Rapid plasma viral suppression in naive HIV-infected patients with high CD4 cells and low viraemia initiating a dual nucleoside reverse transcriptase inhibitor strategy: a proof-of-concept study


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Objectives: To evaluate whether a dual nucleoside reverse transcriptase inhibitor (NRTI) strategy can control HIV replication in antiretroviral therapy (ART)-naive HIV-infected patients with a high CD4 cell count and a low viral load (VL).

Methods: This observational study included all HIV-infected treatment-naive patients with a CD4 cell count >300 cells/mm³, a plasma HIV RNA between 1000 copies/mL and 30,000 copies/mL and wild-type virus who initiated dual NRTI ART between January 2008 and December 2012. HIV RNA and CD4 cell count were assessed at Day 0, Week (W) 4, W12, W24 and W48. The primary endpoint was the proportion of patients with a plasma VL (pVL) <50 copies/mL at W24.

Results: Twenty patients were included. The median (IQR) baseline characteristics were: time since HIV diagnosis, 25 months (8–66 months); CD4 cell count, 592 cells/mm³ (405–798 cells/mm³); HIV RNA, 10395 copies/mL (4106–16566 copies/mL); and HIV DNA, 464 copies/10⁶ peripheral blood mononuclear cells (195–1168 copies/10⁶ PBMC). Nineteen patients received tenofovir/emtricitabine and one patient received abacavir/lamivudine. At W12, 88% of the patients with available data (n=16/18, 95% CI 0.65–0.99) had a pVL <50 copies/mL. Overall, the proportion of patients with a pVL <50 copies/mL was 100% (n=20/20, 95% CI 0.83–1.0) at W24 and 95% (n=18/19, 95% CI 0.74–0.99) at W48 (with one patient lost to follow-up and one patient with poor treatment compliance). The median increase in CD4 cells was 83 cells/mm³ (40–310 cells/mm³). There was no discontinuation of antiretroviral therapy for any reason such as lack of efficacy or toxicity.

Conclusions: This pilot study suggests that, in patients with a high CD4 cell count and a low VL, a dual NRTI strategy may represent a potentially effective treatment strategy to control HIV replication. This needs to be confirmed in larger controlled clinical studies.

Keywords: antiretroviral therapy, NRTIs, antiviral

Introduction

All current guidelines recommend an earlier initiation of antiretroviral therapy (ART) in HIV-infected individuals regardless of CD4 cell counts. The goals of ART include maximal viral suppression to reduce drug resistance and prevent virus transmission, along with robust immune restoration to improve survival. Despite a better tolerability of newer antiretroviral drugs, a long exposure to the currently recommended antiretroviral drugs is associated with drug-induced toxicity and comorbidities. One of the third recommended agents in triple-drug combinations is a protease inhibitor; protease inhibitors are associated with metabolic disorders, such as insulin resistance, diabetes and dyslipidaemia. Avoiding a long exposure to protease inhibitors when using a dual nucleoside reverse transcriptase inhibitor (NRTI) regimen could potentially reduce the long-term risk of non-AIDS-related morbidities such as cardiovascular diseases, which occur in up to 20% of HIV-infected patients. Furthermore, in the absence of strategies to cure HIV, life-long suppressive therapy remains the rule. In this context, minimizing drug exposure without jeopardizing antiretroviral efficacy has become a field of clinical investigation. This appears even more important in the context of earlier ART initiation when HIV-infected patients initiate ART usually with a lower viral load (VL) and a higher CD4 cell count. It has been
well known since the early years of ART use that the two main drivers of the virological response following ART initiation in ART-naïve patients are the intensity of HIV replication and, to a lesser extent, the number of CD4 lymphocytes.7

The question of whether an alternative to a triple-drug approach is possible in ART-naïve patients treated at an early stage of HIV infection has become more relevant today in the context of universal ART. This pilot proof-of-concept study aimed to evaluate the efficacy of a dual NRTI strategy as first-line therapy in ART-naïve patients with a low VL and a high CD4 cell count.

Patients and methods

This observational study aimed to evaluate the virological efficacy of a dual NRTI strategy in ART-naïve patients followed at the HIV clinical unit of the Department of Infectious Diseases at Pitié-Salpêtrière University Hospital (Paris, France). All clinical data from HIV-infected patients who gave their consent were systematically recorded via an electronic file (NADIS) with direct access to the biological parameters and retrospectively assessed. From January 2008 to December 2012, we evaluated all ART-naïve HIV-1-infected adult patients with a plasma HIV RNA level between 1000 and 30000 copies/mL and a CD4 cell count ≥300 cells/mm³ who initiated ART with dual NRTIs consisting of tenofovir/emtricitabine or abacavir/lamivudine, in the context of a wild-type virus (determined by a genotypic resistance test) and with more than 6 weeks of follow-up. All patients were routinely monitored for HIV RNA level and CD4 cell count assessed at Day 0 (D0), Week (W) 4, W12, W24 and W48. Plasma HIV VL (pVL) was quantified using the CobasAmpliPrep/CobasTaqMan HIV-1 assay version 2.0 (Roche Diagnostics). The quantification of whole blood HIV DNA level was retrospectively performed on frozen samples at D0 and W24 using a real-time PCR method as previously described.8

The study's primary endpoint was the proportion of patients with a pVL <50 copies/mL by intention-to-treat (ITT) analysis at W24. Secondary endpoints included the rate of viral suppression with a pVL <50 copies/mL at W48, time to viral suppression, the change in CD4 cells and the evolution of total HIV DNA in peripheral blood mononuclear cells (PBMCs) retrospectively assessed at W24. Treatment failure was defined as two consecutive plasma HIV-1 RNA values ≥50 copies/mL 2 weeks apart or as any modification or discontinuation of treatment. The exact CIs were calculated for the proportions of success at any time. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as medians and IQRs. Nominal variables are expressed as percentages.

Results

From a total of 1272 patients initiating ART between January 2008 and December 2012, 213 patients had baseline pre-ART values with CD4 cell counts ≥300 cells/mm³ and an HIV RNA level between 1000 and 30000 copies/mL; of these, 24 initiated dual NRTI therapy. All the criteria were fulfilled by 20 patients, who constituted our study population. This comprised 12 males and 8 females with a median age of 41 years (IQR 30–51 years). The median time since HIV diagnosis was 25 months (IQR 8–66 months). At baseline, the median CD4 cell count was 592 cells/mm³ (IQR 405–798 cells/mm³), the plasma HIV RNA 10 395 copies/mL (IQR 4106–16 566 copies/mL) and the total blood HIV DNA 464 copies/10⁶ PBMCs (IQR 195–1168 copies/10⁶ PBMCs) The main viral subtypes were HIV-1 group M subtype B virus (n=9/20) or circulating recombinant forms (CRFs) (5 CRF02 and 1 CRF22). One patient was coinfected with HIV and hepatitis B virus. Nineteen patients received dual therapy with tenofovir/emtricitabine once daily and one patient received abacavir/lamivudine. All patients except one (Patient 14), who moved to a foreign country, were followed for up to 48 weeks. All patients remained on the initial ART regimen during the follow-up.

By ITT missing equal failure analysis, the proportion of patients meeting the primary endpoint at W24 with a pVL <50 copies/mL was 100% (n=20/20, 95% CI 0.83–1.0) (Table 1). The dynamics of HIV RNA following dual NRTI administration showed a median decrease in pVL of −2.2 log₁₀ (IQR −2 log₁₀ to −2.4 log₁₀) at W4 and −2.7 log₁₀ (IQR −2.4 log₁₀ to −2.8 log₁₀) at W12, when 88% of patients (n=16/18, 95% CI 0.65–0.99) had a pVL <50 copies/mL. The median time to viral suppression to <50 copies/mL was 4 weeks (W4–12 weeks). At W48, the proportion of patients with an HIV RNA <50 copies/mL was 95% (n=18/19, 95% CI 0.74–0.99).

One patient (Patient 12) with transient poor compliance had a virological rebound with a pVL of 325 copies/mL at W48 after two values below 40 copies/mL from W4 to W24 and with no selection of mutations at the time of virological failure. The addition of a boosted protease inhibitor to the dual NRTI regimen led to rapid viral suppression.

A decrease in HIV DNA was observed in all patients from a median value of 464 copies/10⁶ PBMCs (IQR 195–1168 copies/10⁶ PBMCs) at baseline to 206 copies/10⁶ PBMCs (IQR 65–340 copies/10⁶ PBMCs) at W24, with a median decrease of −0.4 log₁₀ (IQR −0.2 log₁₀ to −0.6 log₁₀). Overall, the increase in the median CD4 lymphocyte count was 83 cells/mm³ (IQR 40–310 cells/mm³) and 132 cells/mm³ (IQR 49–440 cells/mm³) at W24 and W48, respectively. There was no reported clinical or biological adverse effect. The estimated glomerular filtration rate remained >60 mL/min (Cockcroft–Gault) in all patients.

Discussion

This pilot study reported a total of 20 HIV-1-infected ART-naïve patients with high CD4 cell counts and low viraemia treated with a dual NRTI regimen who achieved a maximal viral suppression (defined as a plasma HIV RNA level <50 copies/mL), leading to a success rate of 100% (n=20/20, 95% CI 0.83–1.0) at W24. The median time to viral suppression was 4 weeks. Importantly, all patients met the criteria for successful first-line therapy with a pVL <400 copies/mL at W12 according to French guidelines1 except for Patient 1, with the highest baseline VL, in whom the pVL was 69 copies/mL at W12. Not surprisingly, once viraemia was suppressed by 12 weeks of dual therapy, maximal virological suppression was maintained for up to 48 weeks for all compliant patients. One patient (Patient 12) self-reported a discontinuation of treatment 3 weeks before virological measurement. Meanwhile, in this patient, the efficacy of the regimen up to W24 and the absence of emtricitabine resistance were in favour of a loss of efficacy due to a transient discontinuation of therapy.

The patients who were selected initiated a dual NRTI strategy with a high CD4 cell count and a low VL and were at an early phase of HIV chronic infection with a median duration of HIV diagnosis of 2 years. None had been treated at the time of primary infection, thus excluding any potential decrease of VL under the pressure of the early immune response. The initiation of ART in patients with ‘early’ HIV infection with a high CD4 cell count and a low VL has become a common situation with the current recommendation of
Table 1. Evolution of HIV RNA, HIV DNA and CD4 cell count in patients initiating a dual NRTI strategy

<table>
<thead>
<tr>
<th>Patient</th>
<th>NRTI regimen</th>
<th>HIV RNA (copies/mL)</th>
<th>HIV DNA (copies/10⁶ PBMCs)</th>
<th>CD4 cell count (cells/mm³)</th>
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<tr>
<td></td>
<td></td>
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<td>W4</td>
<td>W12</td>
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<tr>
<td>1</td>
<td>TDF/FTC</td>
<td>29500</td>
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<td>&lt;40</td>
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<tr>
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TDF/FTC, tenofovir/emtricitabine; NA, not available; ABC/3TC, abacavir/lamivudine.

extending HIV testing and an early initiation of therapy. Indeed, in the most recent clinical randomized trials in ART-naive patients, there has been a progressive shift in the baseline characteristics of ART-naive patients, with earlier HIV infection, as attested to by a median baseline VL ~4–4.5 log₁₀, i.e. less than 50 000 copies/mL, and a median baseline CD4 cell count around 350 cells/mm³. The well-established and universal goals for initiating ART are to reduce HIV-associated morbidity, prolong the duration and quality of survival, restore and preserve immunological function and prevent perinatal and behaviour-associated HIV transmission. HIV suppression with ART may also decrease inflammation and immune activation, which are thought to contribute to the higher rates of comorbidities reported in HIV-infected patients.

Given the high potency of current antiretroviral drugs and the need to control life-long viral replication, and keeping in mind that lower drugs exposure should be of long-term benefit, there is a need to revisit antiretroviral strategies and investigate new approaches to individualize ART in patients with early HIV infection without any change in the objective of maximal rapid viral suppression. There have been studies investigating strategies such as protease inhibitor monotherapies, which were able to maintain virological suppression in over 85% of patients without any development of resistance, meaning no loss of treatment class efficacy in case of viral rebound and no deleterious effect on HIV DNA. In the days prior to the era of highly active antiretroviral therapy (HAART), in the context of patients with a CD4 cell count between 200 and 500 cells/mm³, a dual NRTI combination led to a mean decrease in HIV VL of 1.5 log₁₀ copies/mL after 24 weeks of the dual NRTI strategy.

However, this approach is not completely new. More than a decade ago, dual combination strategies, although statistically less potent than a triple-drug approach, were able to maintain virological suppression in a substantial number of patients. Interestingly, those patients had a VL in the lower range. More recent data have reported the efficacy of a dual NRTI regimen in 37 patients mostly in maintenance therapy, including eight taking a first-line regimen, with an overall success rate of 89% in patients with a high median pre-ART CD4 cell count and a low median HIV RNA VL of 3.9 log₁₀ copies/mL. In a retrospective analysis of 68 ART-naive patients receiving dual NRTI therapy, predictive factors for virological success, defined as a VL <400 copies/mL, were a pre-treatment CD4 cell count >150 cells/mm³, pre-treatment viralemia <50 000 copies/mL and no previous NRTI exposure.

All except one patient received the dual combination of tenofovir/emtricitabine, an NRTI backbone universally recommended in ART initiation, which has been shown over the past decade to be a highly potent NRTI combination, with a higher efficacy, tolerability and resistance profile compared with first-generation NRTIs such as zidovudine or stavudine combined with lamivudine.
with regard to HIV DNA and emphasizes the virological benefit of initiating treatment at an early stage of HIV infection.

Our study has obvious limitations including its single-centre observational design, the limited size of the population and a profile of patients who wanted to be treated and were thus likely to be highly compliant. However, we think that these results deserve further investigation. Achieving maximal viral suppression with minimum drug exposure should be the goal of clinical studies in HIV over the next decade. A dual NRTI regimen could represent a potential option for long-term virological control in HIV-1 ART-naive patients with a low pVL and a high immunity, but further investigations are needed to validate such a strategy.

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Transparency declarations
None to declare.

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