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REVIEW ARTICLE

# Do Combination Antiretroviral Therapy Regimens for HIV Infection Feature Diverse T-Cell Phenotypes and Inflammatory Profiles?

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Immune abnormalities featuring HIV infection persist despite the use of effective combination antiretroviral therapy (cART) and may be linked to the development of noninfectious comorbidities. The aim of the present narrative, nonsystematic literature review is to understand whether cART regimens account for qualitative differences in immune reconstitution. Many studies have reported differences in T-cell homeostasis, inflammation, coagulation, and microbial translocation parameters across cART classes and in the course of triple vs dual regimens, yet such evidence is conflicting and not consistent. Possible reasons for discrepant results in the literature are the paucity of randomized controlled clinical trials, the relatively short follow-up of observational studies, the lack of clinical validation of the numerous inflammatory biomarkers utilized, and the absence of research on the effects of cART in tissues. We are currently thus unable to establish if cART classes and regimens are truly accountable for the differences observed in immune/inflammation parameters in different clinical settings. Questions still remain as to whether an early introduction of cART, specifically in the acute stage of disease, or newer drugs and novel dual drug regimens are able to significantly impact the quality of immune reconstitution and the risk of disease progression in HIV-infected subjects.

**Keywords.** combination antiretroviral therapy (cART); immune recovery; T-cell phenotypes; inflammation.

Randomized controlled trials (RCTs) and observational cohort studies enrolling HIV-infected subjects with sustained viral suppression have shown that CD4+ T-cell counts remain stable for >10 years in most individuals; <9% of subjects have reductions in CD4+ counts, and this drop is transient in >90% of cases [1]. These data have supported the World Health Organization's suggestion to reduce the frequency of routine CD4+ T-cell monitoring in adults once CD4+ counts are >200 cells/mmc and viral load is undetectable [2].

Questions nonetheless remain as to whether the CD4+ T-cell count is the most appropriate marker of combination antiretroviral therapy (cART)–induced immune reconstitution to monitor the immune status of treated HIV-infected individuals. Indeed, despite long-term antiretroviral therapy with constant viral suppression and significant CD4+ T-cell gain, individuals fail to normalize the levels of immune activation/inflammation and hypercoagulation [3–9]. This persistent alteration of the immune system has a clinical impact, given data in the literature to support its association with the development of noninfectious comorbidities, increased mortality, and impaired immune reconstitution in the setting of treated HIV infection [10].

In particular, inflammation markers do not predict clinical events in cART-naive subjects [11], yet they are independently associated with clinical outcome in treated individuals [12, 13]. These findings strongly suggest that clinical events in HIV infection are driven by differential mechanisms, that is, by the replicating virus in the former and by residual inflammation (which is not solely virus-related) in the latter.

A plethora of antiretroviral compounds that are equally effective in abating the HIV load are available in clinical practice; however, drugs and their combinations may have a diverse result on the immune and inflammatory perturbations that feature HIV infection—hence the risk of developing noninfectious comorbidities for cART-treated individuals. Several studies have investigated the effects of antiretroviral drugs in areas other than suppression of HIV replication, focusing on peripheral markers of inflammation, immune activation, and immuno-senescence [14–25].

The scope of the present work is to review, in a narrative and nonsystematic manner, evidence in favor of or against qualitative differences in immune recovery according to antiretroviral classes/regimens in antiretroviral-naive and cART-experienced patients.

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## DIFFERENCES IN IMMUNE RECOVERY ACCORDING TO CART REGIMEN?

### Immune Recovery in Antiretroviral-Naive HIV-Infected Patients Starting cART

In terms of the cART backbone used in this setting, a few subtle differences exist when comparing subjects treated with abacavir (ABC)- and tenofovir (TDF)-containing regimens, with demonstrated transient decreases of high-sensitivity C-reactive protein (hsCRP) in the former and interleukin (IL)-6 in the latter [26]. Another study described a minor reduction of residual inflammation and endothelial activation markers in individuals receiving an ABC-based regimen vs a non-ABC-containing regimen [27]. In contrast, ABC and TDF resulted in comparable expression of inflammatory, oxidative, and apoptotic stress genes in coronary endothelial cells without differently affecting endothelial activation and inflammation [28, 29]. Taken together, these findings may explain the conflicting reports on atherosclerotic risk in individuals treated with ABC [30–41]. In this respect, the recent introduction of tenofovir alafenamide (TAF) has rekindled new hopes of less toxic antiretroviral regimens: Although linked to the improvement of bone and kidney function [42–48], TAF has been shown to be equivalent to TDF regarding immune activation and inflammation [49].

Literature studies have also assessed differences in cART-induced immune reconstitution according to the third drug used in triple combination regimens.

Earlier studies compared protease inhibitor (PI)– with non-nucleoside reverse transcriptase inhibitor (NNRTI)–containing regimens. A prospective, single-center observational study enrolling naive subjects sequentially treated with PI (indinavir [IDV] or lopinavir [LPV]) and NNRTI (efavirenz [EFV]) found a greater reduction in fibrinogen levels in the course of the latter, despite similar improvements in inflammation and coagulation parameters [7]. Similarly, in the A5224s study, cystatin C, a renal function marker known to correlate with other inflammatory biomarkers, and hs-CRP were lower in subjects treated with EFV than those treated with atazanavir (ATV) [26, 50]. On the other hand, PIs have also been associated with increased HIV antigen- and mitogen-stimulated T lymphocyte proliferation [26], albeit transitory in nature [24]. Further, contrasting data exist on the effect of the third drug on peripheral T-cell phenotype, with some studies pointing to a greater reduction of immune activation parameters (CD4+/DRII+, CD8+/DRII+, CD4+/CD25+, CD4+/CD25+) in PI-treated individuals [26] and others demonstrating greater reduction of immune activation parameters in NNRTI-treated subjects [51], as well as evidence of impaired CD8+ T-cell maturation (reduced CD8+/28-/CD45RA+ levels) in patients receiving PI- rather than in NNRTI-based cART [52].

More recently, studies have focused on the potential benefits of integrase strand transfer inhibitors (INSTIs) on immune restoration.

A post hoc analysis of the STARTMRK study of raltegravir (RAL) vs EFV, each in combination with TDF/FTC, demonstrated that INSTI use was associated with higher rates of CD4/CD8 normalization [53]. Several studies have also shown that first-line RAL-based regimens normalized monocyte homeostasis [54] and contained T-cell activation, coagulation, and inflammation [6] as well as microbial translocation [55], whereas non-RAL-including cART did not. Similarly, another RCT demonstrated that elvitegravir/cobicistat (EVG/c) was associated with lower levels of monocyte activation and systemic inflammation than EFV, given the greater reduction of sCD14 and hs-CRP in subjects treated with the INSTI-based regimen [56]. In line with the possible beneficial immune effects linked to first-line INSTI use, a cohort study demonstrated an association between INSTI treatment and normalization of the CD4/CD8 T-cell ratio in naive subjects following 1 year of therapy [57]. In antithesis, a post hoc analysis of the SINGLE study (which nonetheless was not controlled for the backbone regimen) showed that NNRTIs performed better than INSTIs, leading to a higher increase in the CD4+/CD8+ ratio as well as several T-cell recovery markers in subjects randomized to receive EFV/TDF/FTC instead of DGT/ABC/3TC [58].

Despite the above-mentioned findings of possible differences in immune parameters between INSTIs and other third-drug classes, findings from the A5260 study failed to detect a differential effect of a first-line cART with RAL or with a PI (ATV/r or DRV/r), in terms of T-cell senescence (CD28-CD57+) and exhaustion (PD-1 expression) [59, 60].

Regarding the quality of immune recovery following the introduction of HIV entry inhibitors, a pilot RCT reported that quadruple therapy was associated with better duodenal immune reconstitution, greater reduction of cell-associated HIV-DNA in the duodenum, and higher decline in systemic levels of inflammatory markers in patients starting cART with TDF/FTC + maraviroc (MVC) + RAL rather than with TDF/FTC + MVC or TDF/FTC + EFV, possibly due to increased higher mucosal gut penetration of MVC [61]. In contrast, a post hoc analysis of the MERIT trial, comparing MVC and EFV in combination with AZT/3TC, showed a higher rate of CD4/CD8 normalization in the NNRTI arm, driven by a greater CD8+ T-cell decline [62].

### On the Opposite Sides of the Spectrum: Immune Recovery in Antiretroviral-Naive HIV-Infected Patients Starting cART in Acute and Late Stages of Infection

Antiretroviral-naive subjects introducing cART in the acute phase of HIV infection represent an intriguing clinical scenario in terms of immune recovery. Indeed, the literature has shown a possible method of controlling reported damage to the immune system if cART is started in the earliest stages of disease, with timely immune reconstitution (CD4+ T-cell count >500 cells/mm$^3$, CD4% >30%, and CD4/CD8 ratio >1), a decrease in T-cell activation/inflammation, and a lower risk of non-AIDS comorbidities [3, 63–69].

Standard triple regimens are currently recommended by European and American guidelines [70–72] for the treatment of acute HIV infection and have shown the ability to reduce immune activation in this setting [73]. Nonetheless, 4-drug regimens have also been studied, aiming to hinder the establishment of the viral reservoir: a prospective RCT demonstrated that starting TDF/FTC + RAL + MVC, compared with TDF/FTC + RAL, promoted a faster reduction of 2-LTR circles and a recovery of CD4+ T cells with a partial decrease in the total reservoir size [74]. Quadruple cART with AZT + 3TC + ABC + fosamprenavir (APV) in acutely infected patients was also associated with a more rapid decline in viremia and CD8+ T-lymphocyte activation reaching normalization at 48 weeks [75]. While RCT and prospective studies are currently evaluating the impact of different regimens (EFV- vs RAL-based cART, cART plus telmisartan [76]; EVG/c/TDF/FTC [77]; ABC/3TC + dolutegravir [DGV] [78, 79]; bictegravir + TAF [80]) in the setting of acute infection, data on the use of MVC have shown that this drug does not lead to significant improvements in the levels of inflammation, endothelial activation, and coagulation [81], probably reflecting the scarce effects of MVC intensification on residual viremia in acutely HIV-infected individuals [82].

Another factor known to play a key role in the quality of cART-mediated immune reconstitution is the CD4+ T-cell nadir [23, 25, 83]. Indeed, antiretroviral-naive patients starting LPV/r- [23] and EFV-based cART [25] with a baseline CD4+ count >200/mmc present better immunological improvement than patients starting with a lower CD4+ count. In contrast with these findings, however, subjects starting EFV-based cART with CD4+ T cells <300/mmc experienced not only a better immune reconstitution, but also a greater reduction of systemic inflammation markers compared with individuals starting with CD4+ >300/mmc [83]. In the context of advanced presentation, an RCT showed that the addition of MVC did not reduce monocyte/macrophage activation to a greater extent than standard triple cART [84].

#### Immune Recovery in cART-Treated HIV-Infected Patients Switching to Other Regimens

Conflicting results on the different effects of second-line NNRTI- and PI-based cART on inflammation and HIV persistence stem from early observational studies assessing a wide range of biomarkers that are not validated as surrogate markers of clinical events [17, 18, 85–91].

More recently, an RCT showed that switching from a PI/r- to an RAL-containing regimen resulted in a reduction of markers proven to be linked to cardiovascular disease (hs-CRP, IL-6, D-dimer) [92]. In addition, a further RCT on overweight women randomized to an immediate or 24-week delayed switch from an NNRTI- or PI-based cART to an RAL-based regimen demonstrated a significant decline in sCD14 following cART change [93]. RAL also appears to have positive effects on the gastrointestinal tract, a major site of HIV pathogenesis: A partial normalization of the gut microbiota composition, as well as markers of microbial translocation and inflammation, was observed in subjects receiving RAL and not a PI- or NNRTI-based regimen [94]. In addition to the reduction of systemic inflammation, as demonstrated by reduced D-dimer [95] and T-cell activation [96], different RCTs showed that intensification of current cART with RAL decreased low-level viral replication [95] yet did not affect measures of HIV persistence [96].

Other potential beneficial effects of INSTIs have been described following treatment with EVG that resulted in immune activation and partially restored T-cell function [97].

With respect to MVC, a meta-analysis of clinical trials in treatment-experienced patients showed that this compound was associated with a significant increase in CD4+ T-cell count regardless of virologic suppression [98]. Even if adding MVC alone [99] or MVC + RAL to the current cART had no effect on the size of the latent HIV reservoir, intensification of a PI-regimen with MVC + RAL was associated with a reduction of cell-associated HIV-DNA, T-cell CD8+ activation, and rectal proviral HIV-DNA [100]. Evidence from the literature also favors the use of MVC in selected clinical settings given its immune-modulating and anti-inflammatory effects. A recent study showed improved responsiveness to HBV vaccination in MVC-treated subjects, possibly due to reduced CD4+ T-cell activation and proliferation [101]. Another report demonstrated lower levels of monocyte activation in individuals receiving MVC compared with those on MVC-free regimes [102], supporting in vitro evidence on the possible role of CCR5 inihitors in hindering atherosclerotic plaque formation [103–105].

In contrast to the reported findings of possible differences in immune restoration parameters in subjects undergoing a therapeutic switch, other studies have failed to demonstrate variations of biomarkers in this context.

An RCT conducted in patients randomized to switch from AZT/3TC- to either ABC/3TC- or TDF/FTC-based cART did not highlight differences in biomarkers of coagulation and inflammation (d-dimer, IL-6, or hs-CRP) [106]. Similarly, a large cohort study showed comparable monocyte activation (sCD14) in NVP- and EFV-treated individuals [107]. No differences were detected in T-cell activation and homeostasis when adding either MVC or DRV/r to RAL and ETV in patients experiencing viral failure [108]. Parameters of viral persistence (total HIV-DNA and 2-LTR circle levels) were also unchanged in subjects enrolled in an RCT switching from enfurvitide (T20) to RAL [109]. Of note, an RCT on cART intensification with RAL in suppressed individuals failed to detect any difference in gut and blood proviral DNA [110].

#### Immune Recovery in the Course of cART Intensification Strategies for HIV-Infected Individuals Lacking CD4+ T-Cell Gain

Despite stable viral suppression, ~20%–30% of cART-treated subjects fail to obtain adequate CD4+ T-cell recovery. The literature has failed to demonstrate that changing cART regimen may favor

CD4+ gain in this setting [1], yet several intensification studies have shown the possible role of antiretroviral drugs in lowering markers of immune activation and exhaustion, microbial translocation, and inflammation in the peripheral blood and tissues, which feature subjects with persistently low CD4+ T-cell counts [111–115].

The addition of MVC to ongoing cART did not lead to increases in the CD4+ T-cell count [116–118]; however, it reduced immune activation and apoptosis [116, 118] and increased the frequencies of CD8+ T cells [117]. In addition, MVC-intensified subjects displayed, compared with placebo, a significant increase in T-cell activation in rectal tissue and peripheral blood and redistribution of CD8+ T cells from the gut to peripheral blood [119]; however, in another study, MVC had no effect on CD4+ T-cell counts, CD4+/CD8+ ratio, microbial translocation, immune activation, or immune exhaustion parameters measured in the peripheral blood and gut [120].

Intensification strategies in immunological nonresponders (INRs) using RAL have not been shown to account for CD4+ T-cell recovery, but have shown reduced CD8+ T-cell activation [121] and inflammation [122] compared with PI-based cART [123]. In contrast, other studies failed to demonstrate RAL-induced CD4+ T-cell recovery or reduction of T-cell/monocyte activation as well as microbial translocation [124, 125].

## IMMUNE RECOVERY IN CART-TREATED HIV-INFECTED PATIENTS WITH FEWER DRUG REGIMENS

Clinicians are currently facing an exciting new era of significant changes in the management of antiretroviral therapy for HIV infection, featuring dual regimens with excellent viro-immunological properties in both naive and experienced subjects [126–130], as well as fewer drug-related toxicities compared with standard triple cART [131]. Nonetheless, whether such novel therapeutic strategies are also able to limit inflammation in the course of HIV infection is currently under investigation. Fewer drug regimens may, on the one hand, account for the loss of control over enduring inflammation given the reduced pharmacologic pressure on residual viral replication [132]; on the other hand, they may result in less drug-induced oxidative stress, contributing to the containment of inflammation and immune activation [133].

A large observational cohort study showed an increase in the absolute number of CD8+ T cells in patients on stable triple cART who were switched to dual regimens containing NRTI or to NRTI-sparing dual therapies, compared with subjects who were switched to a new triple regimen [132]. A similar increase in CD8+ lymphocytes was confirmed in another cohort study including patients switching from a TDF/ABC-based triple regimen to a dual therapy, but only for subjects interrupting TDF and not ABC [134].

The first RCT on dual regimens was conducted in subjects undergoing simplification to PI-containing cART. Findings from the ATLAS study showed that ATV/r plus 2 NRTIs and ATV/r plus 3TC resulted in similar levels of peripheral inflammation [135] and a comparable reduction of the viral reservoir [136].

More recently, the immune effects of dual INSTI-based treatment strategies from a well-powered RCT were published in the literature.

The findings of the SWORD-1 and SWORD-2 RCT showed diverging results: On the one hand, a significantly greater sCD14 increase from baseline to week 48 was reported in subjects receiving standard triple cART than those switching to DTG + RLP [137]; on the other, while a greater decrease in IFABP levels was found in the latter, no significant changes from baseline to week 48 were detected for IL-6, sCD163, sVCAM-1, and D-dimer between groups [137]. Given the lack of a consistent pattern in the kinetics of these biomarkers, The authors did not claim that increased inflammation features particpants on the 3-drug regimen compared to those receiving the dual–drug regimen [138]. Results from the TANGO study, in which virally suppressed subjects were randomized to either receive a DTG/3TC dual regimen or continue a TAF-based 3- or 4-drug regimen, also showed uncertain effects on the same inflammation biomarkers (D-dimer, sCRP, IL-6, sCD14), given their reported differing directions in the 2 study groups [130]. The findings of an NEAT001/ANRS143 substudy that randomized cART-naive subjects to DRV/r in combination with TAF/FTC or RAL demonstrated a significantly higher gain in blood telomere length in the former, pointing to amelioration of HIV-associated immune-senescence [139]. In contrast, sCD14 levels decreased significantly in a retrospective crossover study on suppressed patients on a 3TC + PI/r dual therapy switching to 3TC + DTG, suggesting decreased monocyte activation in individuals treated with INSTI-based, and not PI-based, dual cART [140].

Taken together, these results highlight the need for longer follow-up, which may reveal the true inflammatory consequences of switching to dual regimens and imply a word of caution on the interpretation of heterogeneous findings related to biomarker changes in this clinical setting [141].

Finally, few studies have comparatively investigated immune activation and systemic inflammation in mono vs triple cART regimens. Despite maintaining undetectable viremia, in the MONARK study, the monotherapy arm with LPV/r showed comparable parameters of immune recovery and residual viremia to those observed in the standard triple regimen (AZT/3TC + LPV/r regimen) [142]. Similarly, immune activation, inflammation, and HIV-DNA did not improve with ATV monotherapy in the MODAT trial [143]. In a retrospective study, higher T-cell activation and microbial translocation were found in patients switching to monotherapy with LPV/r compared with triple cART [144].

## CONCLUSIONS

While extraordinarily effective in suppressing viral load and reconstituting the CD4+ T-cell compartment, cART fails to

normalize the effects of chronic inflammation in HIV infection [3]. To date, no therapeutic approach has effectively abated inflammation and immune activation in aviremic individuals. Indeed, chronic inflammation persists despite the introduction of novel, effective, and well-tolerated antiretroviral drugs and is known to drive morbidity and mortality in HIV-infected patients [4, 5, 10].

The present nonsystematic review, albeit lacking evidence synthesis, was conducted to offer breadth of literature coverage on the topic of cART-related differences in immune reconstitution parameters.

Overall, evidence points to possible differences in qualitative immune recovery during suppressive treatment for HIV, yet a limited number of studies are randomized, adequately powered, and have a sufficient follow-up to detect robust changes linked to cART classes and regimens (Tables 1 and 2). Further, many biomarkers were assessed over the years and were independently associated with clinical outcome in the setting of HIV

**Table 1. Overview of the Major Studies Evaluating the Quality of Immune Reconstitution Under Antiretroviral Therapy—Randomized Controlled Trials**

| Author, Reference | Study Population | cART Regimen | Evaluation of Immune Recovery | Study Design | Main Results |
|---|---|---|---|---|---|
| Antiretroviral naive patients | | | | | |
| McComsey et al. [26] | 244 pts | Blinded ABC/3TC + open-label EFV or ATV/r vs blinded TDF/FTC + open-label EFV or ATV/r | *Peripheral blood*<br>*Inflammation*: hs-CRP, IL-6, TNF-α, sTNFR-I, -II<br>*Vascular inflammation*: sVCAM-1 and sICAM-1 | RCT substudy | No differences in sTNF-R and adhesion molecule decrease by regimens. Higher decrease in hsCRP in ABC/3TC vs TDF/FTC and in EFV vs ATV/r. Greater IL-6 reduction in TDF/FTC than in ABC/3TC |
| Serrano-Villar et al. [53] | 563 pts | TDF/FTC + RAL vs TDF/FTC + EFV | *Peripheral blood*<br>*Immune activation:* CD4/CD8 T-cell ratio | RCT (post hoc analysis of STARTMRK study) | Higher rates of CD4/CD8 ratio normalization in the RAL arm |
| Blanco et al. [58] | 833 pts | DTG/ABC/3TC vs EFV/TDF/FTC | *Peripheral blood*<br>*Immune activation*: CD4/CD8 T-cell ratio, CD4 T-cell count (absolute and percentage values) | RCT (post hoc analysis of SINGLE study) | Greater increase in CD4/CD8 ratio or multiple T-cell marker recovery (MTMR: CD4 T cells >500/mm$^3$ and CD4% >29% and CD4/CD8 ratio >1) in EFV/TDF/FTC than in DTG/ABC/3TC |
| Kelesidis et al. [59, 60] | 328 pts | TDF/FTC + ATV/r vs TDF/FTC + DRV/r vs TDF/FTC + RAL | *Peripheral blood and PBMCs*<br>*Markers of CD4± T-cell senescence*: CD28–CD57+<br>*Markers of CD4± and CD8± T-cell exhaustion*: PD-1+<br>*Inflammation and immune activation:* HLA-DR+ CD38+ expression; sCD163<br>*Inflammation and coagulation:* hsCRP, IL-6, sCD14, D-dimer<br>*Macrophage and T-cell activation:* %CD38+ HLADR+ on CD4+ and CD8+ T cells, sIL-2r, sCD14, sCD163, intermediate CD14+ CD16+ monocytes, inflammatory CD14+ CD16+ | RCT (A5260) substudy | Decrease of CD4+ T-cell senescence and exhaustion after ART. No changes in CD8+ T-cell senescence after ART and no differential changes in all markers in ART groups. No consistent differences in immune activation and reduction of inflammation between PI and RAL-based cART |
| Serrano-Villar et al. [62] | 721 pts | AZT/3TC + MVC vs AZT/3TC + EFV | *Peripheral blood*<br>*Immune activation*: CD4/CD8 T-cell ratio, CD8+ T-cell count | RCT (post hoc analysis of MERIT study) | Higher rate of CD4/CD8 ratio normalization sustained by a greater CD8+ T-cell decline in the EFV arm than in the MVC arm |
| Hileman et al. [56] | 200 pts | EVG/TDF/FTC vs EFV/TDF/FTC | *Peripheral blood and PBMCs*<br>*Inflammation:* hs-CRP, IL-6, TNFr1<br>*Vascular inflammation:* Lp-PLA2<br>*MT:* LPS<br>*Monocyte activation:* sCD14, sCD163 | RCT (Gilead 102) | EVG/c/TDF/FTC showed higher reduction in inflammation and MT, compared with EFV/TDF/FTC |
| Funderburg et al. [49] | 194 pts | E/C/F/TAF vs E/C/F/TDF | *Peripheral blood*<br>*Monocyte activation*: sCD14, sCD163<br>*Systemic inflammation*: IL-6, hsCRP, sTNFR-I, and D-dimer<br>*Vascular inflammation*: Lp-PLA2 | RCT | Equivalent declines in monocyte activation and systemic inflammation with TAF or TDF for 48 weeks, suggesting that TAF and TDF have equivalent impact on immune activation and inflammation |
| Pallikkuth et al. [55] | 30 patients | RAL vs non-RAL cART | *Peripheral blood and PBMCs*<br>*Immune activation*: HLA-DR/CD38 in CD4/CD8 T cells<br>*Immune exhaustion*: PD1 in CD4/CD8 T cells<br>*T-cell subsets, cytokine production:* HIV gag–specific IL-2, IFN-γ, CD107a responses in CD4/CD8 T cells<br>*MT:* LPS and sCD14 | RCT substudy | RAL in first-line treatment regimens results in rapid immune reconstitution with residual low-level MT. The week 48 immune profile was more favorable in patients taking RAL-cART than in pts treated with non-RAL-cART |

**Table 1. Continued**

| Author, Reference | Study Population | cART Regimen | Evaluation of Immune Recovery | Study Design | Main Results |
|---|---|---|---|---|---|
| Serrano-Villar et al. [61] | 32 HIV+ pts 12 HIV- pts | TDF/FTC + EFV vs TDF/FTC + MVC vs TDF/FTC + MVC + RAL | *Peripheral blood and PBMCs*<br>*Rectal and duodenal biopsies, immune phenotypes on CD4±/CD8± T cells*<br>*T-cell density in gut*<br>*Plasma and tissue antiretroviral drug concentrations*<br>*Inflammation:* plasma IL-6, LTA *MT:* sCD14<br>*Gut permeability:* zonulin-1<br>*Total cell-associated HIV DNA in PBMCs, rectal and duodenal mononuclear cells* | Pilot RCT | Quadruple regimen resulted in higher CD8+ cell density decline, greater normalization of mucosal CCR5+ CD4+ cells, and increase in naive/memory CD8+ cells ratio, greater decline in sCD14 and duodenal HIV-DNA. MVC had the highest gut concentrations, which negatively correlated with percentages of activated CD8+ in duodenum. MVC use was associated with activation of mucosal naive CD8+ cells, improvement of distribution of CD8+ cell maturational subset and higher zonulin-1 expression |
| Acute/primary HIV infection | | | | | |
| Chaillon et al. [82] | 18 pts | Standard ART + MVC vs standard ART | *Peripheral blood and PBMCs:* levels of HIV DNA and cell-free RNA; deep sequencing of C2-V3 *env*, *gag*, and *pol* | RCT | There was no difference in CD4+ T cells between groups. There was a longitudinal decay of HIV-DNA after initiation of ART with no difference between MVC intensification groups. |
| Puertas et al. [74] | 30 pts | TDF/FTC+RAL vs TDF/FTC+RAL-MVC | *Peripheral blood and PBMCs*<br>*Cell-associated HIV-1 DNA*: total, integrated, and episomal<br>*Immune activation*: HLA-DR+ CD38+ CD4/CD8 T cells, frequency of CCR5 staining in CD38+ and CD38- in the CD45RA+ and CD45RA- cells<br>*Inflammation, coagulation, endothelial function*: IL-6, D-dimer, CRP, Lp-PLA2, VCAM-1<br>*MT*: sCD14 | RCT (Maravi-Boost study) | Intensification with MVC results in faster reduction of 2-LTR newly infected cells, recovery of CD4+ counts, and a modest reduction in total reservoir size after 48 weeks. MVC also was associated with a slower decrease in plasma viremia and immune activation |
| Late presentation | | | | | |
| Patro et al. [84] | 65 pts | TDF/FTC/EFV + MVC or placebo | *Peripheral blood and PBMCs*<br>*Monocyte and macrophage activation*: CD14+ CD16+ monocytes, CD163 monocytes, CD169 monocytes, tetherin, sCD14, sCD163<br>*CD4 and CD8 activation*: HLADR+ CD38+ CD4/CD8+ T cells | RCT (CADIRIS) substudy | MVC did not affect biomarkers of monocyte and macrophage activation, but resulted in higher percentages of CCR5-positive monocytes in PBMCs |
| cART-treated patients—switch studies | | | | | |
| Chege et al. [110] | 24 pts | RAL vs placebo | *Peripheral blood and sigmoid biopsies:* proviral HIV-1 DNA in CD4+ T cells in blood and the sigmoid colon | Double-blind placebo-controlled RCT 1:1 | Intensification with RAL did not result in further decay of CD4+ T cells carrying HIV-1 proviral DNA in either the blood or gut after 48 or 96 weeks of therapy, or in any increase in CD4+ T-cell counts |
| Llibre et al. [96] | 69 pts | Standard ART vs standard ART + RAL | *Peripheral blood and PBMCs*<br>*Total HIV1-DNA and 2-LTR circles, ultrasensitive plasma viremia CD4/CD8 T-cell subsets* | Open label RCT 2:1 (NCT 00554398) | RAL intensification is associated with a significant impact in CD8+ T-cell immune activation markers, as well as a transient increase in 2-LTR circles |
| Lake et al. [93] | 37 pts | NRTI backbone + PI or NNRTI vs NRTI backbone + RAL | *Peripheral blood*<br>*Inflammation*: hsCRP, sCD14, IL-6, TNF-α, sTNF-RII, sVCAM-1<br>*Monocyte and macrophage activation:* sCD14<br>*Microbial translocation:* sCD163, I-FABP | Open label RCT | Greater sCD14 decline in subjects switching to a RAL-based ART than in those remaining on a PI- or NNRTI-based therapy |
| Hatano et al. [95] | 31 pts | Standard ART + RAL vs standard ART + placebo | *Peripheral blood and PBMCs*<br>*Viral replication:* 2-LTR circles<br>*Inflammation and hypercoagulation:* IL-6, D-dimer | RCT | Greater increase in 2-LTR circles and greater decrease in D-dimer levels in the RAL intensification arm compared with placebo |
| Rasmussen et al. [106] | 35 pts | AZT/3TC vs ABC/3TC or TDF/FTC | *Peripheral blood*<br>*Inflammation and endothelial dysfunction/cardiovascular biomarkers:* IL-6, hs-CRP, sICAM-1, sVCAM-1, E-selectin, MPO, D-dimer, fasting lipids | RCT (SWAP substudy) | No difference in biomarkers among groups, with the exception that transient increases were seen in E-selectin and sVCAM-1 in ABC-based compared with TDF-based cART |
| Martinez et al. [92] | 273 pts | PI/r vs RAL | *Peripheral blood*<br>*Inflammation*: hsCRP, MCP-1, osteoprotegerin, IL-6, IL-10, TNF-α, ICAM-1, VCAM-1, E-selectin and P-selectin, adiponectin, insulin, and D-dimer | RCT (SPIRAL trial) | hsCRP, MCP-1, osteoprotegerin, IL-6, TNF-α, insulin, and D-dimer decreased in RAL compared with PI/r, whereas IL-10, ICAM-1, VCAM-1, E-selectin, P-selectin, and adiponectin remained unchanged |
| Delaugerre et al. [109] | 60 pts | T20 vs RAL | *Peripheral blood and PBMCs:* total HIV-1 DNA and 2-LTR circle levels | RCT (EASIER-ANRS 138, substudy) | No differences in measures of viral persistence between groups |

**Table 1. Continued**

| Author, Reference | Study Population | cART Regimen | Evaluation of Immune Recovery | Study Design | Main Results |
|---|---|---|---|---|---|
| cART-treated patients—immunological nonresponders | | | | | |
| Rusconi et al. [117] | 97 pts | ART vs ART + MVC | *Peripheral blood and PBMCs:* T-cell subsets<br>*Inflammation*: plasma IL-7 | Multicentric, parallel, open label, phase 4 superiority RCT 1:1 (NCT00884858) | MVC intensification was associated with a significant rise in IL-7 by week 48 and a trend in temporary reduction in activated HLA-DR+ CD38+ CD4+ by week 12 that was not maintained at week 48 |
| Massanella et al. [121] | 44 pts | ART vs ART + RAL | *Peripheral blood and PBMCs*<br>*CD4 T-cell compartment:* total, activated, and memory T cells<br>*CD8 T-cell compartment:* total, activated, and memory T cells<br>*Thymic output*: CD45RA+ CD31+, CD31-CD45RA+, CD45RA-<br>*Microbial translocation*: sCD14<br>*Viral replication:* 2-LTR circles | RCT | No differences between groups in biomarker levels, except for lower T-cell activation in the RAL intensification arm |
| Negredo et al. [125] | 44 pts | ART vs ART + RAL | *Peripheral blood and PBMCs:* CD4 T-cell counts, total and episomal HIV DNA in PBMCs | RCT | No difference between groups, except for a rapid yet limited CD4+ T-cell gain in the RAL intensification arm |
| Hunt et al. [119] | 45 pts | ART + MVC vs ART + placebo | *Peripheral blood, PBMCs, rectal mucosa*<br>*Rectal CD T-cell density:* CD8 and CD4 T cells<br>*Peripheral T-cell activation:* CD8 and CD4 T cell, CD38, HLA-DR<br>*Rectal T-cell activation*: CD38+ HLA- DR+<br>*T-cell maturation*: naive (CD45RA+ CCR7+), central memory (CD45RA+ CCR7+), effector memory (CD45RA+ CCR7+), and terminally differentiated effector memory (CD45RA+ CCR7-)<br>*CCR5 T cells and plasma MIP-1b levels, monocyte activation*: sCD14, sCD163<br>*Neutrophil levels, peripheral count, and rectal MPO*<br>*Microbial translocation*: plasma LPS<br>*Low-level viremia:* HIV-RNA | RCT | In the MVC arm: rectal tissue and peripheral blood increase in T-cell activation; CD8 T-cell count increase in the peripheral blood and decrease in rectal tissue; increase in peripheral MIP-1b, monocyte/macrophage activation markers (sCD14 and sCD163), and peripheral blood and rectal tissue neutrophil count |
| cART-treated patients—dual and mono therapies | | | | | |
| Belmonti et al. [135] | 139 pts | ATV/r plus 3TC vs ATV/r plus 2 NRTIs | *Peripheral blood*<br>*Systemic inflammation*: IL-6, CRP, sCD14, and D-dimer | RCT (ATLAS-M) substudy | No significant differences in changes from baseline to week 48 were observed between dual and triple therapy. No relationship was observed between baseline biomarker level and persistent residual viremia and HIV-1 DNA load |
| Lombardi et al. [136] | 201 pts | Triple ATV/r-based ART vs ATV/r plus 3TC | *Peripheral blood and PBMCs, HIV-1 reservoir*: total HIV-1 DNA levels in whole blood and PBMCs | RCT (ATLAS M) substudy | Dual therapy resulted in a similar decline in HIV-1 DNA levels |
| Aboud et al. [137] | 1024 **pts** | ART vs DTG + RPV | *Peripheral blood*<br>*Inflammation:* sCD14, IFBAP, IL-6, sCD163, sVCAM, D-dimer | RCT (SWORD 1–2) | Greater sCD14 increase from baseline to week 48 in subjects receiving standard triple cART than those switching to DTG+RLP. Greater IFABP decrease in DTG+RLP. No significant changes from baseline to week 48 were detected for IL-6, sCD163, sVCAM-1, or D-dimer between groups |
| Van Wyk et al. [130] | 743 **pts** | TAF-based ART vs DTG/3TC | *Peripheral blood*<br>*Inflammation:* sCD14, IL-6, sCD163, D-dimer, hs CRP | RCT (TANGO) | No clear-cut differences between groups |
| Stella-Ascariz et al. [139] | 201 **pts** | DRV/r + RAL vs DRV/r + TDF/FTC | *Peripheral blood:* telomere length | RCT | Significantly higher gain in blood telomere length in TDF/FTC + DRV/r than DRV/r + RAL |
| Merlini et al. [143] | 40 **pts** | ATV/r + 2NRTI vs ATV/r | *Peripheral blood and PBMCs*<br>*HIV reservoir*: total HIV-DNA<br>*T-cell immune phenotype*: activated: HLADR+ CD38+; senescent: CD57+; apoptotic: CD95+; exhausted: PD-1+<br>*Inflammation*: sCD14, IL-6 | RCT (MODAt substudy) | Comparable activation an inflammation biomarkers |

Abbreviations: 3TC, lamivudine; ABC, abacavir; (c)ART, (combination) antiRetroviralTherapy; ATV, atazanavir; AZT, zidovudine; c, cobicistat; CCR, C-C chemokine receptor; (s)CD, (soluble) cluster of differentiation; DNA, deoxyribonucleic acid; DRV, darunavir; DTG, dolutegravir; E, elvitegravir; EFV efavirenz; EVG, elvitegravir; F, emtricitabine; FTC emtricitabine; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; hs-CRP, high sensitivity C-reactive protein; (s)ICAM, (soluble) intercellular adhesion molecule; IFABP, intestinal fatty-acid binding protein; IFN, interferon; IL, interleukin; Lp-PLA2, lipoprotein-associated phospholipase A2; LPS, lipopolysaccharide; LTA, lipoteichoic acid; LTR, long terminal repeat; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; MT, microbial translocation; MTMR, multiple T-cell marker recovery; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PBMCs, peripheral blood mononuclear cells; PD, programmed death; PI, protease inhibitor; r, ritonavir; RAL, raltegravir; RCT, randomized controlled trial; RNA, ribonucleic acid; sIL-2r, soluble IL-2 receptor; (s)TNFR, soluble tumor necrosis factor receptor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TNF, tumor necrosis factor; TNF-R, tumor necrosis factor receptor; (s)VCAM, vascular cell adhesion molecule.

**Table 2. Overview of the Major Studies Evaluating Quality of Immune Reconstitution Under Antiretroviral Therapy—Non–Randomized Controlled Trials**

| Author, Reference | Study Population | cART Regimen | Evaluation of Immune Recovery | Study Design | Main Results |
|---|---|---|---|---|---|
| Antiretroviral-naive patients | | | | | |
| Funderburg et al. [6] | 39 HIV+ pts 21 HIV- pts | TDF/FTC + RAL | *Peripheral blood and PBMCs* *Immune phenotypes on CD4±/CD8± T cells* *Inflammation:* plasma IL-6, TNFr1 *MT:* sCD14, LPS *Coagulation*: d-dimer | Prospective, open-label, multicenter, pilot study (A5248) | RAL-based ART reduced CD4+/CD8+ activation, cell cycle entry, and markers of coagulation and inflammation, without reaching HIV-uninfected levels. |
| De Salvador-Guillouët et al. [57] | 567 patients | PI-based cART vs NRTI-based cART vs NNRTI-based cART vs INSTI-based cART | *Peripheral blood* *Immune activation*: CD4/CD8 T-cell ratio | Retrospective | INSTI-based regimens associated with a CD4/CD8 ratio normalization 1 year from cART introduction. |
| McCausland et al. [54] | 29 HIV+ pts 15 HIV- pts | TDF/FTC + RAL | *Peripheral blood and PBMCs* *Immune phenotypes on monocytes* | Prospective, open-label, multicenter, pilot single-arm study (A5248) | RAL-based ART reduces monocyte activation and increases expression of chemokine receptors CCR2 and CX3CR1 on inflammatory and patrolling monocytes. |
| Late presentation | | | | | |
| Tincati et al. [24] | 34 pts | DRV/r or EFV as third drugs of standard antiretroviral regimens | *Peripheral blood and PBMCs* *Proliferation and maturation on CD4±/CD8± cells* *Activation on CD8± cells* *HIV- and CMV-specific responses:* IL-2, IFN-γ production by CD4/CD8 cells *Plasma inflammatory markers:* IL-6 and sCD14 | Retrospective, ex vivo study | No differences in T-cell maturation, activation, and function. Patiens on DRV/r show a transitory recovery of HIV-specific IL-2+ IFN-γ-CD4+ cells and IL-2- IFN-γ+ CD8+ cells. |
| Marchetti et al. [23] | 40 pts | TDF/FTC + LPV/r | *Peripheral blood and PBMCs* *Quality of immune reconstitution:* CD38+ CD8+, CD45R0+ CD38+ CD8+, CD95+ CD4+/CD8+, CD127+ CD4+/CD8+ *Microbial translocation:* sCD14, LPS | Prospective | No differences in T-cell activation decline between groups. Subjects starting ART with "moderate immune depression" (CD4 + 200- 350/μL) had a greater control over microbial translocation than those with "severe immune depression" (CD4+ < 100/μL). |
| Soria et al. [25] | 24 pts | TDF/FTC + EFV | *Peripheral blood and PBMCs Immune phenotypes on CD4±/CD8± T cells:* total, naïve, and activated Treg *Intracellular cytokine production:* IL-2, IFN-γ | Pilot clinical trial (IMMUNEF) | EFV-based ART reduces the percentages of apoptotic and proliferating T cells at 24 weeks. |
| cART-treated patients—switch studies | | | | | |
| Villanueva-Millàn et al. [94] | 45 cART HIV+ pts 5 untreated HIV+ pts 21 HIV- pts | PIs vs NNRTIs vs INSTIs | *Peripheral blood and fresh stool samples* *MT*: sCD14, LBP *Systemic inflammation*: IL-6 *Vascular inflammation*: ICAM, VCAM *Gut microbiota composition* | Cross-sectional study | INSTIs were associated with levels of systemic inflammation and microbial diversity similar to that of uninfected controls. NRTIs + PIs presented the highest reduction in bacterial species compared with other antiretrovirals and naive subjects. |
| Merlini et al. [97] | 30 pts | Switch from TDF/FTC + DVR/r or ATV/r to EVG/c/FTC/TDF | *Peripheral blood and PBMCs Peripheral immune activation:* immune phenotypes on CD4+/CD8+ T cells *T-cell responsiveness:* IFN-γ/IL-2 after HIV/SEB exposure *Residual low-level viremia:* HIV-RNA *HIV reservoir:* HIV-DNA | Observational cohort study | Switch to EVG/c/FTC/TDF decreased T-cell activation, increased CD4+ and CD8+ effector memory IFN-γ/IL-2 release, and reduced CD8+ terminally differentiated cytokine expression following SEB stimulation. |
| Cossarini et al. [108] | 41 pts | RAL, ETR, and MVC vs DRV/r | *Peripheral blood and PBMCs Peripheral T-cell subsets* | DRV/r, RAL, ETR, and MVC Expanded Access Programs | Similar decrease in activated CD4+ and CD8+ T cells. A greater loss of naive CD4+ T cells and a reduction in cells expressing CXCR4 were observed with RAL, ETR, and MVC, while DRV/r showed a greater loss of cells expressing CCR5. |
| cART-treated patients—immunological nonresponders | | | | | |
| Lichtenstein et al. [122] | 30 pts | RAL | *Peripheral blood and PBMCs Immune activation* | Pilot study | The addition of RAL resulted in the reduction of several pro-inflammatory biomarkers. |
| cART-treated patients—dual and mono therapies | | | | | |
| Mussini et al. [132] | 1241 pts | Triple ART vs mono/dual ART | *Peripheral blood T-cell subsets*: CD4 and CD8 counts and their ratio | Retrospective study (ICONA Cohort) | An increase in CD8 T cells in dual regimens was reported. Pts on monotherapy did not show significant differences. |

Abbreviations: (c)ART, (combination) antiRetroviralTherapy; ATV, atazanavir; c, cobicistat; CCR, C-C chemokine receptor; (s)CD, (soluble) cluster of differentiation; CMV, cytomegalovirus; CXCR, CXC, chemokine Receptor; DNA, deoxyribonucleic acid; DRV, darunavir; EFV efavirenz; ETV, etravirine; EVG, elvitegravir; FTC emtricitabine; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; MT, microbial translocation; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PBMCs, peripheral blood mononuclear cells; PI, protease inhibitor; r, ritonavir; RAL, raltegravir; RNA, ribonucleic acid; SEB, Staphylococcus Enterotoxin B; TDF, tenofovir disoproxil fumarate; TNF, tumor necrosis factor; TNF-R, tumor necrosis factor receptor; Treg, Regulatory T cells; (s)VCAM, vascular cell adhesion molecule.

infection in only a few cases. Finally, most research was conducted in the peripheral blood and not tissues: given that drug penetration [145], viral replication [146], and immune restoration differ widely among anatomical compartments [68], the study of the systemic circulation may have overlooked possible significant variations in inflammation, activation, and HIV persistence biomarkers linked to the use of specific antiretroviral classes and/or regimens. In addition, recent studies have also shown that other factors, that is, the microbiota, may influence the degree and quality of immune recovery [147–149]. For these reasons, the reported findings are often contradictory and not consistent across studies and do not allow us to conclude that cART class and regimen account for true differences in immune restoration parameters.

While we await results on the use of more recent antiretroviral classes and drugs, clinicians should recall that unequivocal evidence demonstrates that immune recovery is linked to an immediate start of cART rather than to the properties of specific antiretroviral drugs [73–75].

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