Viriom

Hope Health Happiness

EACS European AIDS Clinical Society

15 EUROPEAN AIDS CONFERENCE

October 21-24, 2015
Barcelona, Spain

PE7/4 Safety and antiviral effect of Elpida (VM-1500), a novel NNRTI (+Truvada) in treatment-naïve HIV-1 infected patients

A.V. Kravchenko[1], E.A. Orlova-Morozova[2], F.I. Nagimova[3], O.A. Kozirev[4], T.E. Shimonova[5], V.V. Bichko[6], N.V. Vostokova[7], O.A. Zozulya[7]

1. Russia AIDS Federal Center, Moscow, Russia; 2. Moscow region AIDS Center, Moscow, Russia;
3. Republic Tatarstan AIDS Center, Kazan, Russia; 4. Volgograd region AIDS Center, Volgograd, Russia
5. Moscow city AIDS Center, Moscow, Russia; 6. OOO «VIRIOM», Moscow, Russia; 7. OOO «IPHARMA», Moscow, Russia

Background: Elpida (VM-1500) is the pro-drug of the active compound VM-1500A, a potent, highly selective NNRTI. A study of efficiency and safety of the drug VM-1500 (Phase IIa) was conducted in 16 antiretroviral therapy-naïve patients with HIV-infection with baseline HIV level > 5000 copies/ml and CD4 + lymphocytes level > 250 cells/mm^3 [1]. 8 patients of the first group were randomized in a ratio of 7:1 (monotherapy with VM-1500 in the dose of 20 mg/day or placebo). After 7 days of treatment the average number of HIV RNA in patients, treated with VM-1500, decreased from 82,944 copies/ml to 2,133 copies/ml, and the number of CD4+ lymphocytes increased from 551 to 592 cells/mm^3. In a patient, receiving placebo, no significant dynamics of HIV RNA level and number of CD4+lymphocytes was registered (303,000 and 248,000 copies/ml, 492 and 517 cells/mm^3, respectively). Group 2 patients (8 people) were randomized in a ratio of 7:1 (monotherapy with VM-1500 in the dose of 40 mg/day or placebo). Dynamics of the study indicators in group 2 and group 1 patients was similar: VM-1500 – HIV RNA level – 93,671 – 1,316 copies/ml, CD4+cells – 471 – 525 cells/mm^3; placebo – 126,000 – 116,206 copies/ml and 424 – 388 cells/mm^3, respectively.

Elpida showed excellent activity with a 1.8 log reduction in HIV-1 RNA after 7 days of treatment with only minimal side effects. 3 patients, receiving VM-1500 in a dose of 20 mg, had complaints on feeling mild dry mouth and polyuria, and 1 patient – on mild headache. In patients, receiving 40 mg VM-1500, no adverse events were reported. The PK profile suggests up to once weekly dosing [1].

Objective: to evaluate safety and antiviral effect for different treatment regimens with Elpida/TDF/FTC in comparison with Efavirenz/TDF/FTC in treatment-naïve HIV-1 infected patients.

Methodology: A randomized, placebo-controlled, double-blind dose-finding study in patients with HIV infection who are antiretroviral therapy-naïve with HIV-1 RNA 4.6-4.9 $\log_{10}$ copies/ml and CD4-lymphocytes - 311-379 cells/mm^3. A total of 90 patients were randomized to Elpida (20 mg, group 1), Elpida (40 mg, group 2) or EFV (600 mg, group 3) with 1:1:1 ratio. All patients received TDF/FTC. A fraction of patients who completed 12 weeks of treatment in gr. 1-3 was 100%, 93.9% and 80%, respectively.

Baseline patient characteristics are presented in Table 1.

Table 1. Characteristics of patients at baseline.

Characteristics	VM-1500 20 mg	VM-1500 40 mg	EFV 600 mg
Age (median), years	36.5	35.0	33.0
Male (%)	60	55.2	63
European race (%)	96.7	100	100
Duration of HIV infection, years M±SD	2.9±3.1	2.4±2.5	2.4±3.0
HIV RNA $\log_{10}$ copies/ml median	4.7	4.9	4.6
CD4+lymphocytes cells/mm^3 (median)	379	311	340
Completed 12 weeks of treatment, n (%)	30 (100)	28 (93.3)	24 (80)
Not completed 12 weeks of treatment, n (%)	0 (0.0)	2 (6.7)	6 (20.0)
Use of illegal drugs, n (%)	0 (0.0)	1 (3.3)	0 (0.0)
AEs, n (%)	0 (0.0)	1 (3.3)	2 (6.7)
Patient withdrew IC, n (%)	0 (0.0)	0 (0.0)	1 (3.3)
Lost for observation, n (%)	0 (0.0)	0 (0.0)	3 (10.0)

Results: After 12 weeks of treatment, the median HIV-1 RNA decreased from 4.7 $\log_{10}$ copies/ml to 1,8 $\log_{10}$ copies/ml in patients from gr.1, from 4.9 $\log_{10}$ copies/ml to 1.7 $\log_{10}$ copies/ml (gr.2) and from 4.6 $\log_{10}$ copies/ml to 1.7 $\log_{10}$ copies/ml (gr.3). The fraction of patients with <400 HIV-1 RNA copies/ml in groups 1-3 was 93.3%, 86.2% and 81.5% (MTTI-analysis, Fig.1); 93.1%, 86.2% and 87.5%, respectively (PP-analysis).

With respect to this indicator, VM-1500 was superior to EFV at the dose of 20 mg by 11.8%, at the dose of 40 mg by 4.7% (lower limit of 95% CI -2.6% and -11.5%, respectively, which in both cases is more right δ = -15%). Thus, VM-1500 at the doses of 20 and 40 mg was reliably not inferior to EFV with respect to the effectiveness to reduce the level of viral load to a level of < 400 copies/ml for 12 weeks.

Additional analysis of decrease in the median of HIV RNA content after 12 weeks of therapy depending on baseline viral load (more than or equal to 100,000 copies/ml and less than 100,000 copies/ml) did not reveal significant differences between the patients in all three groups, both with baseline high and baseline low HIV RNA level. In patients with initially low HIV RNA content (median was 4.68 – 4.87 $\log_{10}$ copies/ml) after 12 weeks of therapy median of the indicator declined by 2.95 – 3.15 $\log_{10}$ copies/ml, and in patients with initially high viral load level (median 5.38 – 5.63 $\log_{10}$ copies/ml) it declined by 3.28 – 3.38 $\log_{10}$ copies/ml.

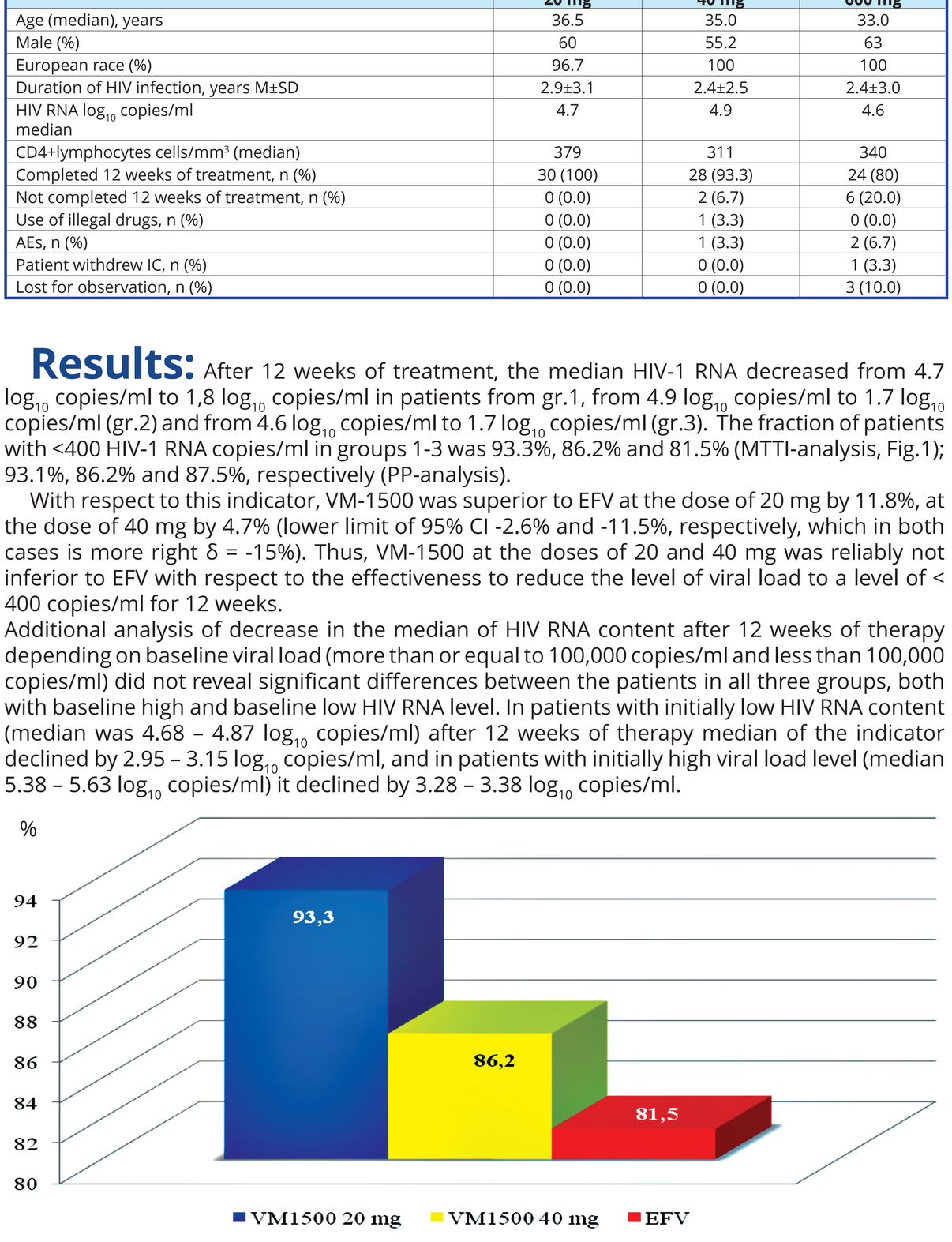

Figure 1. Fraction of patients with HIV RNA level < 400 copies/ml after 12 weeks of therapy (MITT- analysis)

The median CD4-lymphocytes increased from 379 cells/mm^3 to 427 cells/mm^3 (gr.1), from 311 cells/mm^3 to 461 cells/mm^3 (gr.2) and from 340 cells/mm^3 to 467 cells/mm^3 (gr.3) (Fig.2). The average number of CD4+lymphocytes in patients of group 1 after 12 weeks of therapy increased from 385.9 ± 174.7 to 486.2 ± 201.0 cells/mm^3 (p<0.001), group 2 - from 335.0±97.4 to 459.1±125.0 cells/mm^3, and of reference group (group 3) – from 427.1±225.5 to 504.6±220.0 cells/mm^3 (p=0.037). Only in patients of group 1, receiving 20 mg of VM-1500 per day, after 12 weeks of treatment a significant reduction in the average number of CD8+lymphocytes was noted (1076.2 ± 462.9 and 931.4 ± 370.4 cells/mm^3; p<0.001). Changes in this indicator in patients of other groups were not relevant. However, increase in the median of immunoregulatory index (CD4/CD8+lymphocytes ration) was registered in patients of all groups: 0.357-0.378 (before treatment) and 0.487-0.522 (after treatment).

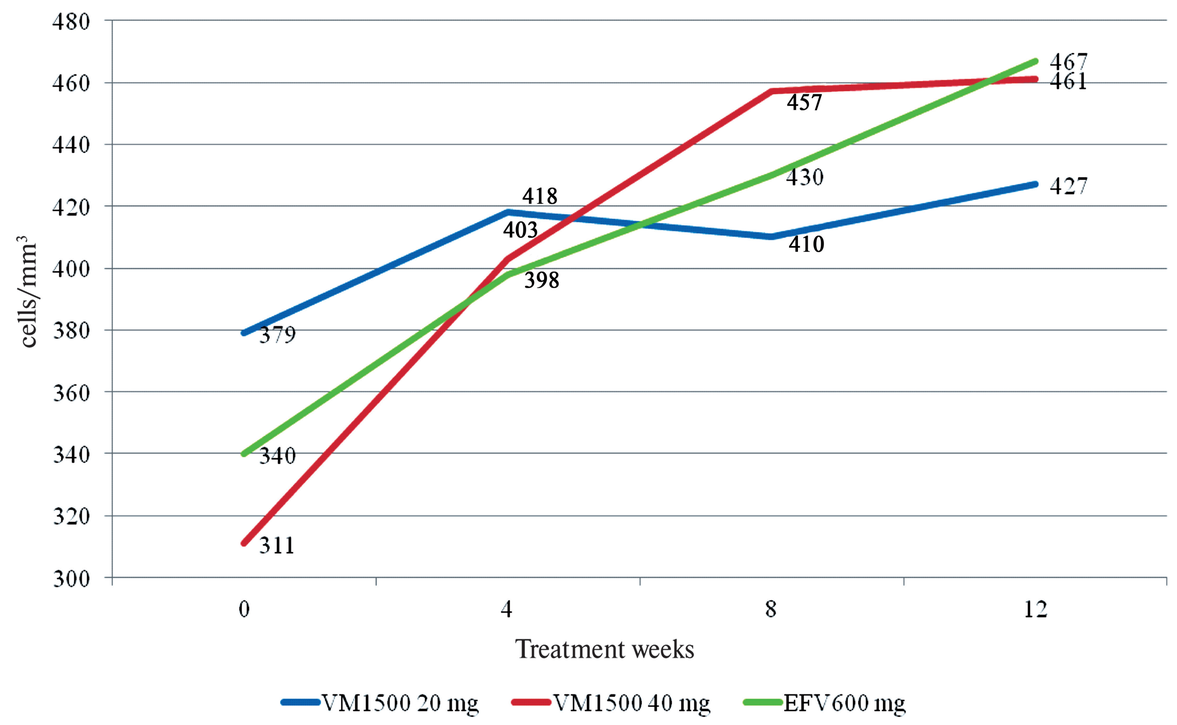

Figure 2. Time course of median number of CD4+lymphocytes during the study (PP-analysis)

Table 2. Distribution of patients with respect to frequency, severity and connection of AEs to the study drugs within 12 weeks of the study

AE	VM-1500 20 mg N=30 X (%)/Y	VM-1500 40 mg N=29 X (%)/Y	EFV 600 mg N=28 X (%)/Y
AE (all)	21 (70.0%)/124	25 (86.2%)/209	24 (85.7%)/275
- severe	2 (6.7%)/2	4 (13.8%)/8	4 (14.3%)/14
- associated	1 (3.3%)/3	4 (13.8%)/17	13 (46.4%)/97
- possibly associated	7 (23.3%)/40	19 (65.5%)/106	14 (50.0%)/122
- SAE	2 (6.7%)/2	No	1 (3.6%)/1

X (%) – the number (percent) of the patients with at least one AE; Y – the total number of AEs

Table 3. Distribution of patients with respect to frequency, severity and connection of AEs of special interest to the investigational drugs within 12 weeks of the study

AE	VM-1500 20 mg N=30,$ X (%)/Y	VM-1500 40 mg N=29 X (%)/Y	EFV 600 mg N=28 X (%)/Y
AE of special interest (all)	8 (26.7%)*	13 (44.8%)**	16 (57.1%)
Neurological disorders	6 (20.0%)/17	11 (37.9%)/38	15 (53.6%)/84
- severe	No	2 (6.9%)/2	3 (10.7%)/8
- associated	1 (3.3%)/1	2 (6.9%)/3	12 (42.9%)/43
- possibly associated	3 (10.0%)/7	7 (24.1%)/29	8 (28.6%)/36
Psychiatric disorders	5 (16.7%)/18	7 (24.1%)/12	9 (32.1%)/61
- severe	No	No	No
- associated	No	1 (3.4%)/1	7 (25.0%)/25
- possibly associated	3 (10.0%)/16	5 (17.2%)/9	4 (14.3%)/35

** – p = 0.096 (vs EFV); ** – p = 0.431 (vs EFV); $ – p = 0.129 (comparison between the doses of VM-1500)*
X (%) – the number (percent) of the patients with at least one AE; Y – the total number of AEs

AEs (grade 2-4) were observed in 33.4%, 65.5% and 75% of patients from cohorts 1-3, respectively, including drug-related AEs (3.3%, 13.8% and 46.4%, respectively) (Tab.2).

Serious AEs (SAEs) unlikely related to ongoing therapy were diagnosed in 3 patients. In 1 patient, receiving VM-1500 in the dose of 20 mg/day, after hypothermia pneumonia of lower right lung lobe of mild severity level was revealed, and in 1 patient from the same group – calculus of right kidney middle calix of moderate severity. 1 patient of EFV group after hypothermia was diagnosed with pneumonia of upper and middle right lung lobe of moderate severity. Development of SAEs in all three patients did not require cancellation or change in antiretrovial therapy.

In this study, AEs of particular interest included neurological and psychiatric disorders that occurred in 26.7% of patients in the first group, 44.8% in the second group, and 57.1% in the third group (Tab. 3). Central nervous system disorders were identified in 20%, 37.9% and 53.6% of patients, respectively. While severe AEs were not noted in patients of group 1, whereas in patients of group 2 and group 3 they were found in 6.9% and 10.7% cases. Only in 1 patient of the first group and in 2 patients of the second group (3.3% and 6.9%) neurological disorders were associated to the investigational drug, while in persons of the third group relation of AEs with EFV administration was established in 12 patients (42.9%). Among neurological AEs, registration frequency was 5% or more, in group 1 patients only the occurrence of headache was noted, in group 2 patients had unusual dreams, dizziness, headache, sleep disturbance, drowsiness, and in persons of group 3 (in addition to the above disorders) insomnia and impaired memory were noticed.

Psychiatric disorders were found in 16.7%, 24.1% and 32.1% of patients, respectively. AEs of high severity were found in none of patients (Tab. 3). Development of depression, nightmares, sleep disturbances were mostly common (>5%) in group 1 patients; group 2 patients had only sleep disturbance. The range of psychiatric AEs in EFV patients included: aggressiveness, apathy, depression, attention deficit disorder, irritability, mood swings, nightmares, sleep disturbance. It should be noted that in 25% of group 3 patients these AEs were definitely associated with the administration of EFV, and in another 14.3% they were possibly associated. Among patients, receiving VM-1500, only in 1 patient (3.4%) sleep disorders were associated with the administration of the investigational drug.

In VM-1500 20 mg group, the development of mild severity leukopenia was recorded in 13.3% of patients, in VM-1500 40 mg group (mild and moderate severity) – in 13.8% of patients, and in the EFV group (mild severity) – in 7.1% of patients. The presence of neutropenia of mild severity was noted in 3.4 – 6.7% of patients, receiving VM-1500, and in 14.3% of patients, treated with EFV.

No significant fluctuations in SGOT and SGPT levels in patients of all groups were identified within 12 weeks of the study. Other biochemical blood analysis indicators (creatinine, urea, albumin, gamma-GGT, LDH, CPK, cholesterol, glucose) changed slightly. In none of cases, correction of biochemical blood analysis parameters was required.

Conclusions: In treatment-naïve patients, Elpida 20 and 40 mg QD (with TDF/FTC) at week 12 demonstrated potent antiviral activity, comparable to EFV, and favourable safety/tolerability profile. Fewer drug-related AEs were observed for Elpida compared with EFV. Elpida 20 mg QD was selected for further study.

References:

1. Ratanasuwan W., Werarak P., Murphy R.L., Bichko V. A randomized, placebo-controlled, double-blind study of VM-1500 in HIV-naïve patients // CROI, 2014.- Boston, MA, USA.- Abstr. 544LB.