Materials and methods: Reviewing of outpatient clinic records, case histories, and AIDS Center reports in the Northwest of Russia in association with studies of the clinical conditions of HIV patients encompassed 120 000 HIV cases. The data were treated statistically using MS Excel and Statistica 10 and software tools.

Results: The onset of HIV epidemic dates back to late 1990s when new found HIV cases amounted to hundreds and, further on, to thousands because of rapid spread of injection drug use with HIV-contaminated needles and syringes. At the time of diagnosis, most patients had normal CD4 cell counts suggesting a recent HIV infection, which had reached Stage II or III.

In 2003–2004, the epidemic subsided, having involved mostly men aged 20 to 25 years, who constituted the main group of HIV risk and at difference from the earlier time were infected with subtype A HIV-1 (more than 90%). The decline of the first wave of HIV incidence may be explained by the exhaustion of the main risk group and by the active preventive interventions. In the Northwest of Russia, the most vulnerable to HIV were territories featuring higher population density and more intense migrant streams (Saint-Petersburg and Leningrad, Kaliningrad, and Murmansk Oblasts).

In patients who according to the presence of opportunistic and concomitant diseases could be referred to HIV infection Stages 4 or 5, blood CD4 cell counts were below 200 $m1^{-1}$, and HIV loads were $10^{4,5}$ to $10^{6,0}$ RNA copies per 1 ml. The duration of infection from the time of HIV contracting, mainly by the injection route, to HIV detection was from 4 to 12 years, probably because a part of HIV cases detected during the first peak of the epidemic were not diagnosed timely. Other patients were infected in a relatively more recent time, during the second wave of HIV. The least numerous group comprised patients at advanced stages associated with immunosuppression who needed HAART at the time of diagnosis. The high numbers of HIV cases at Stage 4 was conducive to tuberculosis and associated with high death rate over the first year after the onset of therapy.

Lethal cases were registered in patients under HAART mainly because of pronounced immunosuppression, the development of severe concomitant infections including tuberculosis, patients' poor adherence to therapeutic regiments, and the discontinuation of therapy.

Conclusion: The current period of HIV epidemic may be characterized as associated with the advances stages of HIV infection associated with numerous concomitant diseases and high death rates upon HAART. All this warrants special attention to early HIV detection and subsequent management of HIV cases and to developing of a complex of preventive, organizational and socio-medical interventions adapted to megalopolises as well as to sparsely populated territories.

Novel dual inhibitors targeting HIV-1 integrase and reverse transcriptase-associated ribonuclease H activity

S.Korolev, M.Pustovarova, A.Atrokhova, A.Zhuze, M.Gottikh

Moscow, Russia

Reverse transcriptase (RT) and integrase (IN) facilitate the early stages of HIV-1 replication. HIV-1 integrase (IN) and reverse transcriptase (RT)-associated ribonuclease H (RNase H) domains belong to the polynucleotidyl transferase superfamily and share common structural features. The catalytic sites of both enzymes contain a central core composed of three highly conserved amino acid residues forming the DDE motif or RNase H-like fold (Asp, Asp and Glu). Among the novel approaches aimed to identify new HIV-1 inhibitors, the development of dual-action inhibitors, single drugs that may act on two different enzymes, such as IN and RNase H. A number of attempts has been made to identify compounds that may act on both enzymes, but still there is no dual inhibitor passed the clinical trials [Corona A., et al. *Antomicrob. Agents Chemother.*, 2014, 58 (10), 6101–6110; Cuzzucolli Crucitti G., et al. *J. Med. Chem.*, 2015, 58 (4), 1915–1928; Esposito F., et al. *Antiviral Chem. Chemother.*, 2014, 23, 129–144].

In our previous works, we have studied in detail the integration inhibition by dimeric bis-benzimidazoles (DBI) [Zhuse A.L., et al. *J.Biomol. Struct. Dyn.*, 2007, 24(6), 666–668; Korolev S.P., et al. *Russian J. of Mol. Biol.*, 44 (4), 633–641.]. The inhibitory effect of these compounds are explainable by the fact that they interfere with a correct binding of the DNA substrate in the IN active center. To enable their potential use however requires to overcome their low solubility in water and to increase their bioavailability. Recently the new series of water soluble DBI has been obtained. The inhibitory activity of these compounds was determined for both recombinant enzymes IN and RNase H. It was shown that the inhibition ability for the set of compounds depends on the length of the spacer connecting the pairs of benzimidazole fragments. The IC_{50} values of the most active one were 50 nM for IN and 5 μM for RNase H. Moreover these compounds demonstrated extremely low cytotoxity (CC_{50}>100 μM). According to preliminary trials the most active DBI showed its inhibitor activity on replication-incompetent VSV-G-pseudotyped vector HIV-1 based. Overall, DBI may be considered as a potent dual-acting inhibitor for treatment of HIV-1 infections.

Inorganic pyrophosphate analogs as multitarget HIV replication inhibitors

A.N.Korovina, O.A.Khomich, S.P.Korolev, M.K.Kukhanova, S.N.Kochetkov, D.V.Yanvarev

Moscow, Russia

Despite the undoubted success in the development of human immunodeficiency virus type 1 (HIV-1) therapy, this