



State of the Art of Dual Therapy in 2015

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Abstract

Dual therapy refers to combinations of two antiretroviral drugs applied in different clinical settings; they are considered and studied due to possibly reduced drug toxicities. In antiretroviral-naïve patients, dual combinations have lower virologic efficacy than standard therapy; the sole efficacious regimen is lamivudine plus lopinavir/ritonavir. Due to a higher possibility of virologic failure, these regimens are generally not allowed in this clinical setting. In antiretroviral-experienced patients, dual regimens are examined in studies with a small sample size, centered on clinical practice, and should be ritonavir-boosted protease inhibitor-based. These combinations have a good virological efficacy; combinations with the integrase inhibitor raltegravir have small sample size and demonstrated efficacy only with etravirine. Virological aspects involving dual therapy should always consider genetic barriers, particularly in simplification strategies, and ritonavir-boosted protease inhibitors are mandatory. As far as immunological aspects are concerned, nucleoside reverse transcriptase inhibitor-sparing regimens have some encouraging data, probably due to the bone marrow toxicity of this class. Combinations with maraviroc were effective in reducing inflammation, but data about immunological recovery are conflicting. The choice of regimen should focus on specific class toxicity since dual regimens are studied in particular for improving safety and tolerability. This review will analyze different dual regimens in the clinical setting, with a peculiar focus on ameliorating toxicities and improving quality of life. (AIDS Rev. 2015;17:127-34)

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Key words

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Introduction

Antiretroviral strategies with fewer drug regimens are currently being considered and studied in clinical practice. Dual therapy refers to combinations of two

antiretroviral (ARV) drugs applied in different clinical settings; the virologic efficacy of these combinations are potentially less than triple standard regimens of combined ARV therapy (HAART). The main benefits are reduced drug-related toxicities.

We will review the virologic efficacy of these combinations in different clinical settings and analyze toxicities and drug-drug interactions.

Dual therapy in antiretroviral-naïve patients

The current recommended ARV treatment for naïve HIV-1-infected patients is a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)

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Table 1. Dual therapy in antiretroviral naive patients; virologic efficacy is percentage of patients with HIV/RNA < 50 copies/ml

Study	Standard group	Dual group	Virological efficacy at week 48 or discontinuation*
PROGRESS ³	TDF/FTC + LPV/r	RAL + LPV/r	TDF/FTC + LPV/r: 84.2% RAL + LPV/r: 83.2%
VEMAN ⁴	TDF/FTC + LPV/r	MVC 150 mg QD + LPV/r	TDF/FTC + LPV/r: 100% MVC 150 mg QD + LPV/r: 100%
MODERN ⁹	TDF/FTC + DRV/r (800/100 mg)	MVC 150 mg QD + DRV/r	TDF/FTC + DRV/r (800/100 mg): 83%* MVC 150 mg QD + DRV/r: 72%*
SPARTAN ⁶	TDF/FTC + ATV/r	RAL + ATV/r	TDF/FTC + ATV/r: 63.3* RAL + ATV/r: 73.6%*
A4001078 ⁵	TDF/FTC + ATV/r	MVC 150 MG QD + ATV/r	TDF/FTC + ATV/r: 83.6% MVC + ATV/r: 74.6%
NEAT-001 ⁷	TDF/FTC + DRV/r (800/100 mg)	RAL + DRV/r	TDF/FTC + DRV/r (800/100 mg): 94% RAL + DRV/r: 89%
GARDEL ¹⁰	2 NRTIs + LPV/r	3TC + LPV/r	2 NRTIs + LPV/r: 83.7% 3TC + LPV/r: 88.3%

3TC: lamivudine; /r: ritonavir boosted; ATV: atazanavir; DRV: darunavir; FTC: emtricitabine; LPV: lopinavir; MVC: maraviroc; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; QD: once daily; RAL: raltegravir; TDF: tenofovir.

and a third agent from another class: integrase strand transfer inhibitor (INSTI) or ritonavir-boosted protease inhibitor (PI/r)¹. Tenofovir/emtricitabine (TDF/FTC) in combination with INSTI (raltegravir, dolutegravir, elvitegravir/cobicistat) or PI/r (darunavir/ritonavir), and abacavir/lamivudine (ABC/3TC) in combination with dolutegravir (DTG) are the preferred regimens.

The NRTI-sparing regimens are an alternative in naive patients, but generally not recommended, and should be considered in the presence of comorbidities contraindicating the use of NRTIs or in the presence of resistance to NRTIs. Actual data do not recommend this strategy to prevent toxicity.

Lopinavir/ritonavir (LPV/r), atazanavir/ritonavir (ATV/r), and darunavir/ritonavir (DRV/r) have been considered in clinical trials combined with raltegravir (RAL) or maraviroc (MVC) 150 mg once daily (NRTI-sparing regimens)²⁻⁵. Table 1 summarizes the virological response at week 48 of these regimens. This response is generally inferior in dual regimens, with the exception of ATV/r plus RAL and LPV/r plus MVC.

These studies were proof-of-concept and enrolled a limited number of subjects. Two trials with DRV/r 800/100 mg once daily have been designed with the sample size calculation to demonstrate non-inferiority of the NRTI-sparing regimen. In a single-arm study (ACTG A5262), DRV/r was combined with RAL. In 112 treatment-naive subjects (median HIV RNA level 4.9 log₁₀ copies/ml [44% > 100,000 copies/ml] and

median CD4 count 271 cells/μl) a high rate of virologic failure was confirmed at week 24 and week 48: only 79 and 71%, respectively, had HIV/RNA levels < 50 copies/ml; 28 subjects had confirmed virologic failure. Integrase resistance was found in five of 25 subjects in whom resistance testing was done; virologic failure was associated with higher baseline HIV/RNA (odds ratio for RNA > 100,000 copies/ml: 3.76) and with lower CD4 counts⁶. In the randomized NEAT-001 trial⁷, the superiority of triple ARV therapy (TDF/FTC plus DRV/r) versus dual therapy with RAL plus DRV/r was evidenced at week 48: 88.5 and 83.7% of subjects had HIV/RNA < 50 copies/ml in patients with baseline HIV/RNA > 100,000 copies/ml, respectively.

A different study with DRV/r plus MVC 150 mg once daily (A4001095, MODERN trial) was designed. The study was terminated in October 2013 following a preliminary interim analysis of week 48 primary efficacy data by the study's external independent Data Monitoring Committee. The Committee assessed the data as demonstrating significant differences between the treatment arms in virologic responses (72% in the maraviroc group, 83% in the standard regimen) and failures. They recommended, and the Sponsor concurred, that the study should be terminated because of the inferior efficacy of the MVC arm as compared to the comparator arm (emtricitabine/tenofovir)⁸.

In selected patients, dual therapy with PI/r plus 3TC could be an option. In ARV-naive patients, a randomized

open-label study (GARDEL) demonstrated that LPV/r plus 3TC was non-inferior to triple therapy after 48 weeks of treatment, regardless of baseline viral load; at week 48, 88.3% of subjects who received dual therapy and 83.7% of those treated with triple standard therapy were responders⁹.

Dual therapy in antiretroviral-experienced patients

Few trials have been performed in this clinical setting, although simplification from a more traditional HAART to a NRTI-sparing regimen appears to be a very fascinating hypothesis.

Combinations of PI/r and nucleoside reverse transcriptase inhibitors (NNRTI) have been tested in several situations. The pilot randomized study NEKA evaluated the safety and efficacy of a combination of LPV/r and nevirapine (NEV) in 31 HIV-1-infected subjects with stable virologic suppression¹⁰. This association was shown to be effective after a follow-up of 48 weeks. No subjects discontinued therapy because of adverse events. The MULTINEKA study analyzed 67 HIV-1-infected subjects who were switched to a NRTI-sparing regimen including NEV and LPV/r¹¹. This study demonstrated an equivalent efficacy of the dual therapy when compared to the traditional triple HAART.

Switching to DRV/r plus efavirenz (ETR) was evaluated in 20 patients¹²: 65% (13/20) switched from dual PI/r regimens, eight combined with efavirenz (EFV) or NEV, and 20% (4/20) switched from conventional HAART. Patients had a median exposure to nine ARV drugs prior to switch (range 3-14), with 90% (18/20) having previous NNRTI exposure; at switch, 60% (12/20) had no previous resistance, 25% (5/20) NRTI mutations only, and 15% (3/20) had NNRTI mutations. At week 24, all patients maintained undetectable viral load.

Other PI/r-based switch strategies have been tested in different settings. The KITE study analyzed the therapeutic switch from standard HAART to LPV/r plus RAL and evidenced a comparable virologic efficacy at week 48 (88 vs. 92%)¹³. The ATLAS study was a single-arm study, which analyzed virologically suppressed HIV-1-infected subjects who were treated with TDF/FTC plus ATV/r after switching them to a dual regimen containing 3TC plus ATV/r¹⁴. The ATLAS study was conducted in 40 HIV-1-infected subjects. After 48 weeks, 4/40 (10%) regimen discontinuations occurred: one death (brain hemorrhage), one study withdrawal (inadequate ATV plasma levels), one re-induction with two NRTIs due to pregnancy, and one virologic failure without

development of resistance. The positive results of ATLAS supported the design of a multicenter randomized clinical trial, which is currently ongoing. In a similar Spanish study (SALT)¹⁵, dual therapy with ATV/r plus 3TC appeared to be as safe and effective in the short term as switching therapy in virologically stable patients requiring a change in treatment owing to simplification, intolerance, or toxicity. If these encouraging data are confirmed, this strategy could be a good alternative to monotherapy and would avoid TDF toxicity without the disadvantages of monotherapy. An observational, uncontrolled, real-life study using the once-daily regimen DRV/r 800/100 mg plus MVC 150 mg enrolled 60 HIV-1-positive subjects coming from traditional triple therapy and switched to dual therapy¹⁶; 44 (73%) patients reached HIV/RNA < 50 copies/ml at week 48. The MITOX study¹⁷ randomized 40 out of 80 patients who had received two NRTI plus PI/r to continue their current regimen or switch to a PI/r plus MVC 150 mg once daily. Six out of 40 patients (15%) receiving MVC plus PI/r failed; four of them received DRV/r plus MVC, and only one out of the six failing patients exhibited a switch in tropism toward a X4-tropic virus.

In the other strategies, MVC plus RAL and RAL plus ETR were studied. The ROCnRAL trial¹⁸ is a single-arm study that switched 44 patients from a suppressive HAART to MVC 300 mg twice daily plus RAL 400 mg twice daily with R5 tropic virus and undetectable viral load from 5.2 years (IQR: 4.4-7.9), nadir CD4 210 cells/mm³ (IQR: 150-276), HAART duration 15 years (IQR: 15-19); seven (16%) patients failed MVC/RAL therapy: five with virological failure and two discontinued treatment due to adverse events. The high rate of virologic failure of this dual combination was confirmed by an Italian study: 9/26 (35%) multi-experienced patients failed simplification therapy with MVC plus RAL at week 24¹⁹. The MVC plus RAL was effective in 10 naive patients treated for 24 weeks with an induction therapy (TDF/FTC plus RAL plus MVC) and then switched to dual therapy: after 48 weeks, undetectable viral load was maintained in all patients²⁰. These different results are not comparable due to patient characteristics (multi-experienced versus naive).

Eighteen patients with six years of viral suppression were switched to RAL plus ETR regimens, with undetectable viral load during 12 months of follow-up²¹; in another recent study including 25 patients, this switch maintained virologic suppression at week 48 in 84% of patients²².

Dual therapies in experienced patients are summarized in table 2.

Table 2. Dual therapy in antiretroviral experienced patients; virologic efficacy is percentage of patients with HIV/RNA < 50 copies/ml

Study	Standard group	Dual group	Virological efficacy at week 48 or discontinuation*
MULTINEKA ¹²	2 NRTIs + LPV/r	NEV + LPV/r	2 NRTIs + LPV/r: 60.6% NEV + LPV/r: 81.8%
KITE ¹⁴	2 NRTIs + LPV/r	RAL + LPV/r	2 NRTIs + LPV/r: 88% RAL + LPV/r: 92%
ATLAS ¹⁵	NA	3TC + ATV/r	3TC + ATV/r: 90%
MITOX ¹⁸	2 NRTIs + PI/r	MVC 150 mg QD + PI/r	2 NRTIs + PI/r: 100% MVC 150 mg QD + PI/r: 85%
ROCnRAL ¹⁹	NA	MVC + RAL	MVC + RAL: 86%*
RAL+ETR ⁷	NA	RAL + ETR	RAL + ETR: 84%

3TC: lamivudine; /r: ritonavir boosted; ATV: atazanavir; ETR: etravirine; FTC: emtricitabine; LPV: lopinavir; MVC: maraviroc; NEV: nevirapine; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; QD: once daily; RAL: raltegravir.

Virologic aspects

So far, the identification of virologic factors that can help identify patients as candidates for dual therapy represents a challenge in the field of HIV-1 clinical research.

In patients starting a first-line PI/r-based dual therapy, the level of plasma HIV-1 RNA at baseline represents an important parameter. In particular, a baseline viral load > 100,000 copies/ml strongly correlates with an increased risk of virologic failure in patients receiving DRV/r plus RAL⁷. In the setting of a higher baseline viral load, the selective pressure imposed by two drugs may take a prolonged time to achieve virologic suppression, thus predisposing to the generation of drug resistance mutations, and in turn to virologic rebound.

The duration of viral suppression²³ and/or the occurrence of residual viremia²⁴ might also influence the probability of maintaining the virologic success in aviremic patients switching from a triple ARV regimen to PI/r-based dual therapy. The role of these factors has not been adequately investigated in dual therapy strategies so far, but some suggestions could be derived from studies on PI/r monotherapy^{25,26}. Moreover, several studies have highlighted a strict correlation between the level of baseline viral load and the burden of the cellular reservoir quantified by cellular HIV-1 DNA²⁷. In this setting, dual therapy may account for a cryptic ongoing viral replication, which could favor the emergence of drug resistance. This is consistent with a recent study showing that long-term virologic success on dual therapy with two NRTIs correlates with a low level of HIV-1 DNA (median 2.5 log copies/10⁶ peripheral blood mononuclear cells)²⁸. In this study, another

factor associated with the maintenance of virologic suppression in patients receiving a two-NRTI-based therapy is early HAART initiation. Since early treatment has been associated with a reduced burden of HIV-1 cellular reservoir, these results highlight the need to investigate a potential threshold of HIV-1 DNA so that dual therapy can be safely administered as first-line therapy.

Another issue that deserves further investigation is the genetic barrier of the PI/r companion drug. In the ACTG A5262 study⁷, virologic failures were associated with the emergence of mutations associated with resistance to RAL. The SPARTAN study has been prematurely terminated due to the frequent emergence of RAL resistance mutations in patients experiencing virologic failure⁵. Similarly, dual therapy with LPV/r plus EFV was associated with high rates of NNRTI resistance during virologic failure²⁹. Therefore, the genotypic sensitivity score as well as genotypic resistance testing on proviral DNA should be included in the evaluation of potential candidates for a dual-ARV regimen. Further studies addressing the issue of the genetic barrier of the companion drug are urgently needed for safe administration of dual therapy in drug-naïve patients. Moreover, when choosing a dual regimen including MVC, a proper assessment of coreceptor tropism is mandatory since the sensitivity of the tropism test (phenotypic or genotypic) to detect minority non-R5 variants is crucial^{30,31}.

Immunological aspects

An adequate immunological response during HAART is defined as an increase in CD4⁺ T-cells counts in the

range of 50-150 per year, generally with an accelerated response in the first three months of treatment. However, the reconstitution of CD4⁺ T-cells is variable among patients, depending on different factors such as nadir of CD4⁺, aging, and comorbidities. Furthermore, the immune response during HAART includes not only the increase of CD4⁺ T-cells, but also the status of immune activation³².

Recent studies on pathogenesis report a direct correlation between persistent immune activation/inflammation and higher levels of microbial translocation, with a poor recovery of CD4⁺ T-cells in individuals suppressed with HAART for a long time³³⁻³⁶.

Moreover, recently published guidelines (US Department of Health and Human Services, European Aids Clinical Society, GeSIDA, Italian Ministry of Health) suggest including also the measurement of soluble markers of the immune activation such as lipopolysaccharide, CD16, and others for immunological monitoring of patients. In this context, some of the studies of dual therapy based on PI/r in combination with one NRTI or RAL or MVC or NNRTI analyzed immunological aspects: both CD4⁺ T-cell response and the markers of immune activation. Soluble CD14 (sCD14) was associated with mortality³⁷ and lipopolysaccharide with clinical progression of HIV infection, independently from CD4⁺ and HIV/RNA³⁸.

Both MVC and RAL have a distinctive role in decreasing T-cell activation. While dual therapy including MVC has been studied in patients with incomplete recovery of CD4⁺ T-cells or naive for HAART, regimens including RAL have been explored as first-line therapy and in simplification studies. The immunomodulatory effect of MVC is related to the function of the coreceptor CCR5. The CCR5 has an important role in the pathogenesis of HIV infection and in the control of proinflammatory effects: the dysregulation of CCR5-mediated lymphocyte trafficking has been associated to several inflammatory conditions such as rheumatoid arthritis and organ transplants. In this context, a different tissue distribution of CCR5⁺ and CD25⁺ T-cells was observed, with a possible decrease in the levels of immune activation after administration of antagonistic anti-CCR5 monoclonal antibody to rhesus macaques³⁹.

However, the results *in vivo* on the effect of MVC to modulate the immune activation are discordant. Hunt, et al. compared the effect of MVC intensification in patients under HAART with CD4⁺ T-cell counts < 350 cells/mm³ and plasma levels < 48 copies/ml on peripheral immune activation and on gut-associated lymphoid tissue versus placebo after 24 weeks of

treatment. The authors observed a twofold increase in T-cell activation in rectal tissue and a lower but statistically significant increase in peripheral blood after an intensification regimen⁴⁰. On the contrary, the ACTG study (A5256) conducted in patients with incomplete recovery of CD4⁺ T-cells showed an apparent reduction of T-cell activation, with a decline in CD38 expression and increased HLA-DR, with a partial reversion after the interruption of MVC⁴¹.

The intensification with MVC in immunological non-responders in a multicentric, randomized, open label, phase IV superiority trial did not demonstrate a significant advantage in reconstituting the CD4⁺ T-cell pool in terms of increases in CD4⁺ cells and parameters of T-cell homeostasis and activation. Patients receiving MVC experienced a significant rise in circulating interleukin 7 by week 48 ($p = 0.01$) and a trend in temporary reduction in activated HLA-DR+CD38+CD4⁺ by week 12 ($p = 0.06$) that was not maintained at week 48⁴².

The ability of HAART to decrease viral load drives the decline of immune activation and influences the survival of patients. The important effect of RAL on the decay of viral load reflects its ability to control the immunological response to dual therapy including RAL and PI/r⁴³, probably due to the direct correlation between the reduction of viral load and of the markers of immune activation⁷.

Safety aspects

Increasing attention has been focused on the long-term adverse effects of HAART, including fat distribution changes observed in lipodystrophy syndrome, the increased risk of cardiovascular disease, and the onset of bone and kidney diseases⁴⁴. The NRTI- and PI-sparing regimens are attractive options to avoid the toxicity associated with NRTIs and high doses of ritonavir.

Dual protease inhibitor and nucleoside reverse transcriptase inhibitor-sparing regimens

In this scenario there are few reported data on kidney and metabolic aspects. The reasons for switching from PIs were mostly toxicity related: metabolic disorder and/or lipodystrophy. In two different studies of switching to dual therapy based on RAL plus entecavir (ETV), the authors registered a decrease in median cholesterol, triglyceride levels, and glucose levels^{21,22}. The French study ROCnRAL was based on the switch

to dual therapy with RAL plus MVC in patients with lipodystrophy: lipid profiles improved with a decrease from baseline values in total cholesterol, but two patients discontinued treatment due to severe adverse events (HBV rebound in a patient HBcAb⁺ and HBsAg⁻, one hypersensitivity syndrome)¹⁸. Due to the limited number of patients and the observational and non-randomized nature of the study, all these data should be carefully considered. Scarce data are available regarding kidney function.

Dual nucleoside reverse transcriptase inhibitor-sparing regimens

Although today's NRTIs are safer than first-generation agents in this class, they still carry some risks of long-term toxicity. No international guidelines recommend NRTI-sparing regimens for first-line or later regimens, but the availability of newer ARVs is making such combinations more popular in practice. An increase in lipid values was observed in patients treated with NRTI-sparing regimens⁴⁵. Furthermore, patients on a combination of PI plus NNRTI were more likely to have an atherogenic lipid profile than patients on PIs only⁴⁶.

In most recent studies on NRTI-sparing regimens conducted in observational cohorts, the authors observed a decrease in triglycerides. Cholesterol and creatinine, by contrast, did not improve and there were no significant differences in hepatic metabolism. It is important to highlight that patients received NRTI-sparing regimens without ritonavir in these two studies⁴⁷.

In the KITE study, the switch to RAL plus LPV/r was associated with increases in fasting plasma total cholesterol, triglycerides, and LDL-cholesterol levels at 24 weeks, but only the increase in triglyceride levels was statistically significant¹⁸.

In the PROGRESS study, LPV/r plus RAL was not associated with a decline in renal function at week 96. In the NRTI-sparing arm, the investigators observed hyperlipidemia and diarrhea, which is consistent with the established profile for LPV/r. There were minimal changes from baseline in TC:HDL ratios, LDL:HDL ratios, and 10-year Framingham cardiovascular risk scores based on LDL and total cholesterol levels in both treatment groups.

On the contrary, in the SPARTAN trial, the overall profile of ATV plus RAL did not appear optimal for further clinical development, given higher rates of resistance to ARVs and hyperbilirubinemia with twice-daily ATV⁵.

In lipoatrophic patients, small studies evaluated the benefit of a switch to a PI-containing/NRTI-sparing regimen compared with maintenance of a NRTI-containing regimen, and showed that the combination LPV/r plus EFV was associated with a significant improvement in body fat⁴⁸.

In the NEAT001 study, DRV/r plus RAL was not associated with a decline in renal function at week 96, but there were statistically significant increases in total cholesterol, LDL cholesterol, and HDL-cholesterol in RAL-based therapy⁷.

Drug-Drug interaction

The clinical pharmacology of dual therapy should be considered to identify appropriate combinations.

The PI/r are CYP3A4 inhibitors and can affect the pharmacokinetics of different drugs.

Dual therapies with NRTIs and PI/r have a low rate of virologic failure; a key factor is the absence of drug interaction between these classes.

Selected dosing was MVC 150 mg once daily in MVC-containing dual therapy; in a *post hoc* reanalysis of the MOTIVATE trial, no concentration relationship was found between the once- and twice-daily arms⁴⁹. In this registration trial, however, the use of DRV/r was not allowed. The pharmacokinetic profile of MVC 150 mg once daily dosed with DRV/r 800/100 mg reported a possible MVC suboptimal exposure in such combination and suggested that MVC exposure was dependent on ritonavir exposure, which is reduced in the absence of TDF/FTC⁵⁰. A lower MVC exposure was related to virologic failure in switch strategy¹⁷ and could be a possible explanation for drug failure in ARV-naïve patients (MODERN study⁸). The MVC exposure, on the other hand, was shown to be adequate when associated with a higher ritonavir dosage, for example with LPV/r⁵¹.

Thus, a dose increase to MVC 300 mg once daily seems reasonable when associated at least with DRV/r once daily and ATV/r.

However, not only drug-drug interactions should be pointed out when the pharmacological compatibility of a dual regimen is considered. Unexpected rates of virologic failure in patients with high baseline viral loads in the ACTG 5162 study⁷ and lower pharmacological performance of the same subgroup of patients in the NEAT001 study⁸ suggested some pharmacodynamic issues could play a role. Even if the combination of DRV/r plus RAL shows an adequate profile of virologic potency, the short half lives of both compounds

lead to limited tolerance of the whole regimen. The latter could become clinically significant in the presence of high viral load and suboptimal adherence⁵².

In a similar way, even in dual PI-sparing, pharmacological compatibility could play a role. In 26 patients treated with MVC plus RAL and a third drug, switching to RAL plus MVC showed a high rate of failure at week 24, and 60% of patients had MVC C_{trough} lower than minimum effective concentration for experienced patients (50 ng/ml)¹⁹. This is contrary to previous data on the MVC plus RAL plus ETV combination, where no excess rate of virologic failure was observed in a similar clinical setting and in the presence of comparable MVC plasma exposure⁵². This finding suggests that the pharmacodynamics of triple regimens could not be fully applicable to dual regimens even within a switch strategy.

The pharmacological compatibility of dual regimens is a key issue in the selection of appropriate combinations, and should rely not only on pharmacokinetics (ruling out of clinically significant drug-drug interactions), but on pharmacodynamic features as well (genetic barrier and tolerance).

Conclusions

Dual antiretroviral therapy is an investigational strategic approach in HIV therapeutics that seeks to ameliorate toxicities and costs, and further improve the quality of life by reducing the drug burden. A large number of regimen combinations have been tested with different efficacy and safety results. Overall, they tend to be less effective than recommended triple regimens, with the risk of virologic failure being particularly greater in subjects with plasma HIV/RNA $\geq 100,000$ copies/ml and CD4 ≤ 200 /mmc. Accordingly, dual antiretroviral therapy should not be openly recommended and only be used with caution in ARV-naïve patients. Dual therapies with lamivudine plus PIs seem to be efficacious initially, based on studies conducted either in ARV-naïve subjects or as simplification strategies. More data and longer follow-up is needed for switch studies testing dual therapy including CCR5 antagonists and integrase inhibitors.

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