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Poor Efficacy and Tolerability of Stavudine, Didanosine, and Efavirenz-based Regimen in Treatment-Naive Patients in Senegal

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Abstract

Objective: To study the effectiveness and tolerance of an antiretroviral therapy (ART) regimen composed of the antiretroviral agents (ARVs) stavudine (d4T) plus didanosine (ddl) plus efavirenz (EFV) in patients with advanced HIV infection in Senegal.

Design and methods: This was an open-label, single-arm, 18-month trial in treatment-naive patients. The primary virologic end point was the percentage of patients with plasma HIV RNA < 500 copies/mL at months 6 (M6), 12 (M12) and 18 (M18). The primary analysis was done as intent-to-treat.

Results: The staging of HIV disease, performed using the definitions of the US Centers for Disease Control and Prevention (CDC), was CDC stage B or C for all 40 recruited patients. At baseline, the mean CD4+ cell count was $133 \pm 92/\text{mL}$ (\pm standard deviation [SD]; range 1346), and 23% of patients had CD4+ cell counts below 50/mcL. The mean baseline plasma HIV RNA level was $5.5 \pm 0.4 \log_{10}$ copies/mL (\pm SD; range 4.65.9). The proportion of patients with plasma HIV-1 RNA below 500 copies/mL fell during the study from 73% (95% CI [56; 85]) at M6 to 56% (95% CI [41; 73]) at M12 and 43% (95% CI [27; 59]) at M18. Plasma HIV-RNA was below 50 copies/mL in 50% of study subjects (95% CI [31; 66]) at M6, 43% (95% CI [27; 59]) at M12, and 33% (95% CI [19; 49]) at M18.

The mean increase in the CD4+ cell count was $105 \pm 125/\text{mL}$ ($n = 38$) at M3 and $186 \pm 122/\text{mL}$ ($n = 21$) at M18. Eight patients died, including 6 because of infectious complications. The last viral load (VL) value before death was < 500 copies/mL in all these patients except 1 nonadherent patient. Fifteen patients (37.5%) had peripheral neuropathy that was severe enough in 5 patients (12.5%) to require ddl and d4T discontinuation.

Conclusion: Virologic efficacy combination therapy with d4T, ddl, and EFV was measured by the percentage of patients with plasma HIV RNA values below 500 copies/mL and 50 copies/mL; for both parameters, virologic efficacy decreased during the study period. This is explained by the high mortality rate (20%) and treatment modifications due to adverse events (13%). These data strengthen the recently revised World Health Organization (WHO) guidelines advocating initiation of highly active antiretroviral therapy (HAART) before profound CD4 lymphocyte depletion occurs and avoiding HAART regimens containing d4T and ddl because of treatment-limiting side effects.

Introduction

The efficacy of antiretroviral treatments in sub-Saharan Africa has been demonstrated in cohort studies and pilot trials.[1-3] The treatment regimens tested in these studies were derived from those used in premarketing trials conducted in industrialized countries. However, the choice of antiretrovirals for national programs in poor countries is largely based on drug availability through the Access program, which provides ARVs at prices negotiated by UNAIDS (the joint United Nations Program on HIV/AIDS), or generic drugs, together with cost and supply considerations, rather than on field evaluations of recommended strategies.

Concomitantly with the development of antiretroviral access programs in the southern hemisphere, first-line treatments in industrialized countries have tended to become simpler and better tolerated, thereby improving their convenience and reducing the incidence and severity of their adverse effects.[4]

These simplified treatments involve fewer tablets and intakes, but they must be evaluated in the countries concerned, given the often very advanced stage of HIV disease at diagnosis, intercurrent health disorders, and local socioeconomic conditions.

In 1998, Senegal launched a national antiretroviral access program, and the first results encouraged other initiatives in sub-Saharan countries.[1] Most patients treated in Senegal received a regimen composed of unboosted indinavir and 2 available nucleoside analog reverse transcriptase inhibitors (NRTIs): d4T, ddI, AZT, or 3TC. The pill burden, together with frequent drug interactions (particularly between protease inhibitors and antitubercular drugs) led us to propose a simplified HAART regimen in 1999. Two open pilot studies of EFV-containing regimens were conducted in an attempt to optimize adherence and quality of life. The first study involved a once-a-day regimen containing ddI, 3TC, and EFV.[5] The second study, reported here, started in 2000, when ddI plus d4T had already been shown to be a very potent NRTI backbone of HAART regimens. We used a combination of ddI enteric-coated (EC), d4T, and EFV in order to simplify the initial HAART regimen for patients in Dakar.

Patients and Methods

Study Population

The inclusion criteria were as follows: HIV-1 infection, no previous antiretroviral therapy, age over 18 years, Karnofsky score above 70%, plasma HIV-1 RNA > 30,000 copies/mL and CD4+ cell count below 350/mcL, negative urine pregnancy test and effective barrier contraceptive for women, ability to be monitored for 18 months, and willingness to participate in the trial.

The main exclusion criteria were HIV-2 infection, active opportunistic infection, anemia (< 7 g/dL), platelets < 50,000/mcL, serum creatinine > 200 mcmol/L, and serum amylase, bilirubin, and liver enzyme values more than 5 times the upper limit of normal.

The trial was approved by the Dakar ethics committee and the Hospital Saint Germain-en-Laye ethics committee (France).

All the patients gave their written informed consent once the aims of the study had been explained to them both in French and in their native language. The drugs were supplied by Bristol-Myers-Squibb, Merck Sharp, and Dohme-Chibret. At the end of the trial, all of the patients were guaranteed to receive antiretroviral therapy through the National Senegalese AIDS Program.

Trial Design

This was a prospective, open-label, single-arm trial in which all of the patients received the following 2 drugs once a day at bedtime: 1 ddI EC 250-mg capsule daily for patients weighing < 60 kg or 400 mg daily for patients weighing 60 kg, plus EFV 600 mg daily (three 200-mg capsules). They also took d4T 30 or 40 mg twice a day according to body weight.

The EFV dose was increased to 800 mg in all patients who were concomitantly receiving rifampicin.

Two Dakar hospitals participated in the study (Service des Maladies Infectieuses and Centre de Traitement Ambulatoire, Fann University Hospital; and Principal Hospital). All of the patients were monitored by the same physicians.

Study Procedures

Patients were examined at screening, on the day of inclusion (day 0), at 2 and 4 weeks, and every month thereafter for 18 months. The screening evaluation included the medical history (CDC stage, concomitant medication, and other health problems), body weight and vital signs, the Karnofsky score, blood cell counts (including CD4 and CD8 cells), blood chemistry, a urine pregnancy test for women, and plasma HIV-1 RNA assay.

The antiretroviral drugs were supplied to each patient by the hospital pharmacist, fortnightly during the first month and monthly thereafter. Clinical status, adverse events, and concomitant medications were noted at each on-treatment visit.

Laboratory tests (including blood cell counts, liver enzymes, bilirubin, and creatinine) were performed at baseline, weeks 2 and 4, and every 3 months thereafter for 18 months. Blood triglycerides, total cholesterol, and glucose were measured at baseline and months 6 and 12.

CD4+ and CD8+ cell counts and plasma HIV-1 RNA were measured at months 3, 6, 9, 12, 15, and 18.

Adherence to the study treatment was assessed by the trial physician and the pharmacist at each visit. Interviews with the patient were done in French or in the local language (Wolof) using standardized questions focusing on adherence to the treatment during the previous 3 days and compliance with drug intake recommendations. In addition, a social survey was conducted at baseline and after 6 months of treatment.

Laboratory Methods

Plasma HIV-1 RNA was measured in the same laboratory in Dakar, using a test with a detection limit of 50 copies/mL (Ultrasensitive Amplicor HIV-1 Monitor 1.5, Roche Molecular Systems, Branchburg, New Jersey). Quality controls were done by Montpellier hospital virology laboratory in France.

CD4 cells were counted using the fluorometric *FACSCount* technique (BD Biosciences, Franklin Lakes, New Jersey) in the same laboratory in Dakar.

End Points and Statistical Analysis

The primary end point was the percentage of patients with plasma HIV-1 RNA < 500 copies/mL at month 6. Secondary end points were CD4+ cell count changes at month 6 relative to baseline, CD4+ cell counts and plasma HIV-1 RNA load (< 500 c/mL and 50 c/mL) at months 12 and 18, serious adverse effects, the percentage of patients who discontinued the treatment, and adherence to treatment.

Results were expressed as percentages and continuous variables as the mean and standard deviation or median and range. Ninety-five percent confidence intervals were also reported.

The data were analyzed on an intent-to-treat basis: losses to follow-up, deaths, and missing data were considered to reflect treatment failure. It was calculated that 40 patients were required to detect a minimum 70% of patients reaching the end point (lower limit of the 95% confidence interval). Calculations were performed with the *SPSS* software package (SPSS Inc., Chicago, Illinois).

Results

Baseline Characteristics of the Patients

From June 2000 to April 2001, 40 HIV-1-infected patients were enrolled in the trial. All of the patients were HIV-2-seronegative, and none had previously taken antiretroviral therapy. Thirty-nine patients were from Senegal and 1 was from Mauritania. Twenty-three patients (58%) were women. All of the patients said they had acquired HIV through heterosexual intercourse. Mean (SD) age was 36 ± 7 years. Mean (SD) body weight was 57 ± 10 kg.

Respectively, 47% and 53% of patients were at CDC stages B and C. Seven of the patients at CDC stage C had a history of pulmonary tuberculosis, and 3 had a history of extrapulmonary tuberculosis. The mean CD4+ cell count was 133 ± 92/mcL (± SD; range 1346), and 23% of patients had counts below 50/mcL. The mean baseline plasma HIV RNA level was 5.5 ± 0.4 log₁₀ copies/mL (+1 SD; range 4.65.9). Baseline biological values are summarized in Table 1.

At inclusion, 30 patients were receiving cotrimoxazole prophylaxis, 3 were receiving rifampicin plus isoniazid as maintenance therapy for tuberculosis, and 1 was receiving clarithromycin as maintenance therapy for *Mycobacterium avium complex* infection.

The baseline social investigations indicated that most of the patients were underprivileged. Seventeen patients (42%) had never been to school. Forty-two percent of the patients were divorced or widowed, and most had to care for at least 2 children. Twenty-two patients (58% overall, 90% of women) had never been employed. Mean income was \$30 per month, but 50% of patients had no income. Thirty-two patients (80%) had no public or private health cost coverage. Thirty patients (76%) had disclosed their HIV status to at least one member of their family.

Virologic and Immunologic Responses

The proportion of patients with plasma HIV-1 RNA below 500 copies/mL at M6 was 73% (95% CI [56; 85]). The proportion of patients with plasma HIV-1 RNA below 500 copies/mL fell during the study, to 56% (95% CI [41; 73]) at M12 and 43% (95% CI [27; 59]) at M18. The proportion of patients with plasma HIV-RNA below 50 copies/mL was 50% (95% CI [31; 66]) at M6, 43% (95% CI [27; 59]) at M12, and 33% (95% CI [19; 49]) at M18 (intent-to-treat analysis; Figure).

By on-treatment analysis, the proportion of patients with VL < 500 copies/mL remained stable: 78% (95% CI [62; 90]) at M6, 82% (95% CI [63; 94]) at M12, and 71% (95% CI [49; 87]) at M18. This may be explained by the high mortality rate (20%) and by treatment switches due to adverse events (13%). The mean reduction in plasma HIV-1 RNA was 3.4 ± 0.7 log₁₀ (N = 35) at M3 and 3.1 ± 1.1 log₁₀ (N = 24) at M18. The mean increase in the CD4+ cell count was 105 ± 125/mcL (N = 38) at M3 and 186 ± 122/mcL (N = 21) at M18.

Adherence and Plasma Drug Concentrations

The mean adherence during the 12-month study period was 97% (median, interquartile range [IQR]: 100% [99% to 100%]). The patients stated that they had taken more than 95% of their entire monthly dose during 88% of the 18 months covered by the study. Based on the pharmacist's questionnaire, 10 patients interrupted their antiret-

Table 1: Baseline Characteristics

Characteristic	Results, mean \pm SD (range) or n (% of patients)
Demographics	
Women	23 (58%)
Age (years)	23 \pm 7 (2252)
Anthropometry	
Body weight (kg)	56 \pm 9 (3777)
BMI	
< 18.5	17 (46%)
18.5-24.9	18 (49%)
> 25	2 (5%)
HIV infection	
Time since known HIV seropositivity (months)	12 \pm 7 (530)
CDC clinical stage	
B	19 (47%)
C	21 (53%)
CD4+ cell count (cells/mL)	
< 50	9 (23%)
51-200	20 (50%)
> 200	11 (27%)
Viral load (log ₁₀ copies/mL)	
< 5 log	6 (15%)
\geq 5 log	34 (85%)
Blood cell count and blood chemistry	
Hemoglobin concentration (g/dL)	11.5 \pm 1.9 (7.7-15.4)
Neutrophil count (10 ⁹ /L)	2203 \pm 1208 (775-7582)
Platelets (10 ³ /L)	256 \pm 103 (56-493)
ALT (UI/L)	23 \pm 15 (6-86)
Amylase (mmol/L)	90 \pm 51 (24-262)

Table 1: Baseline Characteristics (Continued)

Triglycerides (mmol/L)	1.3 ± 0.4 (0.52.5)
Total cholesterol (mmol/L)	1.6 ± 0.5 (0.93.4)

ALT = alanine amino transferase; BMI = body mass index; CDC = US Centers for Disease Control and Prevention; UI = Unité Internationale (International Units)

roviral treatment for more than 6 days, mainly because of special social events and journeys, but also because of intercurrent health disorders or treatment-related adverse events. Two patients were lost to follow-up at month 2.

Clinical and Adverse Events

The mean change in body weight from baseline to month 6 and month 18 was respectively $+4.8 \pm 6.9$ kg and $+3.0 \pm 8.3$ kg. At 6 months, 26 patients (72%) had gained weight, 6 (17%) had lost weight, and 3 (8%) were unchanged. At 18 months, 20 patients (67%) had gained weight, 9 (30%) had lost weight, and 1 (3%) was unchanged.

Nine patients were hospitalized for adverse events and had a positive outcome. The reasons for hospitalization were: disseminated tuberculosis (month 5), reactivation of oropharyngeal Kaposi's sarcoma (month 3), and *Isospora belli* diarrhea with severe dehydration (month 7) in 1 case each; grade 3 malaria in 2 cases (month 1 and month 7), and severe pneumonia in 4 cases (months 2, 7, 8, and 9). When the event occurred, 5 patients had VLs below 500 copies/mL, including the patient with Kaposi's sarcoma and the patient with *Isospora* diarrhea. This latter

patient had 160 CD4 cells/mcL at baseline and 437/mcL at month 7.

Eight patients died; the suspected causes of death are indicated in Table 2. Baseline CD4+ cell counts were < 150/mcL (< 50/mcL in 4 cases) with baseline VL above 5 log₁₀ in all the patients who died. The last VL value before death was < 500 copies/mL in all the patients who died, except for the noncompliant alcoholic patient, and the mean CD4+ cell count before death was 111/mcL (1217).

Treatment-Related Adverse Events

During the first month of treatment, 12 patients experienced EFV-related central nervous system symptoms (mainly dizziness). All of these symptoms resolved after a median of 9 days [range; 330 days].

Fifteen patients (37.5%) had peripheral neuropathy. Ten cases (25%) occurred after a mean of 8 months, were grade 1 or 2, and consisted primarily of paresthesia with mild to moderate persisting discomfort; these cases resolved on symptomatic treatment. Five patients (12.5%) experienced severe neuropathies with incapaci-

Table 2: Suspected Causes of Death and Last CD4+ Cell Count and Viral Load Values Before Death

Suspected Cause of Death	Month	CD4+ Cell Count at Baseline (cells/mcL)	Viral Load at Baseline (log ₁₀ copies/mL)	Last CD4+ Cell Count (cells/mcL)	Last Viral Load (log ₁₀ copies/mL)
Atypical mycobacteriosis	2	1	5.9	1	ND
Acute diarrhea and fever	6	36	4.8	204	< 2.69
Malaria and bacterial septicemia	7	10	5.6	8	< 2.69
Febrile encephalopathy	7	93	5.9	52	5.9
Septicemia	9	122	5.8	183	< 2.69
Purulent meningitis	12	106	5.9	100	< 2.69
Purulent meningitis	16	57	5.8	217	< 2.69
Liver carcinoma with liver failure	17	35	5.9	128	< 2.69

ND = not done

tating and intolerable discomfort requiring a switch from ddI and d4T to AZT and 3TC. When the peripheral neuropathy occurred, 12 patients (80%) had VL < 500 copies/mL.

Biological Tolerability

At month 18, there were significant increases in the following biological variables compared with baseline: hemoglobin (12.5 ± 1.7 g/dL vs 11.9 ± 1.7 g/dL, $P = .03$), mean corpuscular volume (99 ± 9 vs 88 ± 7 femtoliters, $P < .0001$), and the neutrophil count (57 ± 12 vs 45 ± 15 percent, $P = .0035$). There were no changes in glucose, triglyceride, cholesterol, liver enzyme, or amylase levels.

Discussion

Immunologic and virologic responses at 18 months of combination therapy with ddI plus EFV plus d4T were comparable to those of an observational cohort of Senegalese patients on HAART based on unboosted indinavir plus 2NRTIs.[1] Intention-to-treat analysis showed that the percentage of patients with plasma HIV-1 RNA values below 500 copies/mL fell during the study period, whereas the on-treatment analysis suggested that it remained stable. This may be explained by the high mortality rate (20%) and treatment modifications due to adverse events (13%).

The intention-to-treat results were less satisfactory than in an earlier pilot trial in Senegal (ANRS 1204/IMEA 011) with the ddI plus 3TC plus EFV regimen.[5] This may be due to several factors. Contrary to the first pilot study, we enrolled patients with CD4+ cell counts below 50/mcL, in order to reproduce more closely the real baseline characteristics of most Senegalese patients.

We observed a high frequency of peripheral neuropathies relative to other studies of the same combination,[6-8] but Gerstof and colleagues[9] recently observed a similarly high frequency (27%) of neuropathies among patients receiving abacavir plus d4T plus ddI. This could be due to advanced HIV disease status, low CD4+ cell nadirs, and a past history of opportunistic infections and malnutrition.

The low percentage of patients with VL < 500 copies/mL at 18 months of treatment may also be explained by the high mortality rate (20%) relative to that observed in other studies conducted in poor countries. As in the ISAARV study,[1] all but 1 of our patients had good virologic control but a relatively poor immune response at the time of death. The deaths were not due to opportunistic infections as defined by the CDC in the setting of industrialized countries. However, it is well known that causes of death in AIDS patients in sub-Saharan Africa are diverse, with predominance of bacterial sepsis.

In a comparison of patients treated in industrialized and poor countries, a large difference in mortality was noted during the 12 months following the initiation of HAART. This was linked to lower baseline CD4+ cell counts (12% mortality if < 50/mcL), concomitant tuberculosis, and lack of free care.[3,10]

While the d4T plus ddI combination should no longer be used and new WHO guidelines advise against their concomitant use,[11] the choice of NRTIs is difficult in sub-Saharan Africa. Initial results from a recent trial confirm that AZT is unsuitable for populations that have a high prevalence of anemia and low CD4+ cell counts, as the incidence of severe anemia (grade IV) was 6.6% during the first 3 months of treatment with AZT plus 3TC plus tenofovir (TDF).[12] In our experience, the ddI plus 3TC combination is well tolerated, as in industrialized countries.[5,13,14] d4T is part of the first-line ART regimen recommended by WHO since the first guidelines were released in 2002. From then on, it has been integrated in the protocols of most national HIV programs in resource-limited countries and is now used by hundred of thousands of patients worldwide.

However, d4T is no longer recommended in Western countries because of its longer-term toxicity profile that includes, for example, the long-term potential for the disfiguring lipoatrophy complication. In resource-limited countries, peripheral neuropathies are the main reason for changing d4T during the first months of treatment, but the importance of lipoatrophy as a reason for abandoning d4T later in treatment is still to be determined in cohorts

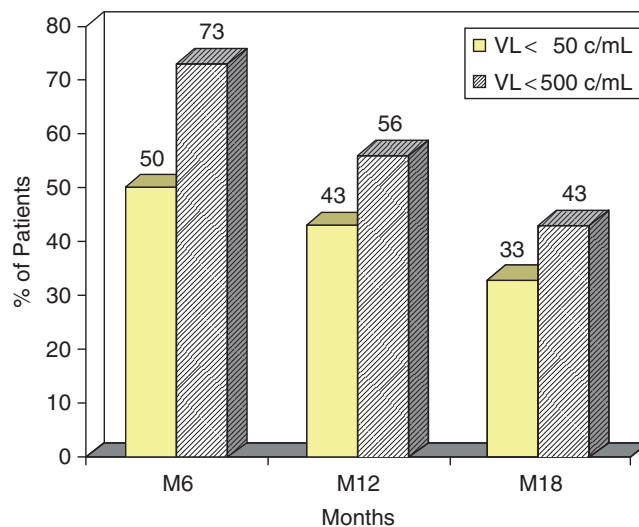


Figure 1
Percentage of patients with undetectable VL (intention-to-treat analysis).

from resource-poor settings. The median follow-up of less than 12 months of d4T therapy in published cohorts is too short to observe this complication.[15] Rare but potentially fatal cases of severe lactic acidosis are also a concern in environments where the capacity to diagnose is limited. The teratogenicity of EFV limits its use by sub-Saharan African women of child-bearing age. Nevertheless, EFV remains an important part of simple fixed-dose combinations, and new evaluations of fixed-dose once-daily combinations with a backbone of abacavir plus 3TC or tenofovir plus emtricitabine have to be tested in sub-Saharan populations.

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Authors and Disclosures

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References

1. Laurent C, Diakathe N, Ngome-Gueye NF, et al.: **The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study.** *AIDS* 2002, **16**:1363-1370. Abstract
2. Calmy A, Clement E, Teck R, et al.: **Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling-up.** *AIDS* 2004, **18**:2353-2360. Abstract
3. Dabis F, Schecter M, Egger M, et al.: **Response to highly active retroviral therapy in low- and high-income countries: analysis of clinical databases.** *Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections; February 2225, 2005; Boston, Massachusetts*. Abstract 23
4. Beck EJ, Vitoria M, Mandalia S, Crowley S, Gilks CF, Souteyrand Y: **National adult antiretroviral therapy guidelines in resource-limited countries: concordance with 2003 WHO guidelines?** *AIDS* 2006, **20**:1497-502.
5. Landman R, Schiemann R, Thiam S, et al.: **Once-a-day highly active antiretroviral therapy in treatment-naïve HIV-1-infected adults in Senegal.** *AIDS* 2003, **17**:1017-1022. Abstract
6. Van Leeuwen R, Katlama C, Murphy RL, et al.: **A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients.** *AIDS* 2003, **17**:987-999. Abstract
7. Garcia F, Knobel H, Samba MA, et al.: **Comparison of twice-daily stavudine plus once- or twice-daily didanosine and nevirapine in early stages of HIV infection: the scan study.** *AIDS* 2000, **14**:2485-2494. Abstract
8. Eron JJ Jr, Murphy RL, Peterson D, et al.: **A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of HIV-1 infected individuals: selection of thymidine analog regimen therapy (START II).** *AIDS* 2000, **14**:1601-1610. Abstract
9. Gerstoft J, Kirk O, Obel N, et al.: **Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine.** *AIDS* 2003, **17**:2045-2052. Abstract
10. Weidle PJ, Malamba S, Mwebaze R, et al.: **Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance.** *Lancet* 2002, **360**:34-40. Abstract
11. **Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach, 2006 revision** [<http://www.who.int/hiv>]. Accessed September 10, 2007
12. Mutuluza CK, Walker S, Kaleebu P, for the DART trial, et al.: **Short-term virological response to a triple nucleoside/nucleotide analogue regimen in adults with HIV infection in Africa within the DART trial.** *Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections; February 2225, 2005; Boston, Massachusetts*. Abstract 22
13. Maggiolo F, Ripamonti D, Gregis G, et al.: **Once-a-day therapy for HIV infection: a controlled, randomized study in antiretroviral-naïve HIV-1-infected patients.** *Antivir Ther* 2003, **8**:339-346. Abstract
14. Molina JM, Ferchal F, Rancinan C, et al.: **Once-daily combination therapy with emtricitabine, didanosine, and efavirenz in human immunodeficiency virus-infected patients.** *J Infect Dis* 2000, **182**:599-602. Abstract
15. Calmy A, Pinoges L, Szumilin E, et al.: **Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort.** *AIDS* 2006, **20**:1163-1169. Abstract