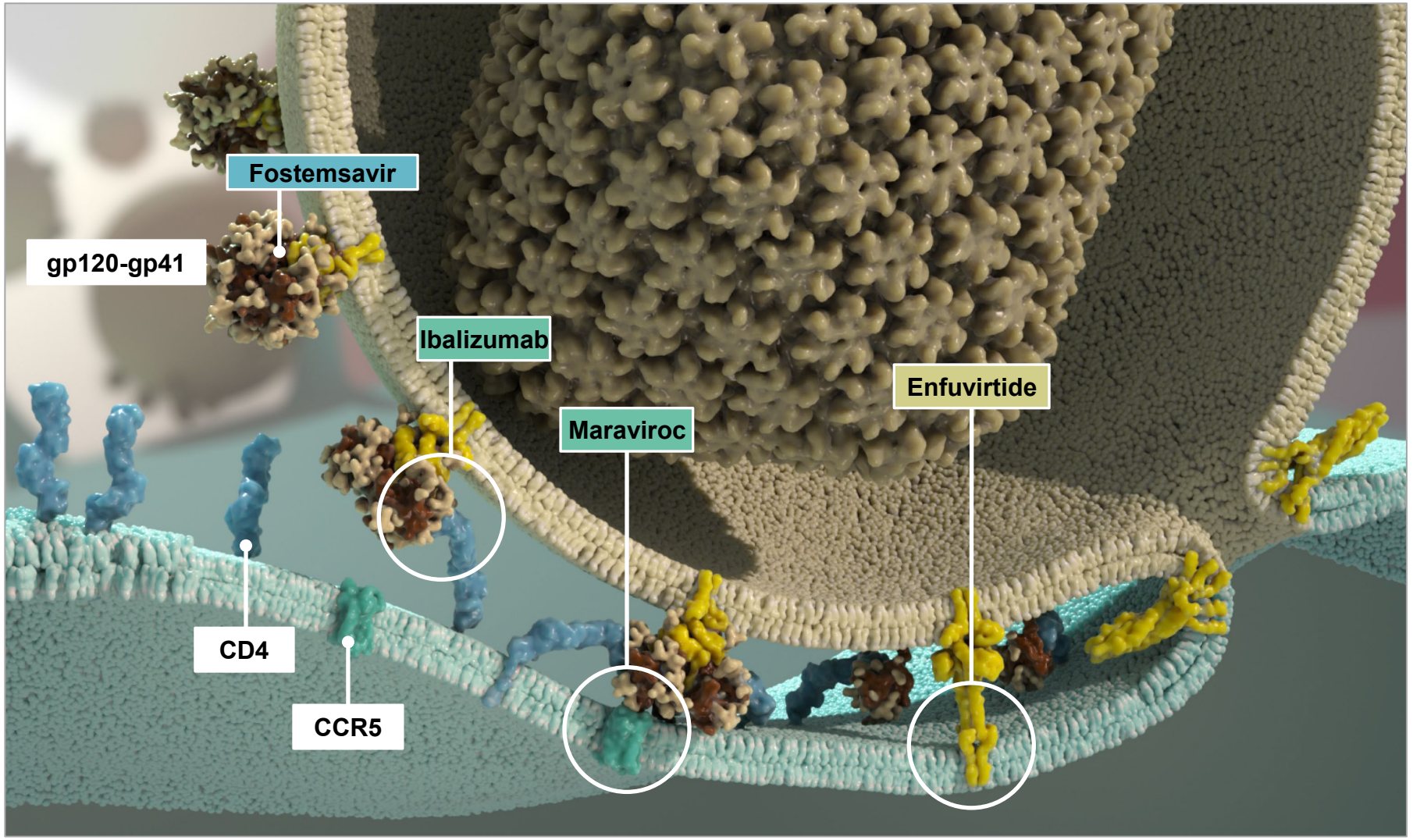
1.Raffetti et al. *BMC Public Health*. 2015;15:235., **2.** Ferrer et al. *J Antimicrob Chemother*. 2015;70:3332-3338. **3.** Touré et al. *AIDS Care*. 2015;24:1272-1276. **4.** Lay et al. *PLoS One*. 2017;12:e0185348. **5.** Akinyemi et al. *Afr J AIDS Res*. 2015;14:201-207. **6.** Mugisha et al. *PLoS One*. 2014;9:e85774. **7.** Tweve et al. *Trop Med Int Health*. 2015;20:791-796. **8.** Lima et al. *Cad Saude Publica*. 2018;34:e00009617. **9.** Hoffman et al. *HIV Med*. 2021;22:372-378. **10.** Chakraborty et al. *PLoS One*. 2015;10:e0117466. **11.** Parchure et al. *Int J Tuberc Lung Dis*. 2016;20:1348-1353. **12.** Kaplan et al. *BMC Infect Dis*. 2018;18:356. **13.** Lai et al. *Biomed Environ Sci*. 2015;28:421-428. **14.** Ravimohan et al. *Lancet Infect Dis*. 2015;15:429-438.

HIV-1 host cell entry is a complex, three-step process.

Step1
CD4 Cell Receptor Attachment
a. gp120 binds CD4

Step 2a, 2b
Co-receptor Binding
a. CD4 bending after gp120 binding
b. gp120 binds CCR5

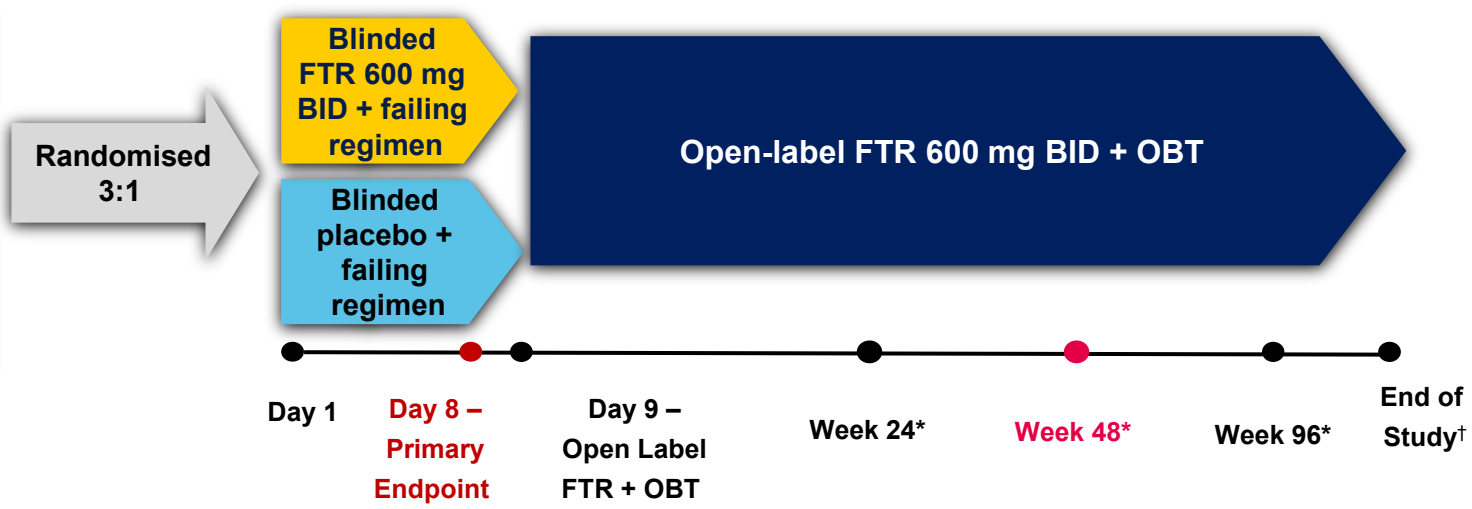
Step 3a, 3b, 3c
Membrane Fusion
a. gp41 inserts into host.
b. gp41 folds and membranes fuse.
c. Fusion pore formed.



Phase III Study: Study Design and Endpoints

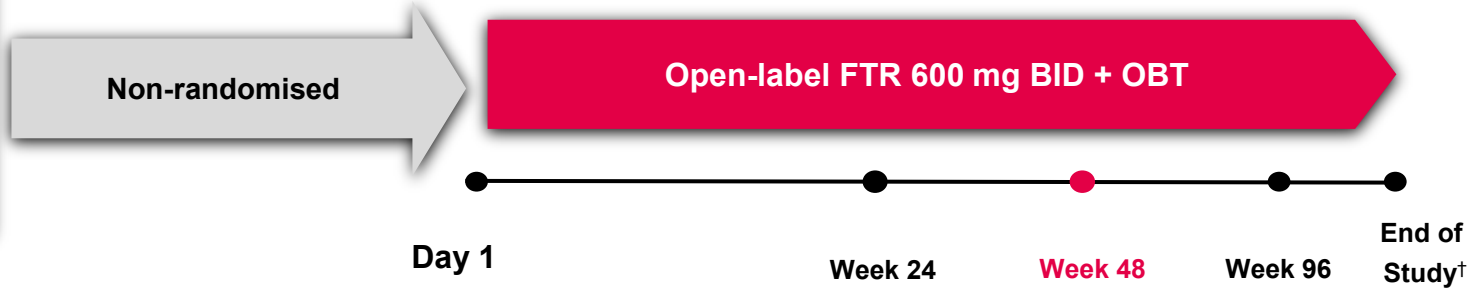
Randomised Cohort §:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 1 or 2 ARV classes remaining & ≥1 fully active & available agent per class
- Unable to construct viable regimen from remaining agents



Non-Randomised Cohort §:
HTE participants, failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

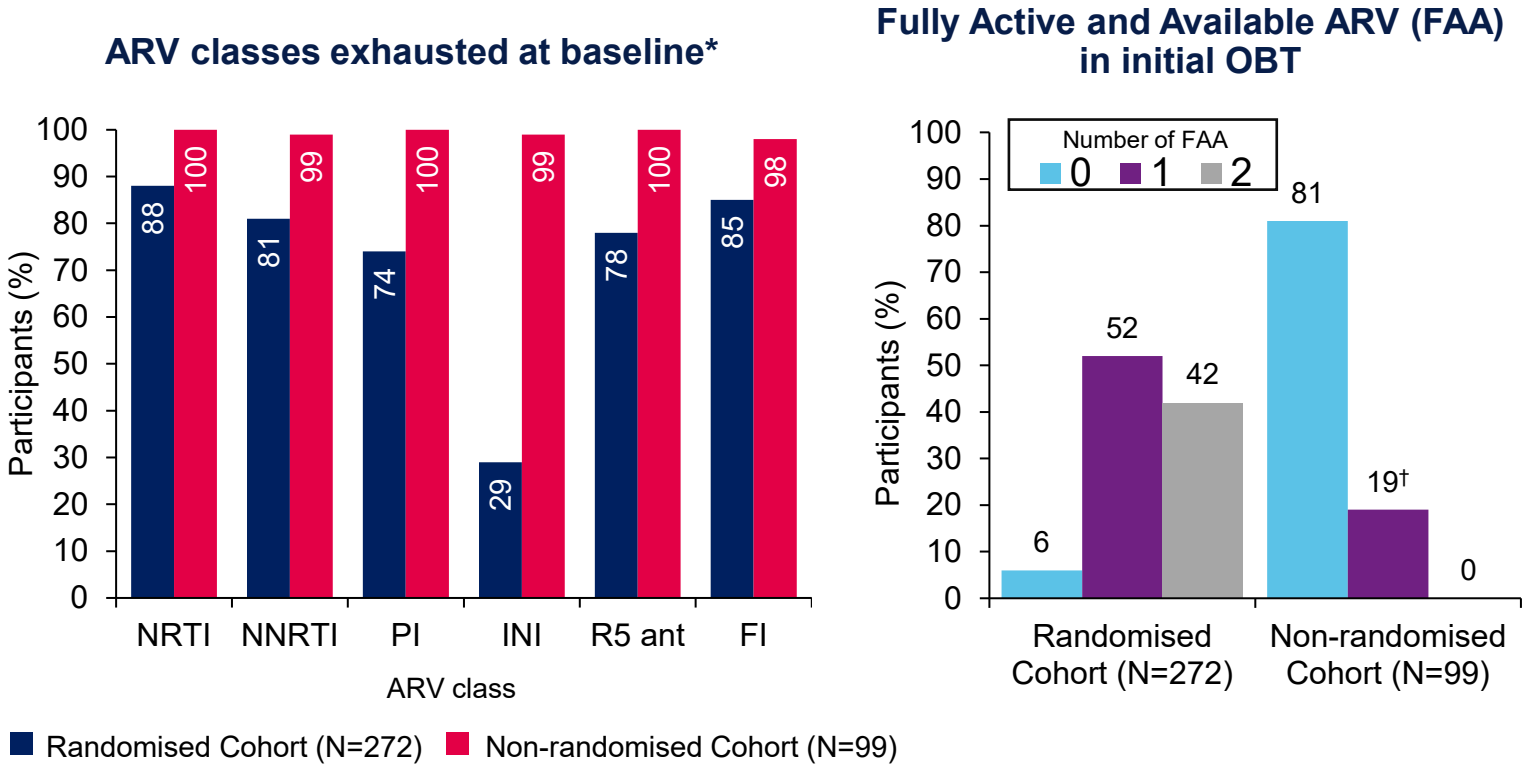
- 0 ARV classes remaining and no remaining fully active approved agents‡



*Measured from the start of open label FTR 600 mg BID + OBT; †The study is expected to be conducted until an additional option, rollover study or marketing approval, is in place; ‡Use of investigational agents as part of OBT was permitted; §There was no screening FTR IC_{50} criteria
BID, twice-daily; OBT, Optimised Background Therapy

Lataillade et al. EACS 2017. Abstract PS8/5, , Kozal et al. NEJM 2020; 382: 1232-43; Lataillade et al., IAS 2019; Abstract MOAB0102.

Baseline Prior ARV Exposure and Resistance



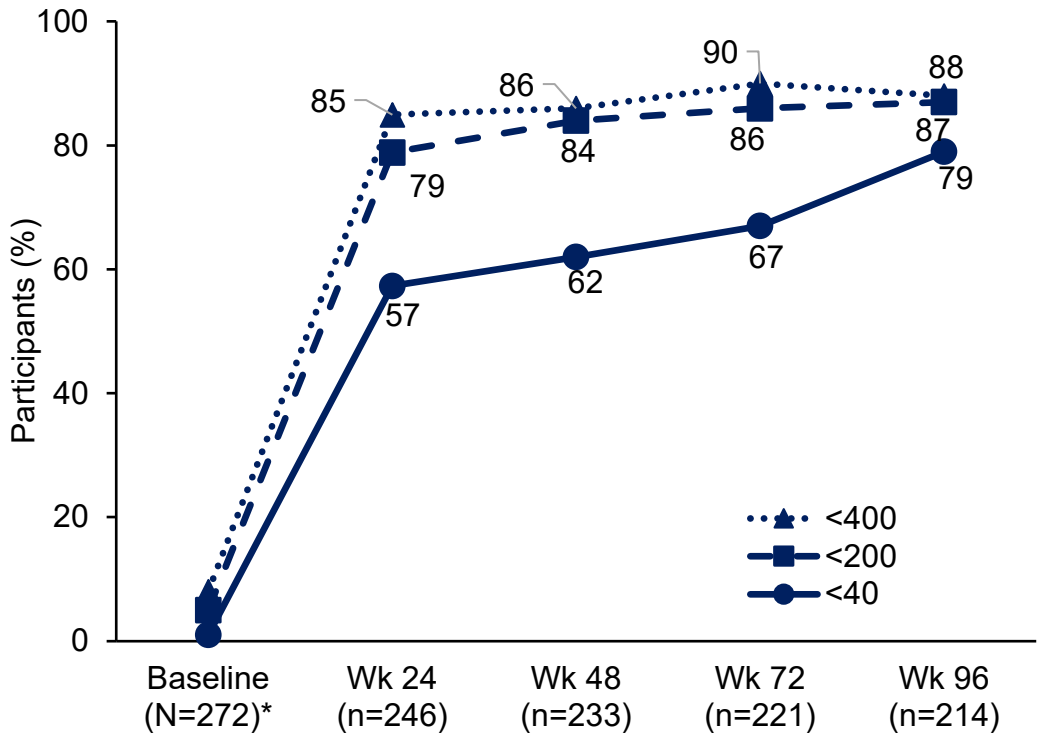
18/29 deaths due to AIDS-related events

*Proportions of participants for whom there are no remaining FAAs within the indicated ARV class, based on Monogram assays (PhenoSense® GT Plus Integrase, Trofile®, and PhenoSense® Entry), historical resistance, eligibility, and tolerability. †15/19 received investigational ARV ibalizumab and 4/19 were incorrectly assigned to the Non-randomised Cohort
FAA, fully active and Available ARV; FI, fusion inhibitor; INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; R5 ant, CCR5 antagonist

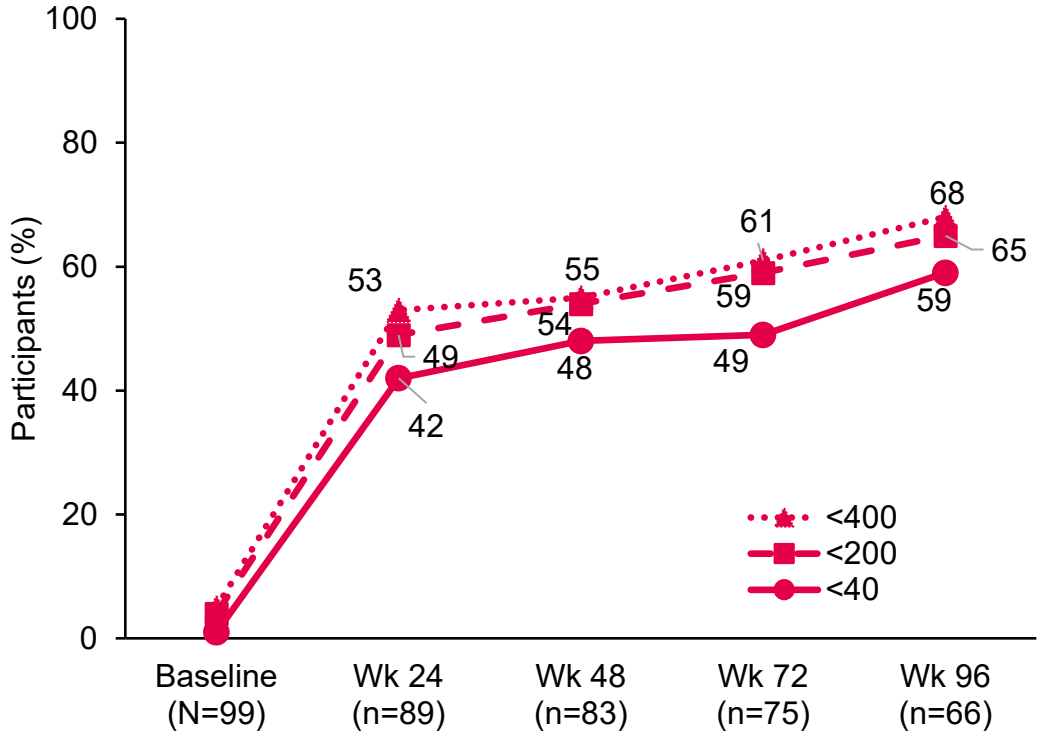
Lataillade, et al. EACS 2017. Abstract , Kozal et al. NEJM 2020; 382: 1232-43; Lataillade et al., IAS 2019; Abstract MOAB0102.

Virologic Response Over Time- Observed Analysis

Randomized Cohort (N=272)



Non-randomized Cohort (N=99)



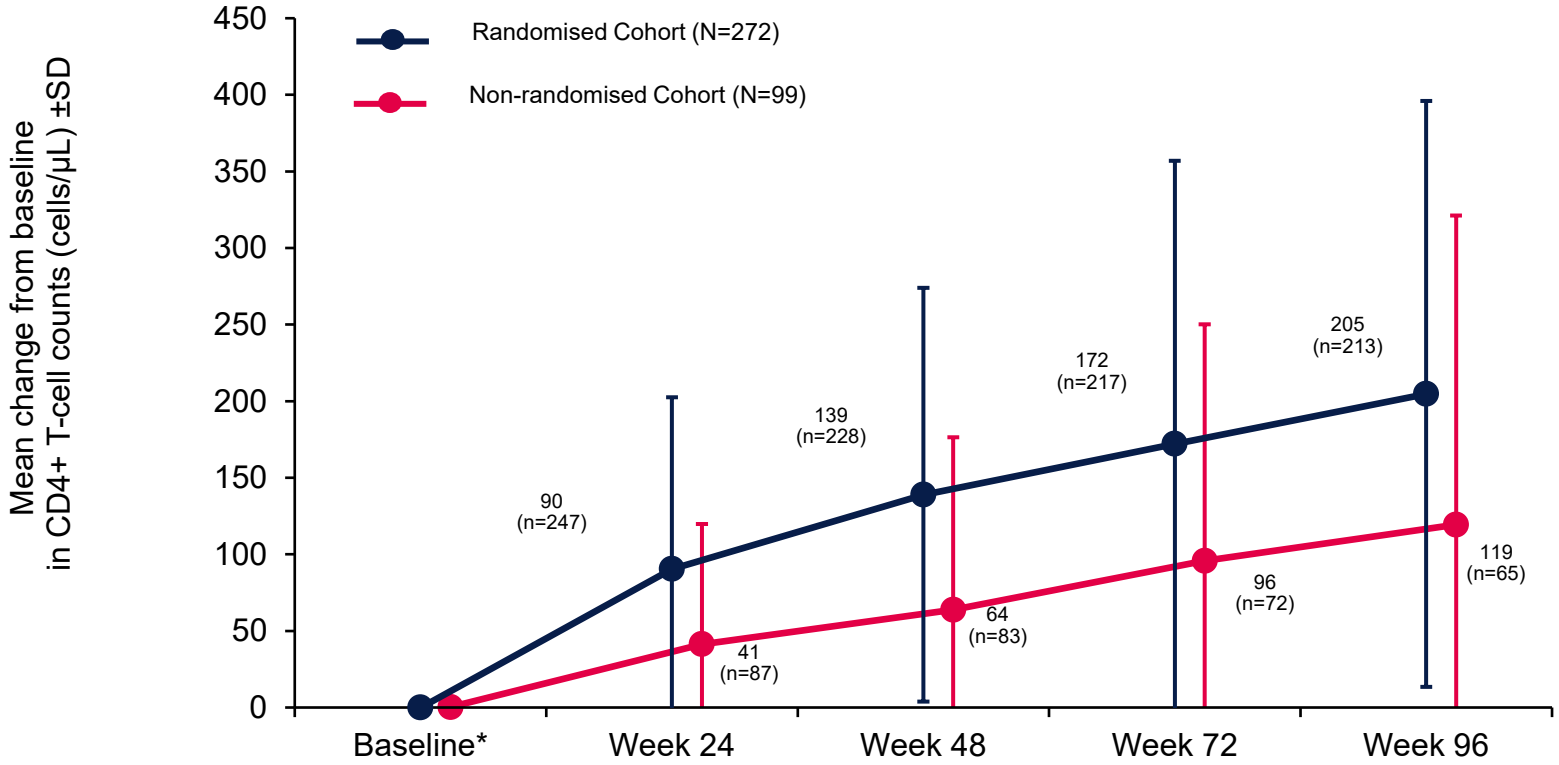
*At baseline 8 participants had HIV-1 RNA <400 copies/mL, 5 had HIV-1 RNA <200 copies/mL, and 1 had HIV-1 RNA <40 copies/mL.
†At baseline 5 participants had HIV-1 RNA <400 copies/mL, 4 had HIV-1 RNA <200 copies/mL, and 1 had HIV-1 RNA <40 copies/mL.

Kozal et al. NEJM 2020; 382: 1232-43; Lataillade et al., IAS 2019; Abstract MOAB0102

Mean Change in CD4 Count Over Time- Observed Analysis

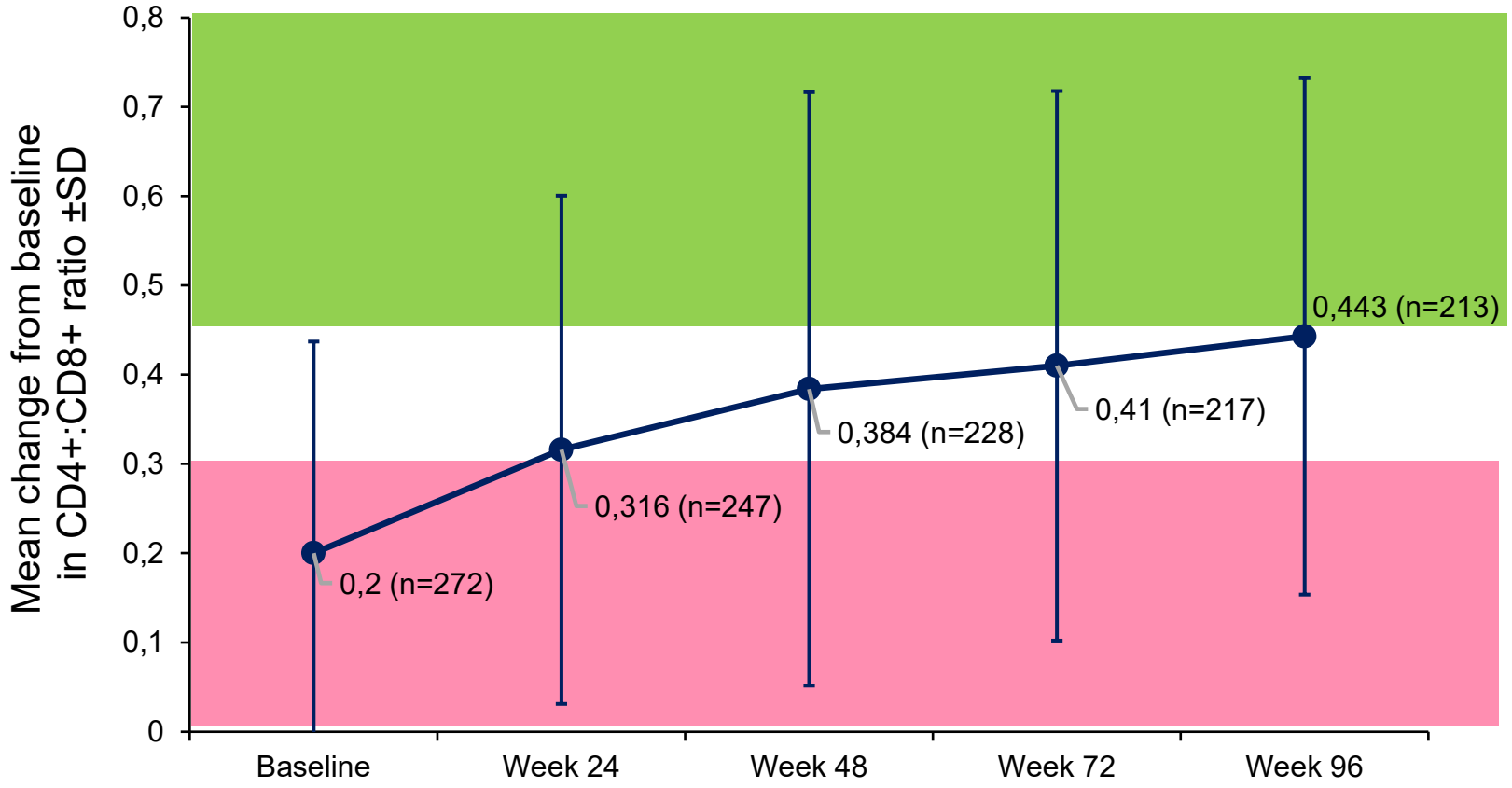
BRIGHTE

- Mean Baseline CD4+ T-cell count for Randomized Cohort was 153 cells/μL and 99 cells/μL for Non-Randomized subjects



Kozal et al. NEJM 2020; 382: 1232-43; Lataillade et al., IAS 2019; Abstract MOAB0102

Mean CD4/CD8 Ratio Over Time; Observed Analysis-Randomized Cohort

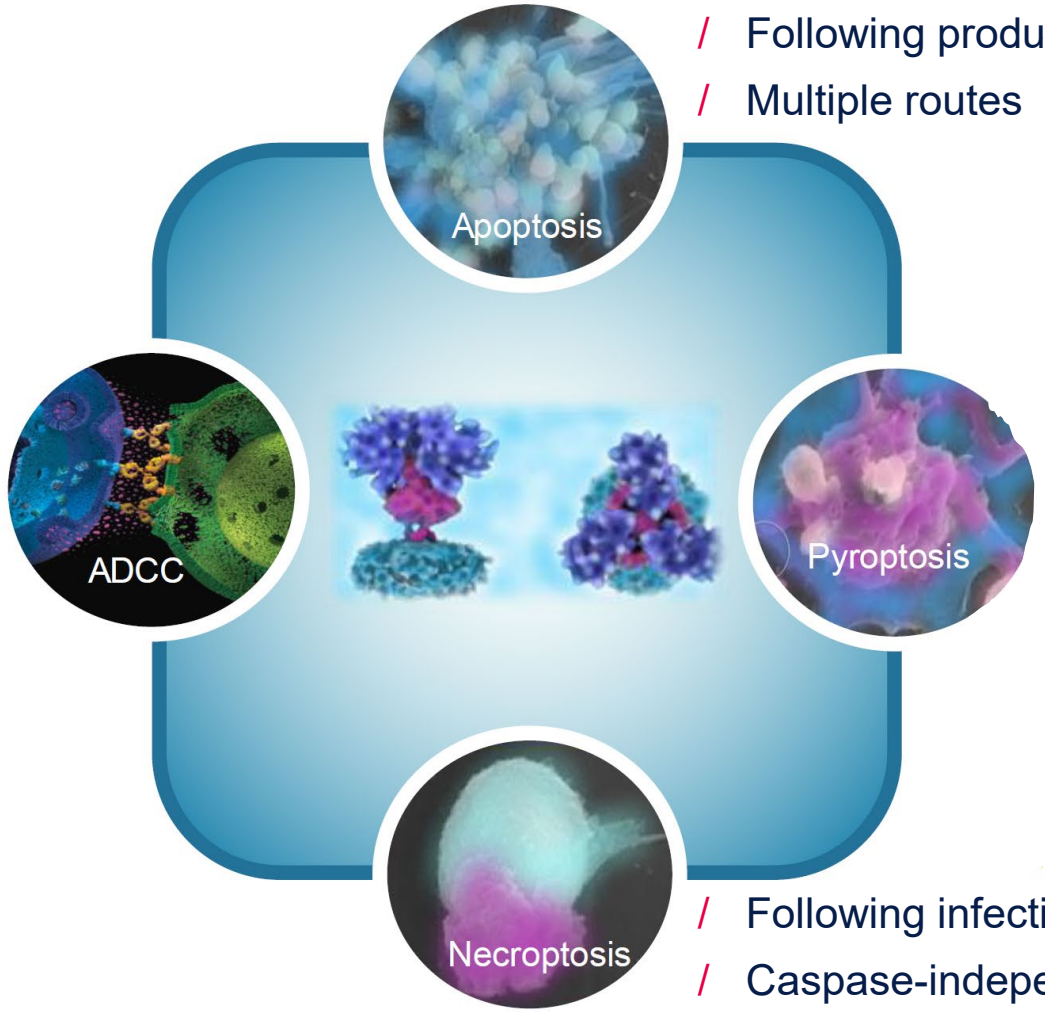


In univariate and multivariate analysis, CD4/8 ratio <0.30 (compared to >0.45) was associated with significantly higher risk of progression to severe AIDS and non-AIDS defining events or death, independent of current CD4 count

Mussini et al. Lancet HIV. 2015;2:e98–106
Lataillade et al. IAS 2019. Abstract MOAB0102.

gp120-mediated depletion mechanisms

- Following productive infection
- Multiple routes



- Targets infected CD4 T cells expressing envelope
- Targets bystander CD4 T cells with bound gp120

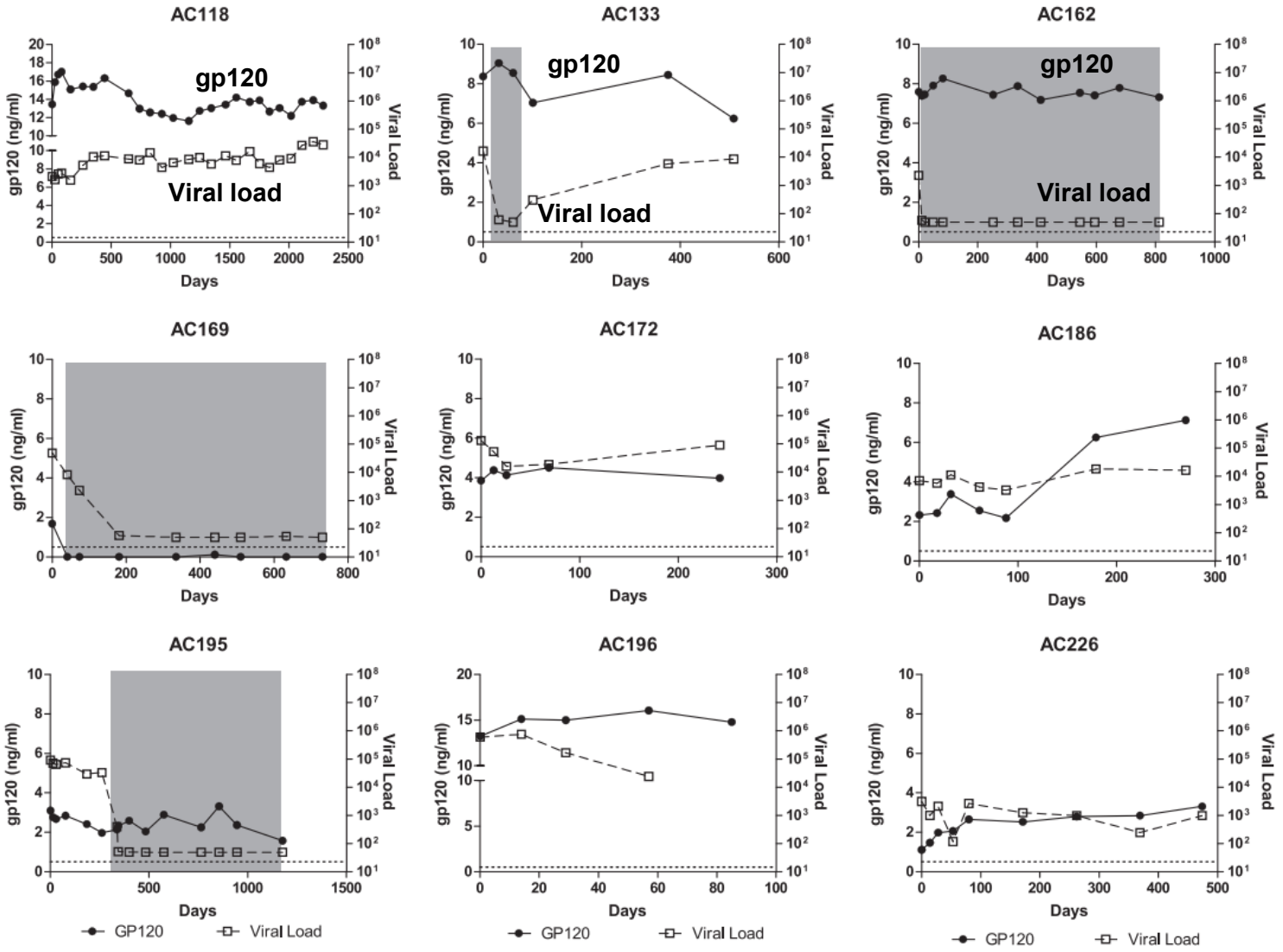
- Following abortive infection
- Leads to exosome formation
- Multiple routes

- Following infection/ inflammatory damage
- Caspase-independent

ADCC, antibody-dependent cellular cytotoxicity

1. Doitsh G, Greene W. Cell Hist Microbe 2016:19:280; **2.** Cox A, Siliciano R. Nature 2014;505:492

Regardless of viral control, gp120 expression remains constant and has been associated with inflammation in people living with HIV

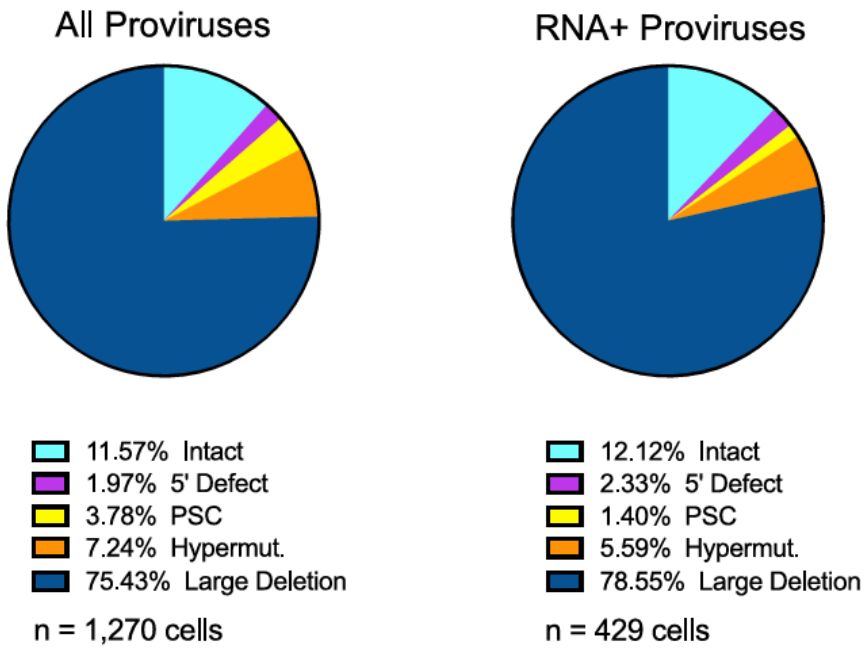


Grey boxes indicate periods when subject was on ART

Rychert J, et al. AIDS Res & Hum Retroviruses 2010;26:1139–45

Intact and defective provirus contribute to HIV transcription

Proviral sequence classification in analysed HIV-1 infected cells and long LTR RNA-expressing HIV-1 infected cells



*Among analysed proviruses
PSC, premature stop codon

Einkauf, KB et al. Cell 2022;185:266–82

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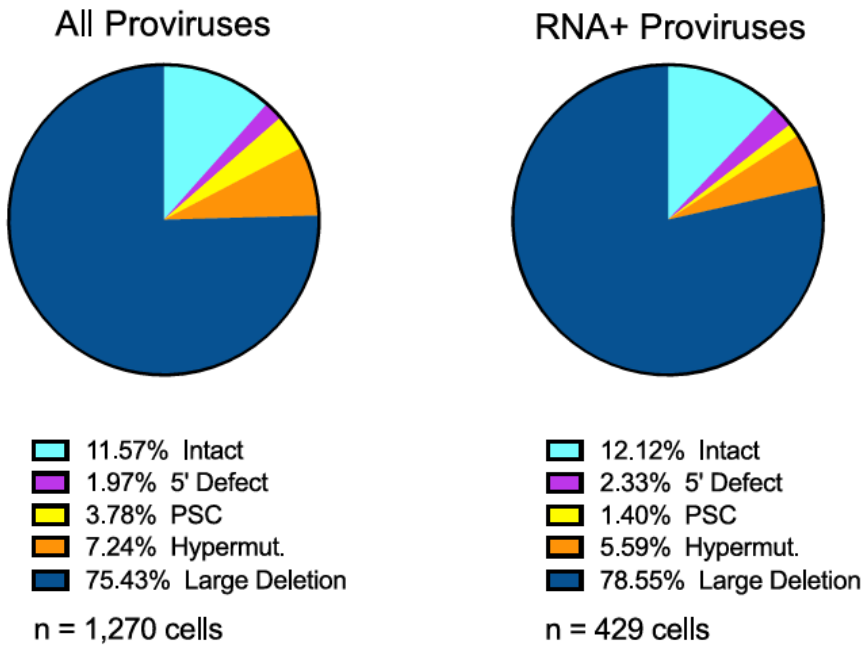
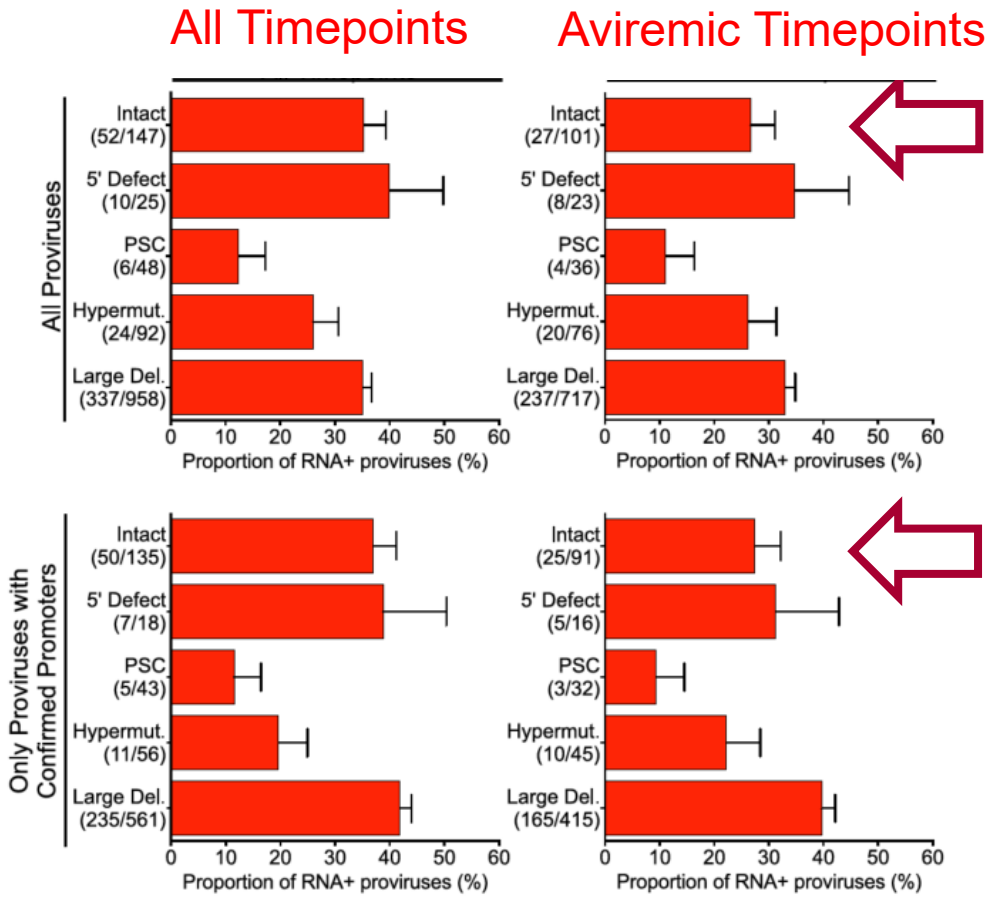


Proportion of HIV-1 long LTR RNA-expressing proviruses,* stratified according to proviral sequence intactness/defects



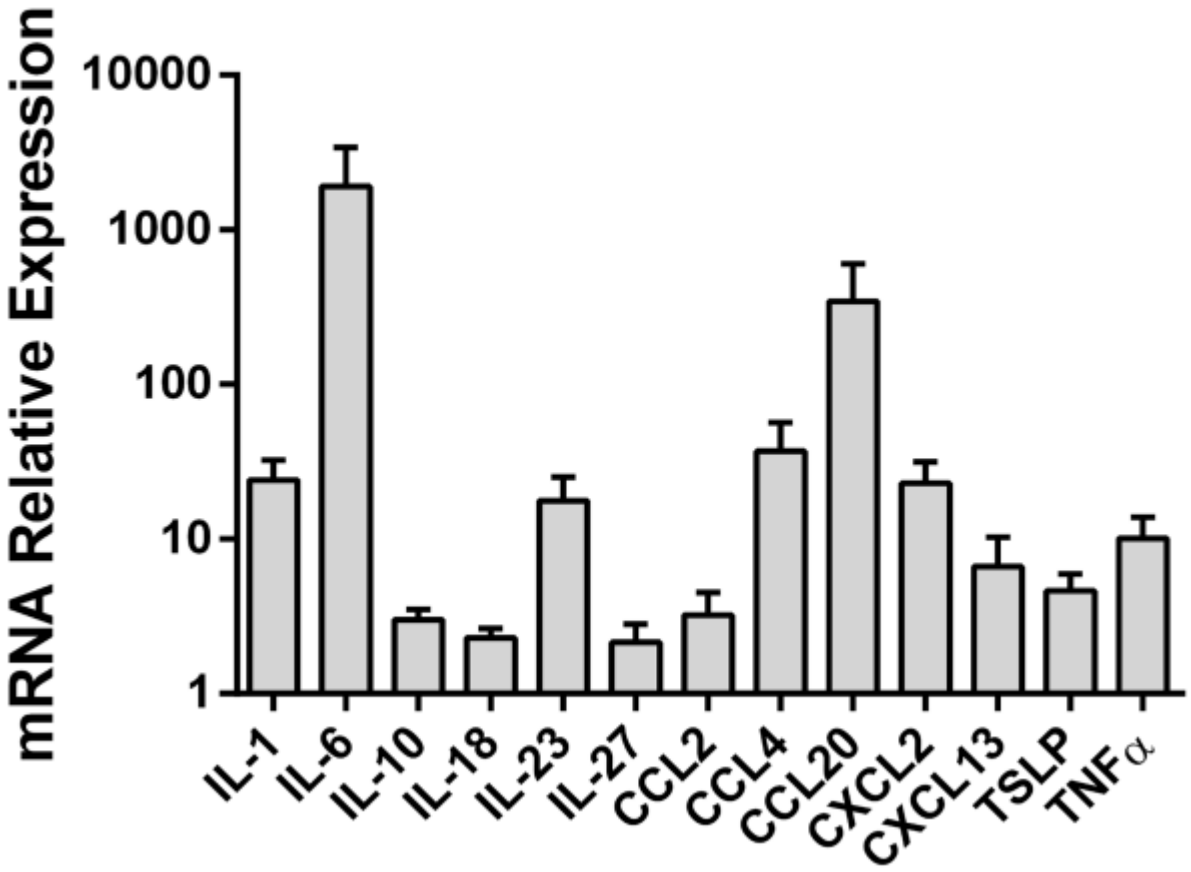
- HIV RNA readily detected across all patients and timepoints, from both intact and defective proviruses

*Among analysed proviruses
PSC, premature stop codon

Einkauf, KB et al. Cell 2022;185:266–82

HIV-1 gp120 leads to cytokine bursting in human monocytes

mRNA expression of cytokines (RT-qPCR) after stimulation with gp120 relative to mock set at 1



Healthy donor PBMCs exposed to gp120:

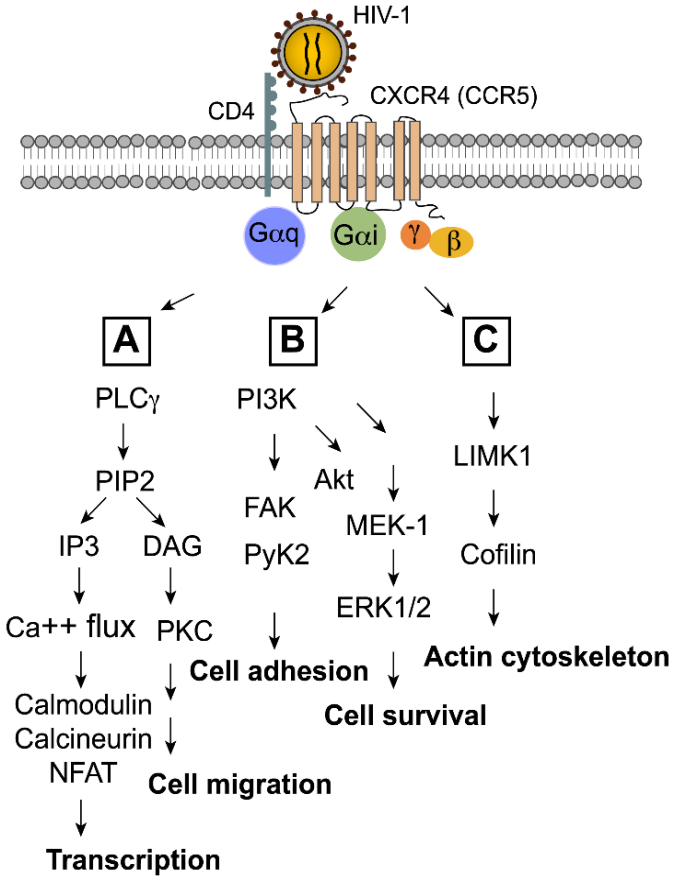
- Strong and diverse cytokine burst
- Mainly due to monocytes (IL-10, IL-1, IL-6 and CCL2)
- Binding to CD4 is the first necessary step in the induction of the cytokine bursting

IL, interleukin; **mRNA,** messenger RNA; **PBMC,** peripheral blood mononuclear cell; **RT-qPCR,** reverse transcription quantitative PCR
TNF-α, tumour necrosis factor alpha; **TSLP,** thymic stromal lymphopoietin

Levast B, et al. PLOS One 2017; 12: e0174550

Multiple HIV-1: Host protein interactions profoundly alter cell function and phenotype

Components of the chemokine coreceptor signalling pathways activated by HIV-1 envelope[1]



DAG, diacylglyerol; **ERK1/2,** extracellular signal-regulated kinase; **IP3,** inositol triphosphate; **LIMK1,** LIM kinase
MAPK, mitogen-activated protein kinase; **MEK-1,** mitogen/extracellular signal-regulated kinase; **NFAT,** nuclear factor of activated T cells
PIP2, phosphatidylinositol-4,5-biphosphate; **PKC,** protein kinase C; **PLC,** phospholipase C; **PyK2,** proline-rich tyrosine kinase

1. Wu Y, Yonder A. PLOS Pathogens 2009; 5: e1000520

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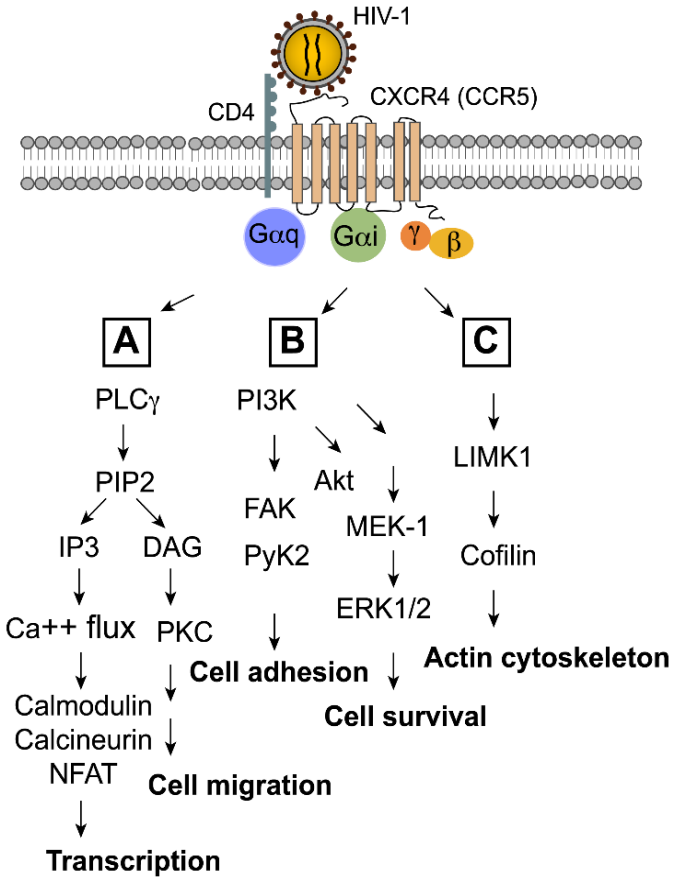
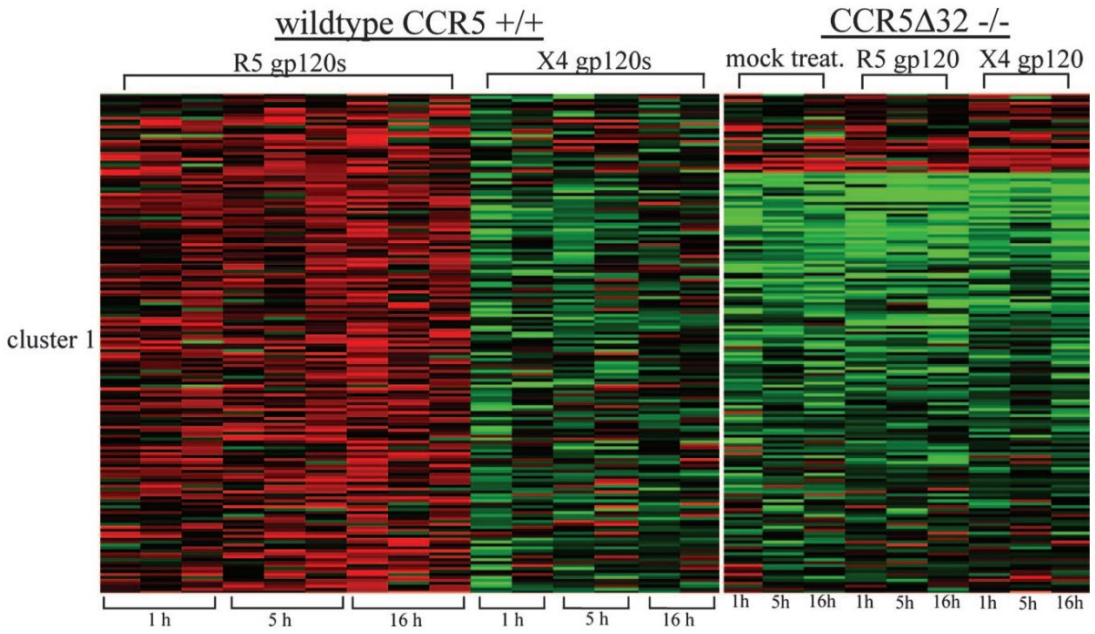


Heatmap of protein expression[2]



- Genes belonging to the MAPK signal transduction pathways
- Genes regulating cell cycle
- Absent in CCR5Δ32 deletion

DAG, diacylglyerol; **ERK1/2,** extracellular signal-regulated kinase; **IP3,** inositol triphosphate; **LIMK1,** LIM kinase
MAPK, mitogen-activated protein kinase; **MEK-1,** mitogen/extracellular signal-regulated kinase; **NFAT,** nuclear factor of activated T cells
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1. Wu Y, Yonder A. PLOS Pathogens 2009; 5: e1000520
2. Cicala C, et al. PNAS 2006; 103: 3746-51

Summary

- Due to primary (virologic) and secondary effects, persistent inflammation impairs CD4+ T-cell homeostasis in people with HIV
- HIV and viral proteins (including gp120) maybe able contributing to this (even if VL<50 c/mL)