Drug resistance to novel non-nucleoside reverse transcriptase inhibitor Elsulfavirine among treatment-naïve, HIV-infected Caucasian and Asian patients.

E. Yakubova[1], A. Kirichenko[2], A. Kravchenko[2, 3], R. Arsienko[1], S. Baranovsky[1], J. Remeeva[1], S. Corritori[1], N. Savchuk[1], D. Kireev[2], R. Murphy[4]

[1]Viriom, Inc., San Diego, United States, [2]Central Research Institute of Epidemiology, Moscow, Russian Federation, [3]Federal Research Centre for AIDS, Moscow, Russian Federation, [4]Northwestern University, Chicago, United States

BACKGROUND

Elsulfavirine (ESV) is an oral pro-drug of VM1500A a novel, potent non-nucleoside reverse transcriptase inhibitor NNRTI with a unique clinical pharmacokinetic profile, very low toxicity and broad-spectrum activity across HIV-1 variants.
A 20 mg oral capsule formulation of ESV was approved in 2017 for treatment of HIV-1 in combination with two nucleoside reverse transcriptase inhibitors (NRTI) as part of a standard antiretroviral therapy (ART) regimen, under the brand name Elpida® in Russia and EAEU (Kazakhstan). ESV has been submitted for obtaining marketing authorization in Thailand, Indonesia, Colombia, initiated a regulatory submission in China and is in development for once weekly, once monthly or less frequent dosing in US, European and Asian countries.
The Post-Authorization Study of Efficacy and Safety (PASS) was initiated in 19 clinical sites across Russia in 2018 to obtain safety and efficacy data from HIV-1 infected patients treated with Elpida in combination with two NRTIs.
In vitro studies shows that ESV has a higher genetic barrier compared to other NNRTIs. For a significant level of DR, a combination of at least two or more mutations is required. [1]
The resistance profile of ESV has been described as combinations of the major mutations V106I / A + F227C and V106I + Y188L, which were often accompanied by mutations A98G, L100I, V108I, E138K, Y181C, M230L, P236L [1].
This study is comparing the prevalence of DR mutations to ESV between Caucasian and Asian treatment-naïve HIV1-infected patients to estimate treatment efficiency prognosis.

MATERIAL AND METHODS

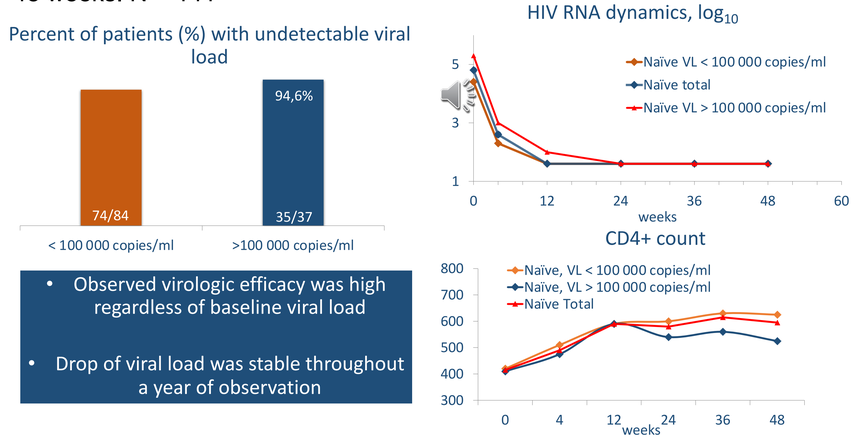
Two different patient cohorts were analyzed in this study.
Cohort 1 contained HIV genetic sequences of 5661 Asian patients. The sequences were obtained from the Los Alamos HIV Database (www.hiv.lanl.gov). All the sequences which had a sampling country tag “CN”, belonged to treatment-naïve patients and contained HIV genome region at 2253-3200 range (according to HXB2 reference sequence), were included in the analyses.
Cohort 2 included 1815 sequences of ART-naive Caucasian patients from the Russian HIV Drug Resistance database http://www.hivresist.ru.
Cohort 2 also included sequences derived from 152 baseline plasma samples taken from treatment-naive PASS study participants. Resistance testing of laboratory samples was performed retrospectively using AmplySens HIV-Resist-Seq kit (CRI of Epidemiology, Russia). Reverse transcriptase gene at the 1-215 amino acid region was analyzed.

The Stanford HIV Resistance Database https://hivdb.stanford.edu/hivdb/by-sequences was used to determine viral subtype and describe the ESV resistance profiles using amino acid analyses in the positions associated with drug resistance (98, 100, 106, 108, 138, 181, 188, 227, 230 и 236).
The PASS study population includes both HIV-1 infected patients who receive 20 mg ESV daily as part of their first line ART regimen. Efficacy endpoints include viral load, CD4+ T cell count, and drug resistance. Safety endpoints include clinical adverse events (AE), serious adverse events (SAE), ECG and laboratory data.

RESULTS

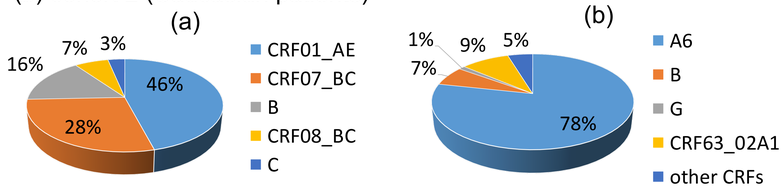
A significant reduction in viral load from baseline was observed from Week 4 and it was sustained through 48 weeks of treatment. At Week 48, 90.1% of patients had an undetectable viral load . The CD4+ T cell count increased from 429 to 597 c/ml, independent of the baseline viral load.

Figure 1. Efficacy overview. MITT sub-population: naïve patients completed 48 weeks. N = 141



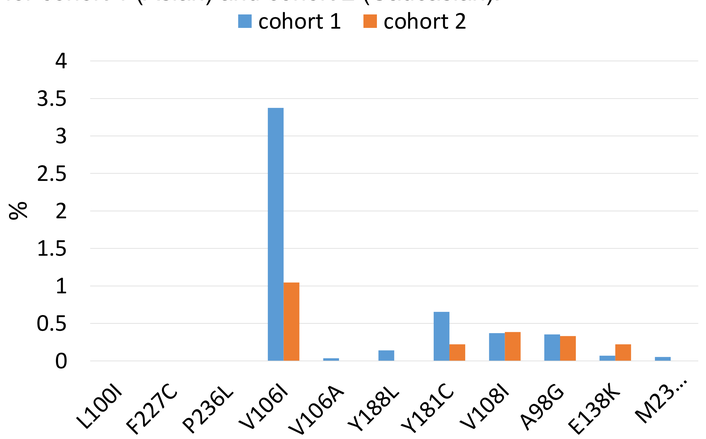
The safety analysis included 332 patients who completed 48 weeks of treatment. The treatment was well tolerated. Most of the observed AEs were of mild/moderate severity. 0.9% of patients reported SAEs, all deemed unrelated to study treatment.
The analysis of HIV subtypes prevalence is presented on the Figure 2.

Figure 2. Major clades determined for (a) cohort 1 (Asian patients) and (b) cohort 2 (Caucasian patients)



The analysis of the pre-treatment primary DR mutations to ESV showed that at least one of them was detected in 200 sequences (3.53%). V106I mutation (n=191; 3.37%), Y188L (n=8; 0.14%), V106A (n=2; 0.04%) were detected most often. The major DR mutation F227C was not discovered. Accessory DR mutations were discovered with the following frequency: A98G in 20 sequences, V108I in 21, E138K in 4, Y181C in 37, M230L in 3. Accessory mutations L100I и P236L have not been discovered. Combinations of one major and two additional mutations were found in 3 sequences, the main and one additional mutations in 4, and two additional mutations in 5 cases. In one sequence, two major mutations were found (V106I and Y188L) (0.055%).
At least 1 mutation from ESV in vitro resistance profile was discovered in 2.3% of patients from the cohort 2. V106I major mutation was detected in 19 cases (1%). V108I, A98G and E138K was detected in 7, 6 and 4 cases respectively (Figure 3). Out of the 11 patients with virologic failure, only one had documented drug resistance mutations (V106I, F227C, E138K) during treatment.

Figure 3. Pretreatment ESV resistance mutations frequency for cohort 1 (Asian) and cohort 2 (Caucasian).



CONCLUSIONS

The analysis of nucleotide sequences of treatment-naïve HIV-infected patients has shown that the prevalence of drug resistance to ESV is low for NNRTIs. The results suggest the ESV could be used as a first line/alternative first line therapy in areas of the world were NNRTIs are considered for first line therapy.

1. Javanbakht H. et al; ***In vitro* resistance development for RO-0335, a novel diphenylether nonnucleoside reverse transcriptase inhibitor.** Antiviral Research, 2010, 86:212-219