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IMMUNE ACTIVATION IN PLHIV

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IMMUNE ACTIVATION IN TREATMENT-NAÏVE PLHIV

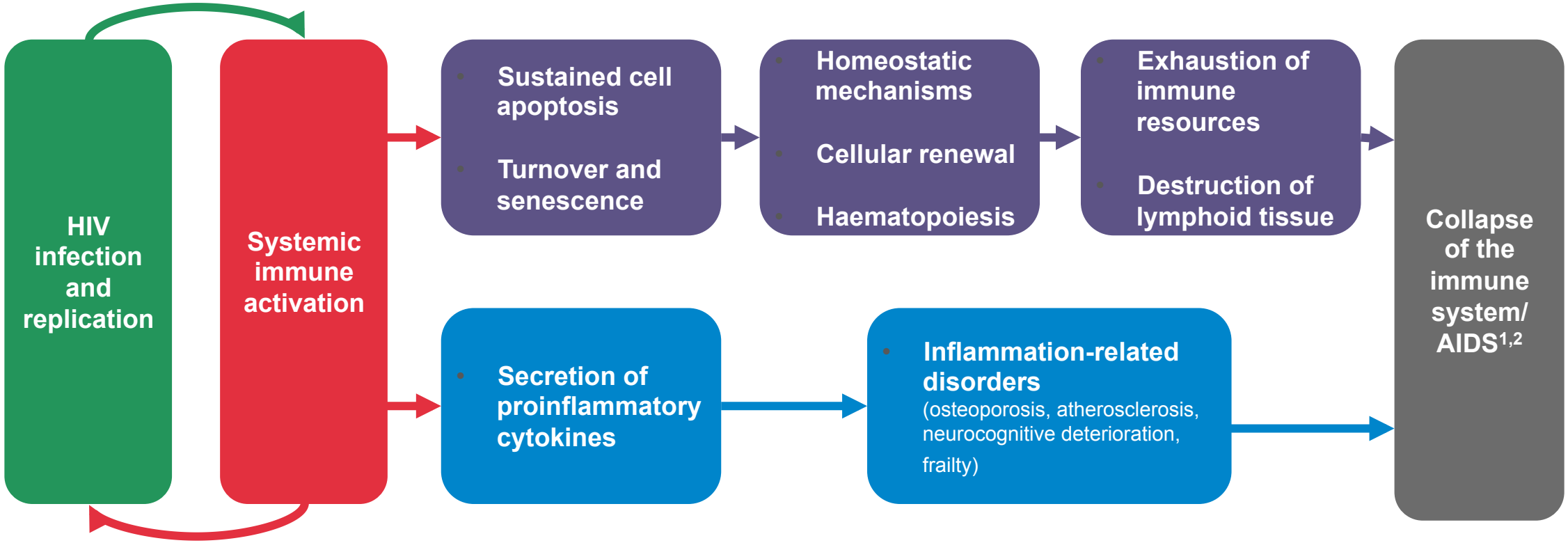
HIV INFECTION IS CHARACTERISED BY HIGH LEVELS OF IMMUNE ACTIVATION, VARIOUS CAUSES PROVOKE THIS IMMUNE HYPERACTIVITY

HIV production	HIV-1 components directly activate innate immune response and stimulates specific immune response
Microbial translocation/ Gut dysbiosis	HIV-1 destroys GALT, increasing the permeability of intestinal epithelium and promoting the translocation of microbial products
Viral coinfections	Eg. HCV, HBV, CMV, EBV, HTLV1
Immune dysregulation	Decrease in T-reg function and increase in Th17 function
Genetic polymorphisms	Eg. IL-10 and IRF7 gene polymorphism
Senescence	Senescent immune cells overproduce inflammatory cytokines (eg. IL-6 and TNF-α)

→ **Immune activation[1–6]**

CMV, cytomegalovirus; EBV, Epstein Barr virus; GALT, gut-associated lymphoid tissue; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV1, human T-cell leukaemia virus type 1; IFN-alpha, interferon alpha; IFN-γ, interferon gamma; IL-2/10, interleukin 2/10; IRF7, interferon regulatory factor 7; KIR2DL3, killer cell immunoglobulin-like receptor 2DL3; Nef, negative regulatory factor; NK, natural killer; Th17, T-helper cell 17; TNF-α, tumour necrosis factor α. 1. Deeks SG, et al. *Blood* 2004;104:942–7. 2. Younas M, et al. *HIV Med* 2016;17:89–105; 3. Routy JP. Centre de santé de l'Université McGill 2018; 4. Corbeau P. *Blood* 2011;117:5582–90; 5. Psomas C, et al. *EBioMedicine* 2016;8:265–76; 6. Chun TK, et al. *J Infect Dis* 2002;185:1672–6.

IN UNTREATED PLHIV, IMMUNE ACTIVATION CONTRIBUTES TO IMMUNE COLLAPSE AND AIDS PROGRESSION THROUGH VARIOUS MECHANISMS



- In untreated PLHIV, immune activation commences during acute infection, continues in chronic infection and is directly associated with HIV viral replication[1,2]

PLHIV, people living with HIV.

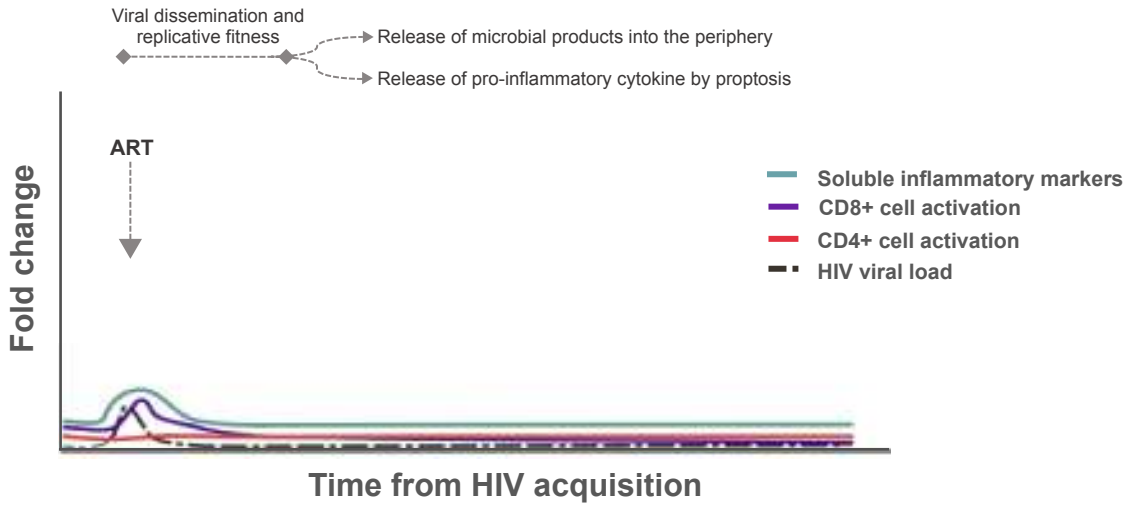
1. Appay V, et al. *J Pathol* 2007;214:231–41; 2. Deeks SG, et al. *Blood* 2004;104:942–7.

Mitigation

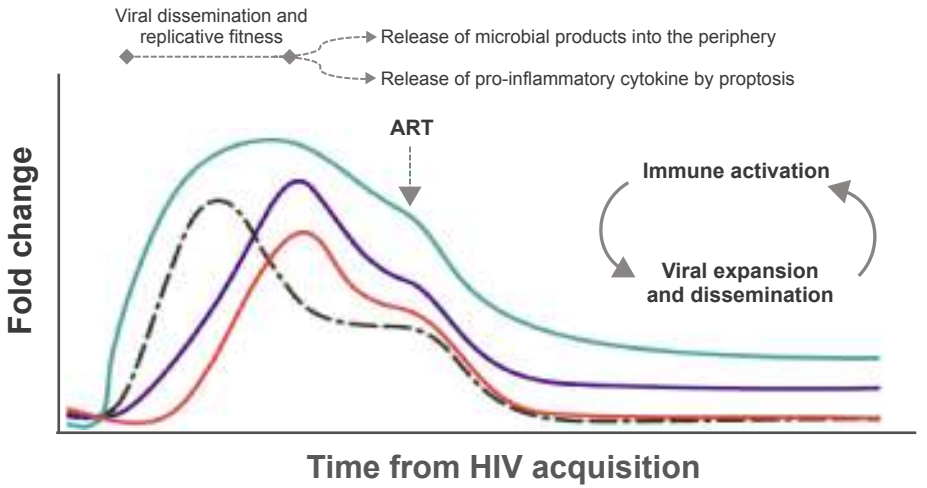
ART INITIATION DURING ACUTE INFECTION MAY CONTRIBUTE TO REDUCED BUT NOT NORMALISED IMMUNE ACTIVATION

Initiating ART during acute infection attenuates inflammation more than during chronic HIV infection[1]

ART initiated in acute infection



ART initiated in chronic infection



- The timing of ART initiation is important: the beneficial effects of early ART lessen as the HIV infection continues[1]
- Early ART initiation is associated with a reduction of cellular and soluble immune activation markers, limiting the viral reservoir seeding while preserving CD4+ cells[1]
- In acute HIV infection most inflammatory soluble markers normalise; however, some remain elevated despite successful ART[1]
- Some triple therapy regimens are the recommended initial treatment for rapid ART initiation[2]

ART, antiretroviral therapy; CD4, cluster of differentiation 4 cells; CD8, cluster of differentiation 8 cells.

1. Krebs SJ, Ananworanich J. *Curr Opin HIV AIDS* 2016;11:163–72; 2. IAS-USA Guidelines. Available at: www.iasusa.org/content/antiretroviral-drugs-treatment-and-prevention-hiv-infection-adults-2018-recommendations. Last accessed: July 2020.

Mitigation

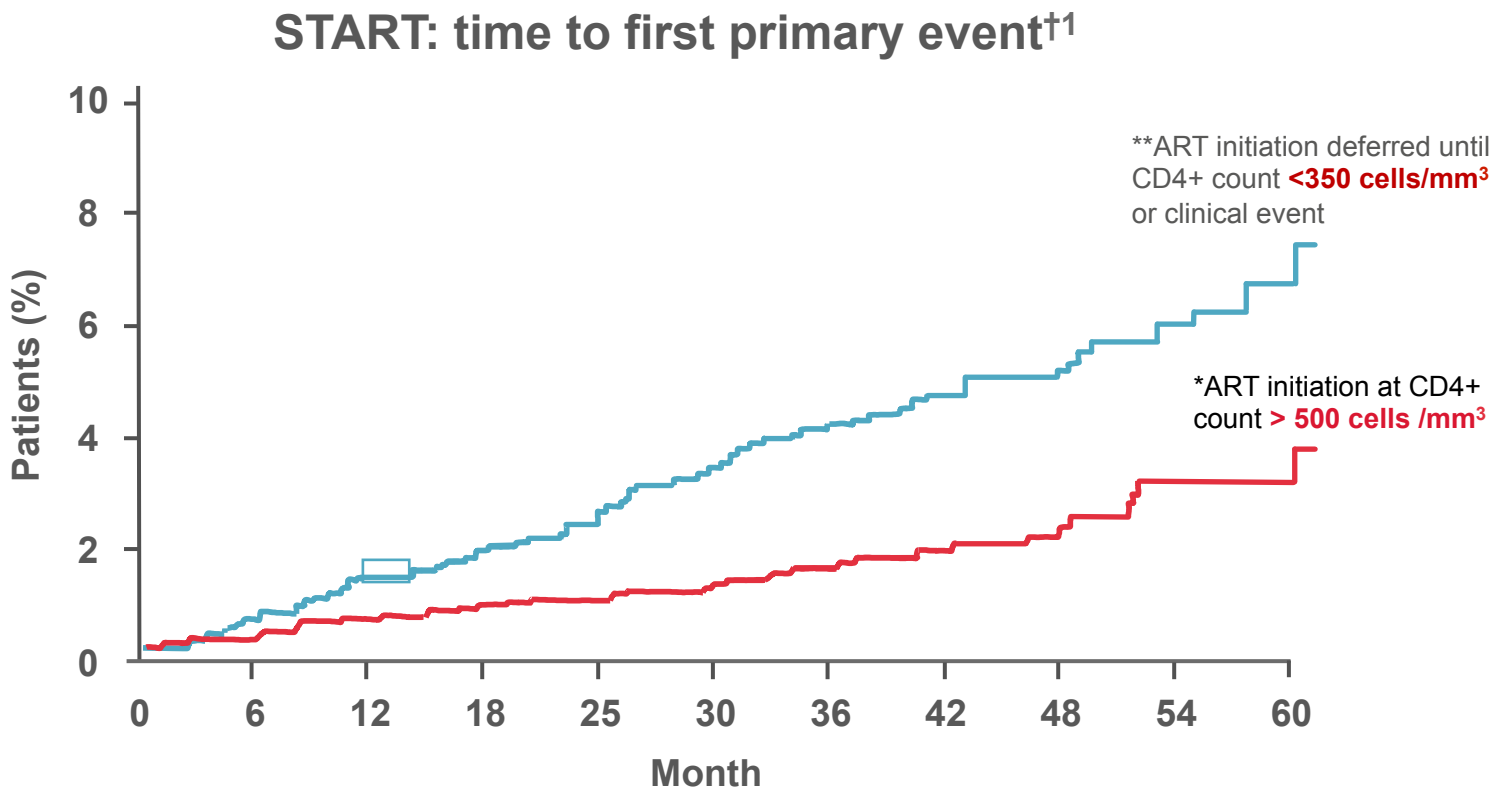
ART INITIATION AT CD4+ COUNT >500 CELLS/MM^3 VERSUS DEFERRED ART INITIATION HAS A FAVOURABLE IMPACT ON CLINICAL OUTCOMES IN PLHIV

START Study:

Earlier ART initiation* vs deferred ART initiation** in PLHIV, stratified by CD4+ cell count (N=4685)

ART initiation at CD4+ count >500 cells/mm^3 was significantly superior to deferring ART and demonstrated:

- Longer time to first primary event[a] (HR 0.43; 95% CI: 0.30–0.62, p<0.001)
- Lower rates of serious AIDS- and non-AIDS-related events:
  - Serious AIDS-related event: 0.28 (0.15–0.50) p<0.001
  - Serious non-AIDS-related event: 0.61 (0.38–0.97) p=0.04



*ART initiation at CD4+ count >500 cells/mm^3; **ART initiation deferred until CD4+ count <350 cells/mm^3 or clinical event; †Earlier ART group study participants met no criteria for starting ART according to WHO guidelines and the deferred ART group was not started on ART until WHO criteria for starting ART were met.

[a]Serious AIDS-related or serious non–AIDS-related event, including death

ART, antiretroviral therapy; CD4, cluster of differentiation 4 cells; CD8, cluster of differentiation 8 cells; CI, confidence interval; HR, hazard ratio; PLHIV, people living with HIV; WHO, World Health Organization.

The INSIGHT START Study Group. *N Engl J Med* 2015;373:795–807.

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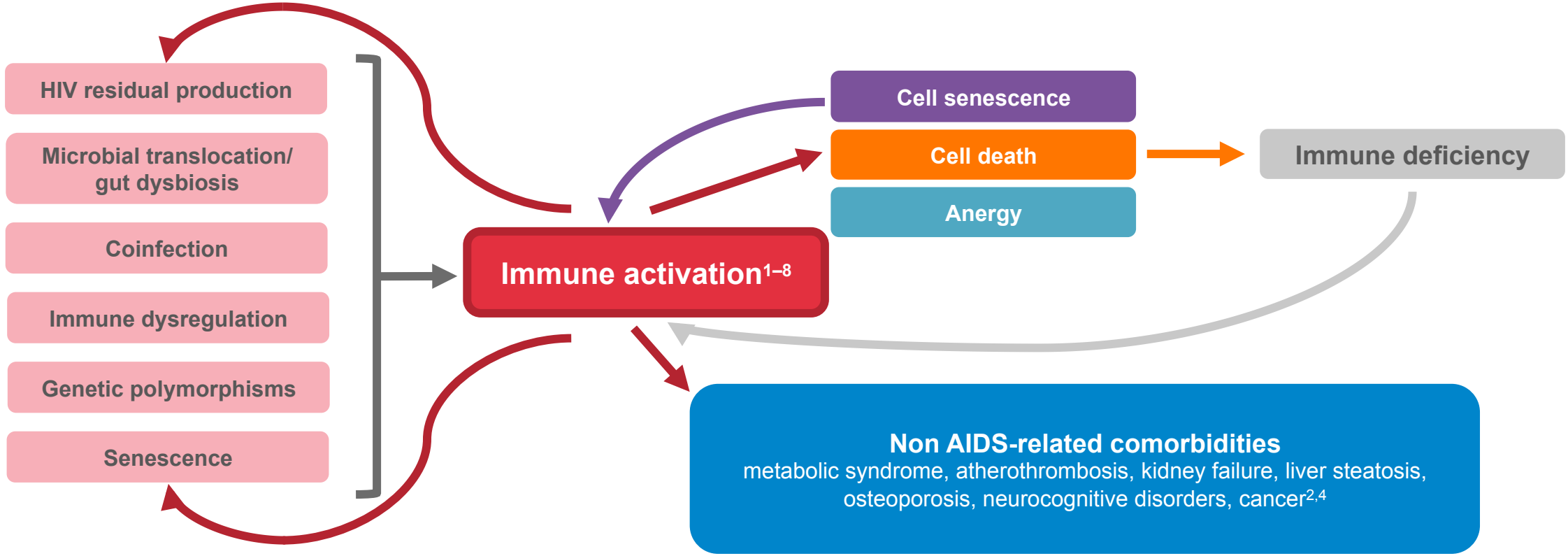
IMMUNE ACTIVATION IN VIROLOGICALLY SUPPRESSED PLHIV

IMMUNE ACTIVATION MAY PERSIST IN VIROLOGICALLY SUPPRESSED PLHIV RECEIVING ART



- Immune activation may contribute to T4 lymphopenia, low CD4:CD8 ratio and increased risk of immune deficiency-linked conditions[1–5]
  - ~6–24% of virologic responders do not restore the CD4+ T-cell count as they should[4]

ART, antiretroviral therapy; CD4, cluster of differentiation 4/8 cells; CD8, cluster of differentiation 8 cells; PLHIV, people living with HIV.

1. Deeks SG, et al. *Blood* 2004;104:942–7; 2. Younas M, et al. *HIV Med* 2016;17:89–105; 3. Corbeau P. *Blood* 2011;117:5582–90; 4. Psomas C, et al. *EBioMedicine* 2016;8:265–76; 5. Chun TK, et al. *J Infect Dis* 2002;185:1672–6; 6. Dillon et al. *Mucosal Immunol* 2014;7:983–94; 7. Vujkovic-Cvijin et al. *Sci Transl Med*, 2013;5:193ra91; 8. Dubourg G, et al. *BMJ Open* Gastroenterol 2016;28;3:e000080.

DESPITE VIROLOGICAL SUCCESS, IMMUNE BIOMARKERS REMAIN INCREASED COMPARED TO HIV-NEGATIVE INDIVIDUALS

Biomarkers[1]	HIV status		
	HIV negative (n = 524), Median (IQR)	**Virologically suppressed*** (n = 540), Median (IQR)	**P- value****
Hs-CRP (mg/L)	1.0 (0.6–1.9)	1.5 (0.7–3.5)	<0.001
D-dimer (mg/L)	0.24 (0.20–0.38)	0.23 (0.20–0.36)	0.078
sCD14 (ng/mL)	1356 (1080–1738)	1576 (1305–2011)	<0.001
sCD163 (ng/mL)	252 (182–342)	289 (207–419)	<0.001

- Residual immune activation is associated with impaired CD4+ T-cell recovery and mortality[2,3]
- Further research is needed to assess the impact of ART on immune activation parameters[2]

*95.7% on ART – time since ART was first initiated, 10.4 years (4.4–14.5 years); **Wilcoxon rank-sum test.
ART, antiretroviral therapy; CD4, cluster of differentiation 4 cells; Hs-CRP, high-sensitivity c-reactive protein; IQR, interquartile range; PLHIV, people living with HIV; sCD14/sCD163, soluble CD14/CD163.
1. Schouten S, et al. *HIV/AIDS* 2014; 59:1787–97; 2. Lichtfuss GF, et al. *Biomark Med* 2011;5:171–86; 3. Younas M, et al. *HIV Med* 2016;17:89–105.

CD4:CD8 RATIO IS A ROUTINE AND GLOBAL MARKER OF IMMUNE ACTIVATION AND MAY PREDICT SPECIFIC COMORBIDITIES

- **In virologically suppressed patients, CD4+ cell count may not accurately reflect the risk of immune dysfunction as immune activation persists despite normalisation of CD4+ cell count[1]**

CD4:CD8 is correlated with other immune activation markers:

- CD4+ T-cell activation (DR+, PD-1+)[2]
- CD8+ T-cell activation (DR+,CD38+, senescence)[3]
- Monocyte activation (sCD14)[3]
- Inflammation (CRP, IL-6)[3]

A low CD4:CD8 ratio is associated with and predictive of specific comorbidities:


Sarcopenia[4]


Decreased eGFR[4]


Lung cancer and chronic obstructive pulmonary disease[5]


Neurocognitive disorders[5]


Atherosclerosis development[4]


Non-AIDS mortality[3]

CD4, cluster of differentiation 4 cells; CD8, cluster of differentiation 8 cells; CD38, cluster of differentiation 38; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; IL-6,interleukin 6; PLHIV, people living with HIV; sCD14, soluble cluster of differentiation 14; PD-1, programmed cell death protein 1.

1. McBride JA, et al. *PLoS Pathog* 2017;13:e1006624; 2. Buggert M, et al. *J Immunol* 2014;192:2099; 3. Serrano-Villar S, et al. *PLoS Pathog* 2014;10:e1004078; 4. Serrano-Villar S, et al. *HIV Med* 2014;15:40–9; 5. McBride JA, et al. *PLoS Pathog* 2014;10:31004078.

IMMUNE ACTIVATION MAY ADVANCE THE AGEING PROCESS AND MAY INCREASE RISK OF NON-AIDS-RELATED COMORBIDITIES IN PLHIV ON ART

Metabolic syndrome[1]

- High level of sTNFR-1, a marker of TNFα production, is linked to three hallmarks of metabolic syndrome (hypertriglyceridemia, lipodystrophia and hyperinsulinemia)

Cardiovascular[2–4]

- IL-6 and hs-CRP are well-known predictors of CVD
- sCD14 independently predicts all-cause mortality and has been associated with subclinical and clinical CVD
- sCD163 is associated with arterial inflammation and coronary plaque on CCTA

Neurocognitive disorders[2,3]

- Elevated levels of sCD14, sCD163 and CCL2 in cerebrospinal fluid and blood as well as CRP, IL-6, TNF-α, IP-10 and neopterin correlate with an increased risk of neurocognitive disorders[2,3]

Kidney failure[2,3]

- Increased levels of TNF-α, IL-6, MCP-1 and CRP have been associated with renal tubular epithelial cell apoptosis
- Recruitment of T cells into the renal tubulointerstitial compartment mediates tubular injury and leads to progressive renal failure

Osteoporosis[2,3]

- TNF-α accelerates osteoclastic bone resorption
- TNF-α and IL-1 inhibit osteoblast function and stimulate osteoblast apoptosis through activation of NO

Cancer[2,3]

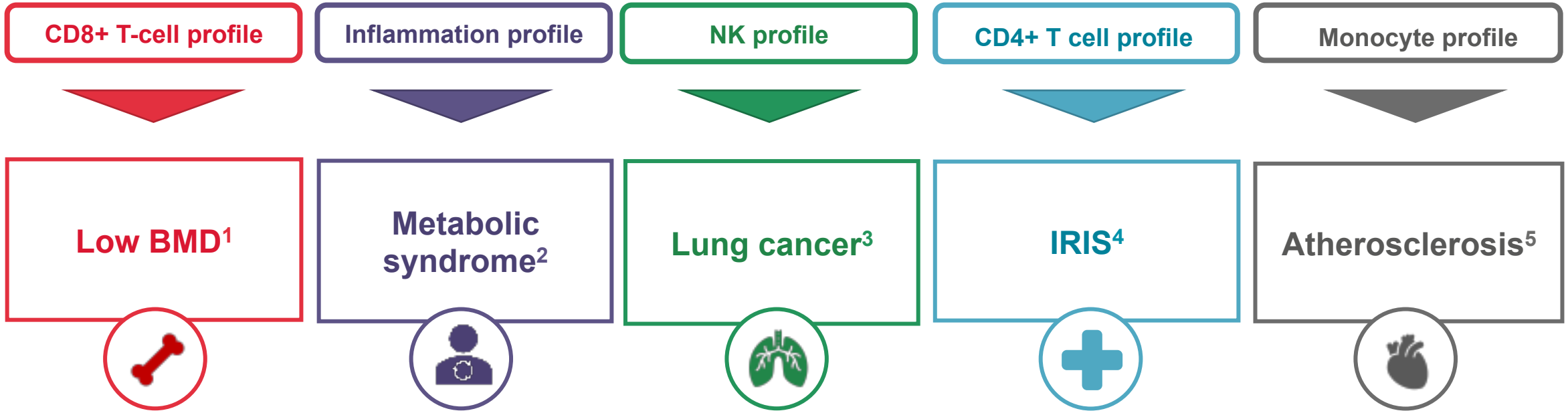
- The risk of cancer increases with lower CD4+ T-cell counts
- ROS and proinflammatory cytokines, such as TNF-α, expression of genes involved in cell proliferation, apoptosis and carcinogenesis

ART, antiretroviral therapy; CCL2, chemokine ligand 2; CCTA, cardiac CT angiograph; CD4+, cluster of differentiation 4 cells; CRP, c-reactive protein; CVD, cardiovascular disease; hsCRP, high sensitivity c-reactive protein; IL-1/6, interleukin 1/6; IP-10, interferon gamma inducible protein-10; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; ROS, reactive oxygen species; sCD14, soluble CD14; sCD163, soluble CD163; sTNFR-1, soluble tumour necrosis factor receptor 1; TNF-α, tumour necrosis factor α.

1. Psomas C, et al. *EBioMedicine* 2016;8:265–76; 2. Sokoya T, et al. *Mediators of Inflammation* 2017; Article ID 6825493; 3. Hunt PW. *Curr HIV/AIDS Rep* 2012;9:139–47; 4. McKibben R, et al. *J Infect Dis*. 2015;211:1219–28.

NOVEL MOLECULAR MECHANISMS LINKING IMMUNE ACTIVATION AND COMORBIDITIES MAY ALLOW PERSONALISATION OF THERAPY MANAGEMENT

- Several studies highlighted a correlation between certain comorbidities and immune activation profiles[1–5]
- Further investigations are needed to confirm the clinical relevance



BMD, bone mineral density; CD4, cluster of differentiation 4 cells; CD8, cluster of differentiation 8 cells; IRIS, immune reconstitution inflammatory syndrome; NK, natural killer; PLHIV, people living with HIV.

1. Gazzola L, et al. *J Transl Med* 2013;11;1–10; 2. Psomas C, et al. *EBioMedicine* 2016;10:318–22; 3. Leal F, et al. *Front Immunol* 2017; 8:1–10; 4. Antonelli L, et al. *Blood* 2010;116:3818–27.
5. McKibben R, et al. *JID* 2015;211:1219–28.

Mitigation

IMMUNE ACTIVATION MAY ENHANCE THE EFFECTS OF MODIFIABLE LIFESTYLE RISK FACTORS ON THE DEVELOPMENT OF COMORBIDITIES

Modifiable risk factors play an important role in chronic comorbidities such as CVD, diabetes, renal and bone diseases – HIV management guidelines recommend evaluation and management of these risks[1]

Lifestyle factors are key in limiting risk of non-HIV comorbidities and ongoing exposure to inflammation

Physical activity
- May trigger anti-inflammatory effects, but HIV-specific research is limited[2]
- Has been shown to reduce the CVD risk but not HIV-related immune activation[2]

Maintenance of a healthy weight and diet
- Weight gain results in a lower decline of IL-6, sTNF-RII, IP-10 and sCD163 following ART initiation[3]
- Alcohol consumption has been associated with worse gut integrity and increased inflammation[4]

Smoking cessation
- Irrespective of ART status, circulating levels of β2-microglobulin, cyclophilin A and RANTES were significantly elevated in tobacco users versus non-users[5]

ART, antiretroviral therapy; CVD, cardiovascular disease; IL-6, interleukin 6; IP-10, interferon gamma-induced protein 10; PLHIV, people living with HIV; sCD163, soluble cluster of differentiation 163; sTNF-RII, soluble tumour necrosis factor-alpha receptor IIF.

1. Peters B et al. *HIV Med* 2013;14:1–11; 2. Ceccarelli C et al. *AIDS Behav* 2019 [Epub ahead of print]; 3. Bares SH et al. CROI 2019 #673; 4. Webel A, et al. *HIV Med* 2016;18:402–11; 5. Steel HC, et al. *Mediators Inflamm* 2018; 8357109.

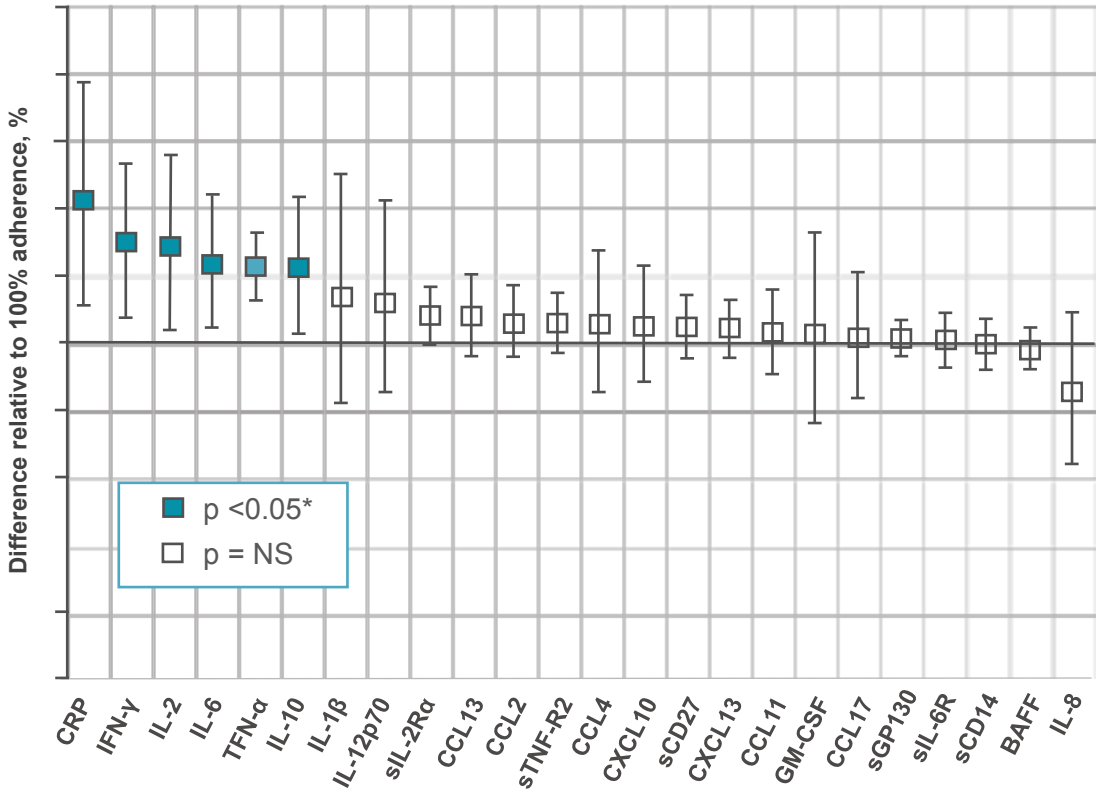
Mitigation

IMPROVING ADHERENCE TO ART MAY REDUCE IMMUNE ACTIVATION BIOMARKER LEVELS DESPITE APPARENT VIROLOGICAL SUCCESS

Multicentre AIDS cohort study of HIV infection in MSM[1,2]

- **Inclusion criteria (N=924)**
  - Available serum biomarker concentrations
  - Reported ART
  - HIV RNA <50 copies/mL
- **Adherence to ART measured using self-reported data collected at each study visit**
  - <100% adherence was associated with higher levels of TNF-α, IFN-γ, CRP, IL-2, IL-6 and IL-10

Difference in biomarker concentration relative to 100% adherence



*TNF-α hazard ratio statistically significant after adjustment for multiple tests, using the Benjamini-Hochberg procedure to control the false discovery rate at 5%.
ART, antiretroviral therapy; BAFF, B cell-activating factor; CCL2/4/11/13/17, C-C motif chemokine ligand 2/4/11/13/17; CRP, c-reactive protein; CXCL10/13, C-X-C motif chemokine 10/13; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL-2/6/10, interleukin 2/6/10; MSM, men who have sex with men; NS, not significant; RNA, ribonucleic acid; sGP130, soluble glycoprotein 130; sIL-2Rα/6R, soluble interleukin 2 receptor alpha/6 receptor; sTNF-R2, serum-soluble tumour necrosis factor receptor 2; TNF-α, tumour necrosis factor α.

1. Castillo-Mancilla J, et al. *Clin Infect Dis* 2016;63:1661–7; 2. Castillo-Mancilla J, et al. CROI 2016, #283.

Mitigation

CONSIDERATIONS FOR SWITCHING ART REGIMENS IN VIROLOGICALLY SUPPRESSED PLHIV

Switching to an ART with better tissue penetration

Some ARTs have better lymph node penetration:

- Greater EVG lymphoid tissue and node penetration compared with DTG and RAL[1]
- Greater TAF lymphoid tissue penetration compared with TDF[2]
- Only pharmacodynamic evaluations are available, further investigation into virologic response is needed[2]

MVC-containing ART regimens may lead to greater gut penetration compared with EFV-containing regimens:[3]

- May be beneficial for reducing immune activation[4]
- Further study needed – greater MVC penetration into gut-associated tissues may reduce immune activation in some settings; however, increasing tissue T cell activation and CCR5 ligand plasma levels may outweigh potential benefits[4]
- Not included in the EACS[5], DHHS[6] and IAS[7] guidelines

Intensification of a triple ART regimen with RAL

- Intensification with the addition of RAL to ART has a beneficial effect decreasing CD8+ T-cell activation and D-dimer levels[8]
- Short-term data (12 weeks) showed intensification of standard ART was well tolerated and reduced plasma HIV VL faster than ART alone; however, there was no discernible clinical benefit and no effect on mortality or rates of IRIS[9]
- RAL intensification* is not currently recommended by EACS[5], DHHS[6] and IAS[7] guidelines

*Intensification defined as the addition of RAL to a triple therapy ART.

ART, antiretroviral therapy; CCR5, C-C chemokine receptor type 5; CD8+, cluster of differentiation 8 cells; DHHS, Department of Health and Human Services; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; EVG, elvitegravir; IAS, International AIDS Society; IRIS, immune reconstitution inflammatory syndrome; MVC, maraviroc; PLHIV, people living with HIV; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load.

1. Fletcher CV, et al. CROI 2018 #27; 2. Fletcher CV, et al. CROI 2019 #103; 3. Serrano-Villar S, et al. *PLoS Pathog* 2016;12:e100538; 4. Hileman C, Funderburg N. *Curr HIV/AIDS Rep* 2017;14:93–100; 5. EACS Society Guidelines, Version 9.1, October 2018. Available at: www.eacsociety.org/files/2018_guidelines-9.1-english.pdf. Last accessed: July 2020; 6. DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Last accessed: July 2020; 7. Saag M, et al. *JAMA* 2018;320:379–96. 8. Massanella M, et al. *PLoS One* 2014;9:e114142; 9. Kityo C, et al. *PLoS Med* 2018;15:e1002706.

Mitigation

IN TREATMENT-EXPERIENCED PLHIV, HIV TREATMENT MAY INFLUENCE IMMUNE ACTIVATION AND CD4:CD8 RATIO LEVELS

Treatment-experienced PLHIV switching from TT to 2DC

- Switch from TT to 2DCs has variable impact on the CD4:CD8 ratio; currently the clinical relevance is unknown[1–5]
- Some studies* suggest 2DCs may not favourably impact the CD4:CD8 ratio and may increase immune activation[3,6,7]
- Other studies** have reported no impact / improvement on the CD4:CD8 ratio with 2DCs[4,8,9]

These results may be explained by:[3,6]

- Small residual viremia which may trigger proinflammatory cytokines production – stimulating immune activation
- Suboptimal ART adherence – associated with increased inflammation despite virologic suppression

These studies have limitations:[3,4,6]

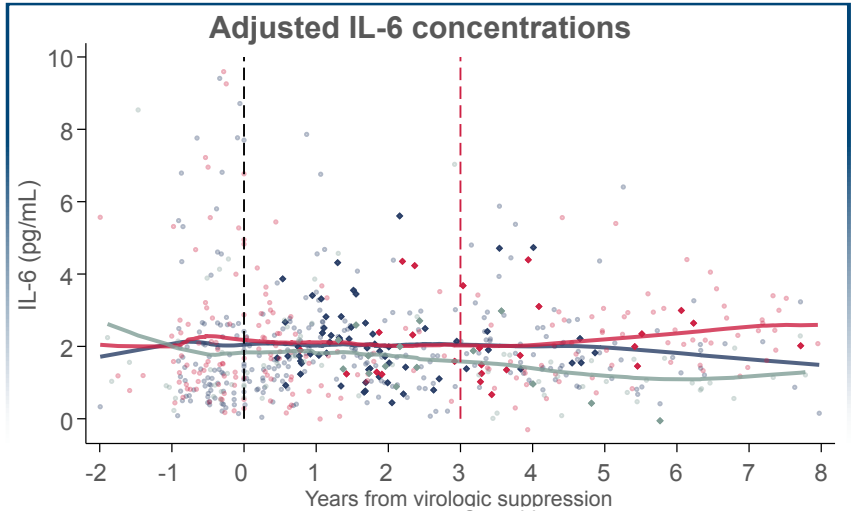
- Some were observational with no comparators
- Heterogeneity of patient population
- Short follow-up
- Retrospective analysis
- Unmeasured ART adherence

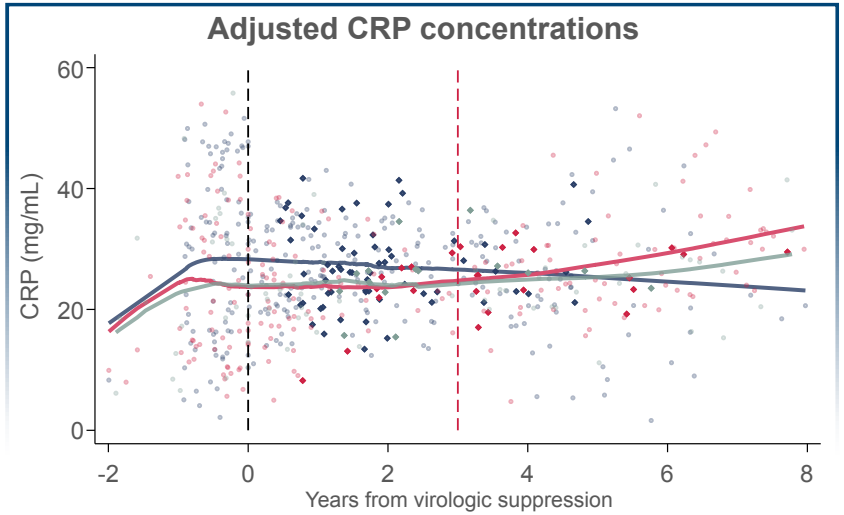
*Most common 2DCs patients were switched to 3TC + ATV/r, 3TC + DRV/r, 3TC + DTG, ETV + RAL, DRV/r + RAL, ATV/r + RAL; **Patients switched to 3TC + DRV/r.
2DC, two-drug combination; 3TC, lamivudine; ATV/r, atazanavir/ritonavir. CD4, cluster of differentiation 4 cells; CD8, cluster of differentiation 8 cells; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EMA, European Medicines Agency; ETV, etravirine; PLHIV, people living with HIV; RAL, raltegravir; TT, triple therapy.

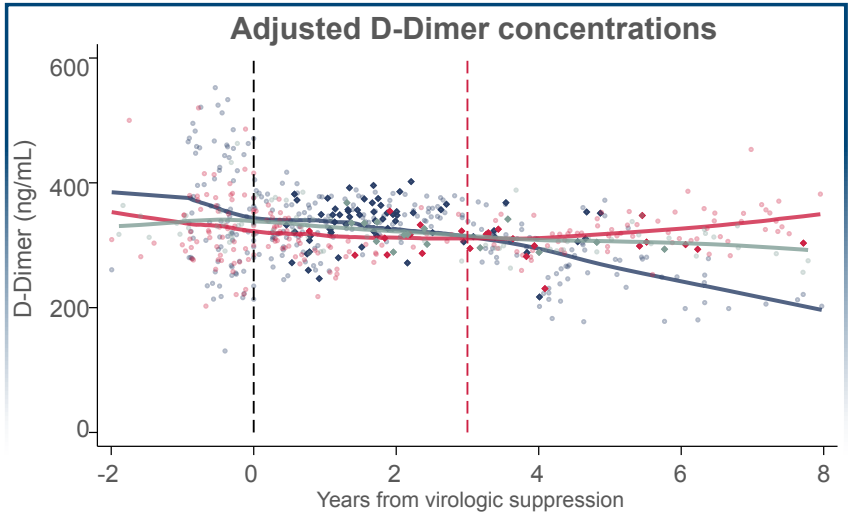
1. Cahn P, et al. *AIDS* 2018, #TUAB0106LB; 2. Hernandez B, et al. HIV & Hepatitis Nordic Conference 2018, P9; 3. Mussini C, et al. *BMC Med* 2018;16:79; 4. Fontecha M, et al. *Infect Dis* 2019;4;293–8; 5. Vallejo A, et al. *HIV Medicine* 2019:10.1111/hiv.12749; 6. Serrano-Villar S, et al. *AIDS* 2020. Oral OAB0304; 7. Quiros-Roldan E, al. *BMC Infect Dis* 2018:18;2–11; 8. Baldin G, *Int. J. Antimicrob. Agent* 2019:54;728–34; 9. Capetti A, et al. *AIDS* 2018:32;1083–4.

SWITCHING TO 2DCS VS MAINTAINING TRIPLE THERAPY MAY IMPACT INFLAMMATORY MARKER TRAJECTORIES

Piecewise Linear Mixed Models for IL-6, CRP and D-Dimer







Trajectories after year 3

- Overall changes: P=0.023
- **TT** vs **2DC**: P=0.010
- **TT** vs **monotherapy**: P=0.900

- Overall changes: P=0.009
- **TT** vs **2DC**: P=0.003
- **TT** vs **monotherapy**: P=0.280

- Overall changes: P=0.002
- **TT** vs **2DC**: P=0.001
- **TT** vs **monotherapy**: P=0.002

IL-6, CRP, and D-Dimer:

- TT: decreased over time
- 2DCs: increased 2–3 years after switch; significant after 3 years

Study limitations:

- Low monotherapy sample size may limit statistical calculations
- Unmeasured confounding ART adherence could impact inflammatory markers measured

*148 PLHIV with 612 prospectively stored samples and up to 8 years of follow-up, inclusion: longer follow-up and at least 3 samples. 4 studied markers CRP, IL6, D-Dimer and iFABP. No difference in trajectories over time of iFABP. ART, antiretroviral therapy; 2DC, two-drug combination; BL, baseline; IL-6, interleukin-6; CoRIS, Cohorte de la red de Investigacion en Sida; CRP, C-reactive protein; iFABP, Intestinal fatty-acid binding protein; PLHIV, people living with HIV; TT, triple therapy.

Serrano-Villar S, et al. *AIDS* 2020. Oral OAB0304.

FURTHER RESEARCH WITH LONGER FOLLOW-UP IS NEEDED TO UNDERSTAND 2DC IMPACT ON IA IN TREATMENT-EXPERIENCED PLHIV

Pooled SWORD-1 and SWORD-2 studies*
Switch to DTG+RPV vs baseline at Week 100[a1,2]

Parameter	Change from BL in early switch to DTG/RPV	p-value
IL-6	Increased	0.002
sCD163	Tended to increase	0.001
sCD14	Tended to increase	0.001
sVCAM-1	Decreased	0.001
FABP-2	Decreased	0.001
CRP	Unchanged	NR
D-Dimer	Unchanged	0.037

Study limitations:
- No comparator arm after Week 48
- Selected patients with no history of VF and a long duration of undetectability before study inclusion

***Primary endpoint: switch to DTG+RPV was noninferior to remaining on TT at Week 48*

TANGO study**
Switch to DTG/3TC vs maintaining TAF-based regimen at Week 48[3]

Parameter	DTG/3TC to TAF-based regimen ratio (95% CI)[b]	P-value
IL-6	Increased in 2DCs	0.006
sCD14	Decreased in 2DCs	0.048
sCD163	Similar in both arms	0.508
CRP	Similar in both arms	0.341
D-Dimer	Similar in both arms	0.440

Study limitations:
- Short follow-up
- Selected patients with no history of VF and a long duration of undetectability before study inclusion

***Primary endpoint: switch to DTG/3TC was noninferior to remaining on TAF-based regimen through Week 48*

Research with longer follow-up is needed to understand the clinical impact of immune activation; currently the clinical relevance is unknown[4–8]

[a]At Week 52, participants randomised to CAR switched to DTG+RPV; [b]Ratio is the estimated adjusted ratio (Week 48 to baseline) in each group calculated using MMRM applied to change from baseline in loge-transformed data adjusting for the following: treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, body mass index (continuous), smoking status, hepatitis C virus coinfection status, loge-transformed baseline biomarker (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.
2DC, two-drug combination; 3TC, lamivudine; ART, antiretroviral therapy; BL, baseline; CAR, current ART regimen; CD4, cluster of differentiation 4 cells; CI, confidence interval; CRP, C-reactive protein; DTG, dolutegravir; FABP-2, fatty acid binding protein 2; IA, immune activation; IL-6, interleukin-6; MMRM, mixed model for repeated measures; PLHIV, people living with HIV; RPV, rilpivirine; sCD163/14, soluble cluster of differentiation 163/14; sVCAM-1, circulating vascular cell adhesion molecule-1; NR, not reported; TAF, tenofovir alafenamide; TT, triple therapy; VF, virological failure.
1. Hernandez et al. HIV & Hepatitis Nordic Conference 2018 #P9; 2. Boswell, R et al. *Ann Pharmacother* 2018;52:681–9; 3. van Wyk J, et al. *Clin Infect Dis* 2020. Epub ahead of print; 4. Mussini C, et al. *BMC Med* 2018;16:79; 5. Fontecha M, et al. *Infect Dis* 2019;4;293–8; 6. Molano MC, et al. HIV Glasgow 2018, P-113; 7. Vallejo A, et al. *HIV Medicine* 2019:10.1111/hiv.12749; 8. Campillo-Gimenez L, et al. *AIDS* 2015;29:853–56.

INFLAMMATORY MARKERS IN THE TANGO STUDY

Evaluation of inflammation biomarkers at Week 48 after switching to DTG/3TC (n=369) vs staying on TAF-based triple therapy (n=371)

Parameter	Treatment	n	BL Geometric Mean (95% CI)	Week 48 to BL Ratio (95% CI)*	Treatment Ratio DTG/3TC to TAF-based (95% CI)	*P* Value
Blood D-dimer, nmol/L FEU	DTG/3TC TAF-based regimen	334/369 334/371	1.69 (1.59, 1.79) 1.66 (1.58, 1.76)	0.97 (.92, 1.02) 0.99 (.95, 1.04)	0.97 (.91, 1.04)	0.440
Serum hs-CRP, mg/L	DTG/3TC TAF-based regimen	342/369 342/371	1.37 (1.23, 1.53) 1.30 (1.16, 1.46)	1.01 (.91, 1.12) 1.08 (.99, 1.20)	0.93 (.81, 1.07)	0.341
Serum IL-6, ng/L	DTG/3TC TAF-based regimen	343/369 340/371	1.64 (1.52, 1.78) 1.67 (1.54, 1.80)	0.99 (.91, 1.08) 0.85 (.80, .91)	**1.16 (1.04, 1.29)**	**0.006**

Significant difference in IL-6 after switch to DTG/3TC vs continuing TAF-based regimen

BL, baseline; FEU, fibrinogen equivalent unit; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukine-6

*Ratio is the estimated adjusted ratio (Week 48 to baseline) in each group calculated using mixed model repeated measures adjusting for the following: treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, body mass index (continuous), smoking status, HCV coinfection status, $\log_{10}$-transformed baseline biomarker (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.

CoRIS: AIR Study, inflammatory markers sub study (Spain)

MAINTAINING TRIPLE THERAPY *VS* SWITCH TO 2-DRUG COMBINATION: INFLAMMATORY MARKERS

Inflammatory sub study comparing trajectories of inflammatory markers in 148 PLWH with 612 prospectively stored samples and up to 8 years of follow-up (inclusion: longer follow-up and at least 3 samples)

Inclusion criteria:

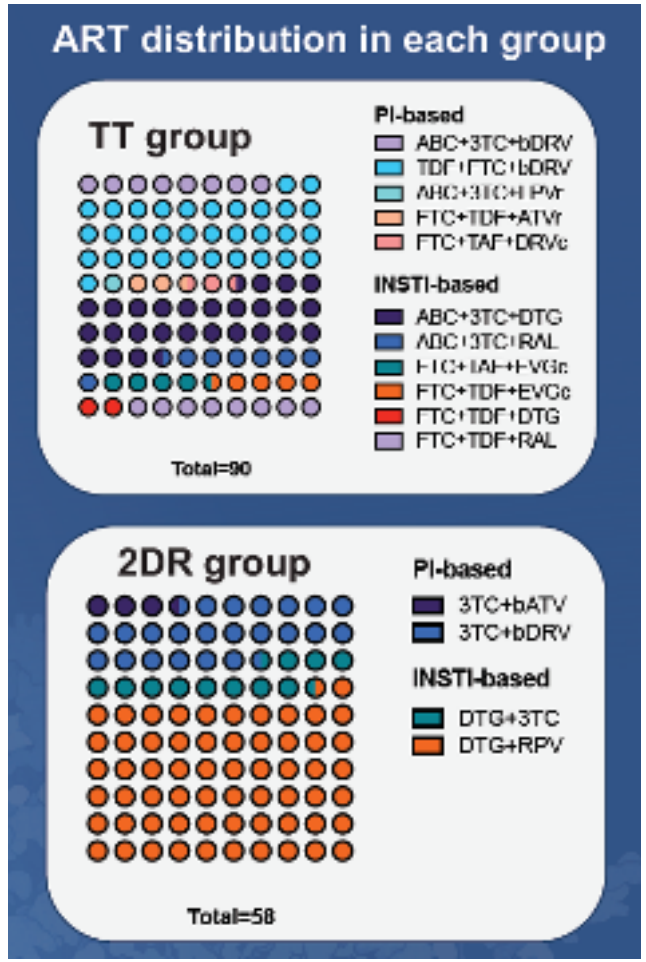
Patients initiating ART in CORIS between 2004-2018 with TT (2NRTI+bPI/INSTI).

- Virological suppression achieved in the first 48 weeks of ART.
- Either remained on TT or switched to 2DR (3TC+bPI, 3TC+DTG, RPV+DTG) or 1DR (LPVr or bDRV).
- At least 3 plasma samples available

Exclusion criteria:

- ART initiation with regimens with <3 drugs
- Virological failure: ≥2 consecutive viral loads more than 50 copies/mL) during the first 48 weeks of ART
- AIDS conditions or serious non-AIDS events (malignancies, cardiovascular disease, end-stage liver disease, end-stage kidney disease), in the first 48 weeks of ART.

	TT N=90	2DR N=58	p value
Age (mean, [SD])	37 (9)	40 (11)	0.227
Male, n (%)	78 (87)	50 (86)	0.936
IDU, n (%)	6 (7)	3 (6)	0.972
Spanish origin, n (%)	59 (66)	36 (62)	0.666
University education, n (%)	22 (24)	18 (31)	0.593
AIDS diagnosis, n (%)	15 (16)	8 (14)	0.769
HCV positive ever, n (%)	12 (13)	6 (10)	0.570
Maximum HIV-1 RNA (c/mL), median (IQR)	114500 (33770-344426)	93599 (36307-219000)	0.376
Time from ART initiation to virologic suppression (years), median (IQR)	0.5 (0.2-0.9)	0.5 (0.3-0.9)	0.524
Time from virologic suppression (years) to ART switch, median (IQR)	-	3.5 (1.9-5.2)	-
Nadir CD4 cell count (cells/µL), median (IQR)	300 (151-373)	259 (112-382)	0.309
Number of samples analyzed, median (min, max)	4 (3-11)	3 (3-8)	<0.001
Follow-up (years), median (IQR)	3.9 (2.5-4.7)	5.3 (3.9-6.8)	<0.001



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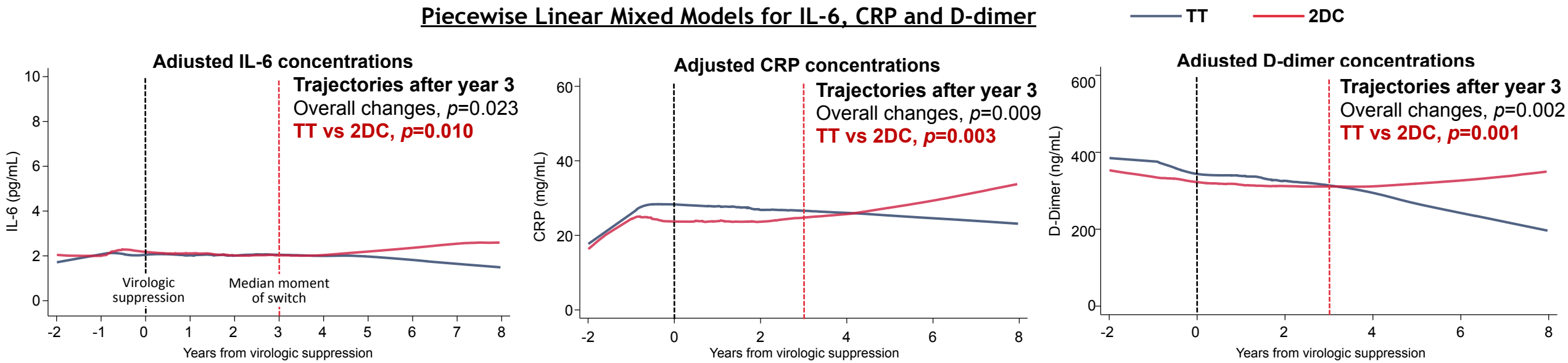
Inflammatory sub study comparing trajectories of inflammatory markers in 148 PLWH with 612 prospectively stored samples and up to 8 years of follow-up (inclusion: longer follow-up and at least 3 samples)*

Piecewise Linear Mixed Models for IL-6, CRP and D-dimer



- **IL-6, CRP, and D-Dimer continued decreasing over time with TT**
- **In patients switched to 2DC combinations, levels of inflammation markers began to increase 2-3 years after switch**

Switching to a 2-drug combination was associated with significant elevations of IL-6, CRP and D-dimer despite continuous virologic suppression

Serrano-Villar S, et al. AIDS 2020. Oral OAB0304

Serrano Villar et al EACS 2021

Potential Clinical Impact of IL-6 Differences With 2DR vs. 3DR

Markov modeling study using data from the TANGO and AIR studies

Outcome

To determine whether differences in IL-6 levels associated with 3DR vs. an oral 2DR affect clinical outcomes (SNAE/death) in virologically suppressed PLWH

Not applicable

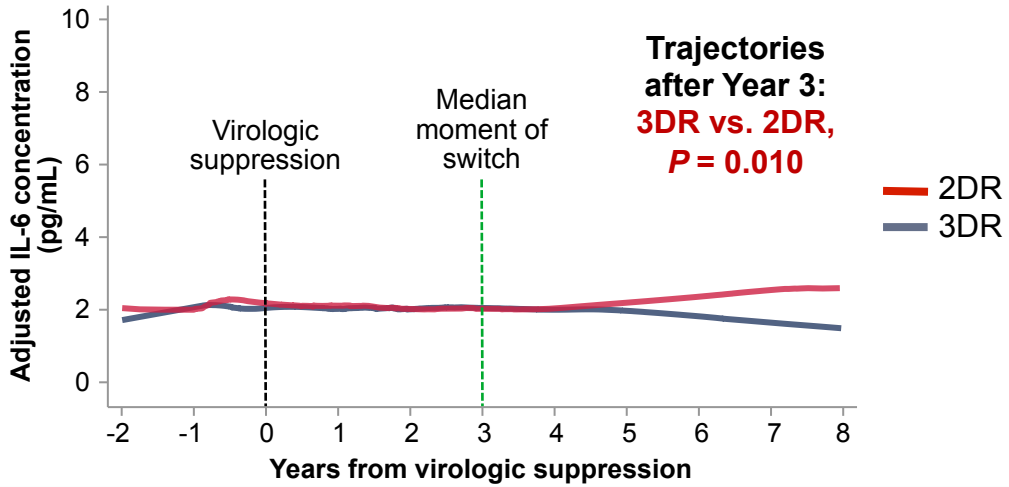
The INSIGHT trials network showed that elevated inflammatory markers (including IL-6) are associated with a higher risk of SNAE or death*[,1]

- Modeling predicted that **a 16% increase in IL-6 may increase the risk of SNAE by ~16%** – the difference in IL-6 level observed in TANGO at Week 48

IL-6 Levels in 2DRs and 3DRs in the TANGO and SALSA Studies

Study	Switch	Change in IL-6 level after switching from 3DR to 2DR	
TANGO	Switch to DTG/3TC vs. continuing a TAF-based 3DR	Week 48	*P* = 0.006 in favor of 3DR[2]
		Week 96	Numerical difference but not statistically significant[3]
		Week 144	*P* = 0.039 in favor of 3DR[4]
SALSA	Switch to DTG/3TC vs. continuing a variety of 3DRs	Week 48	No difference[5]

AIR: Serum IL-6 After Switching From 3DR to 2DR[6]



Inflammatory markers, including IL-6, may differ between some oral 2DRs and 3DRs

*Cardiovascular, hepatic, renal or malignancy event
2DR, 2-drug regimen; 3DR, 3-drug regimen; SNAE, serious non-AIDS event
References in slide notes
Serrano Villar S, et al. EACS 2021, Poster PE2/34

Serrano Villar et al EACS 2021

Potential Clinical Impact of IL-6 Differences With 2DR vs. 3DR: NNT

Primary endpoint

NNT = 43

Based on the model, there would be one additional SNAE/death outcome for every 43 virologically suppressed PLWH aged 30–50 years and treated for 5 years with a regimen associated with higher IL-6

2DR, 2-drug regimen; 3DR, 3-drug regimen; NNT, number needed to treat
Serrano Villar S, et al. EACS 2021, Poster PE2/34

Markov modeling (TANGO and AIR)

Potential Clinical Impact of IL-6 Differences With 2DR vs. 3DR: NNT and Potential Future Studies

Serrano Villar et al EACS 2021

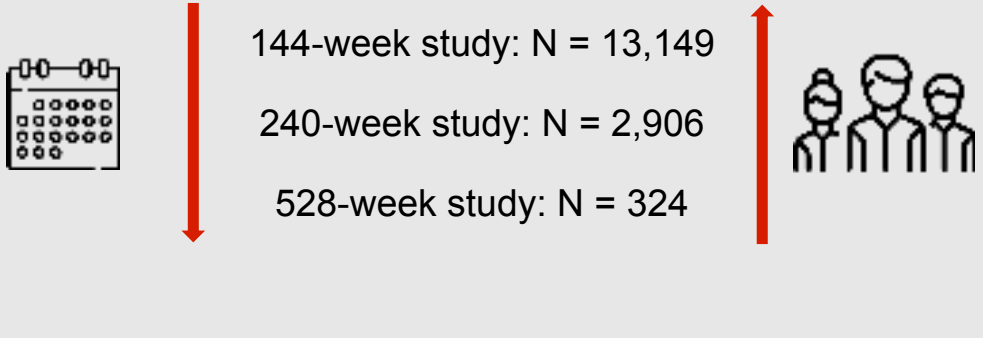
‡

NNT to Observe One Additional SNAE* on a 2DR vs. 3DR, by Time on ART

Time (years)	NNT
3	106
5	43
10	13

Estimates from Markov modeling; considered participant age range: 30–50 years

Estimated Cohort Size Required to Support or Refute an Effect of This Magnitude



2DR vs. 3DR (1:1) over time
Two-sided; significance level: 0.05; power: 80%
Outcome: Incidence of SNAE/death

The IL-6 differences observed with the switch from some 3DRs to some 2DRs may increase the risk of SNAEs and/or death in virologically suppressed PLWH

*Cardiovascular, hepatic, renal or malignancy event
2DR, 2-drug regimen; 3DR, 3-drug regimen; NNT, number needed to treat; SNAE, serious non-AIDS event
Serrano Villar S, et al. EACS 2021, Poster PE2/34

Mitigation

POTENTIAL FUTURE MITIGATION STRATEGIES MAY TARGET DIFFERENT CAUSES OF IMMUNE ACTIVATION

Anti-inflammatory agents

- Aspirin
- COX2 inhibitors
- Prednisone

↓ Microbial translocation

- Modify dysbiosis (pre/pro/symbiotics)
- ↓ Gut bacterial load
- ↓ Endotoxin load
- ↓ Intestinal integrity
- ↓ Gut inflammation

↓ Chronic antigen stimulation

- Suppress residual viraemia (ART intensification)
- Treatment of CMV infection (valganciclovir)

↑ Immune recovery

- Cytokine therapies (IL-2, IL-7, IL-21)
- ↓ Lymphoid tissue fibrosis
- TNF blockade
- ACE inhibitors
- Angiotensin II receptor antagonists

ACE, angiotensin-converting-enzyme; ART, antiretroviral therapy; CMV, cytomegalovirus; COX2, cyclooxygenase-2; IL, interleukin; TNF, tumour necrosis factor.
Hsu D, Sereti I. *Drugs* 2016;76:533–49.

CONCLUSIONS

IA is chronic condition that starts to develop in TN PLHIV and can persist even in virologically suppressed PLHIV with normal CD4 counts[1]

Some of the mechanisms underlying IA in HIV include virus production, gut microbial translocation and viral coinfections[1]

IA may advance the ageing process and increase risk of non-AIDS-related comorbidities in PLHIV on ART[2-5]

CD4:CD8 is a common marker of IA and has been associated with long-term health outcomes in PLHIV[6]

ART start during acute HIV infection may reduce IA more than during chronic infection[7]; initiating ART at CD4+ levels >500 cells/mm^3 reduced the risks of serious AIDS-related and non-related events vs deferred start[8]

Recent data suggested that pro-inflammatory markers in PLHIV on oral 2DCs are elevated compared with TT; however, these findings remain controversial and further research is needed to understand their clinical significance[9]

2DC, two-drug combination; ART, antiretroviral therapy; IA, immune activation; PLHIV, people living with HIV; TT, triple therapy.

1. Younas M, et al. *HIV Med*. 2016;17:89–105; 2, Psomas C, et al. *EBioMedicine* 2016;8:265–76; 3. Sokoya T, et al. *Mediators of Inflammation* 2017; Article ID 6825493; 4. Hunt PW. *Curr HIV/AIDS Rep* 2012;9:139–47; 5. McKibben R, et al. *J Infect Dis*. 2015;211:1219–28; 6. Serrano-Villar S, et al. HIV Med 2014;15:40–9; 7. The INSIGHT START Study Group. N Engl J Med 2015;373:795–807; 8. Krebs SJ, Ananworanich J. *Curr Opin HIV AIDS* 2016;11:163–72; 9. Serrano-Villar S, et al. AIDS 2020. Oral OAB0304.