Daria N. Podlekareva PhD dissertation 8th December 2009

This PhD thesis is based on three original manuscripts and a review manuscript of the results from the EuroSIDA study.

One of the goals of this PhD was to determine risk factors associated with development of opportunistic infections (OIs) at relatively high CD4 cell count. The strongest predictors for that were current CD4 cell count and use of cART. However, the main finding was that irrespective of a significant increase in CD4 cell count, the risk of developing OIs was non-negligible. Thus, this study contributed to the accumulating evidence on earlier (vs. deferred) cART initiation, when immune function is yet not severely compromised, in order to prevent disease progression as early as possible.

Some OIs (i.e. tuberculosis) can develop at any spectrum of immunodeficiency. HIV/TB co-infection provides major challenges for clinicians due to composed pathogenetic mechanisms, treatment complexity and drug-drug interaction. The situation with HIV/TB epidemic in Eastern Europe (EE) is of particular concern due to the high prevalence of TB in the general population, fast growing HIV epidemic and overlapping risk groups for acquiring both diseases (i.e. injection drug users). Therefore a major focus of this research was on HIV-epidemic in EE and HIV/TB co-infection in particular. An independent international HIV/TB project, addressing clinical and epidemiological aspects of this co-infection has been developed and initiated in 2006. The database now consists of 1075 HIV-infected patients from Europe and Argentina diagnosed with active TB between 2004 and 2006.

Profound regional differences in clinical prognosis after TB diagnosis, in particular a 3-5-fold higher one-year mortality rate in EE compared with Western Europe and Argentina were found. This study highlights the concern of a low use of cART in EE compared with the other parts of Europe and Argentina and high prevalence of multi drug resistant (MDR)-TB in this region. It also emphasises the increasing problem of the HIV/TB epidemic throughout Europe and addresses not only clinical, but also public health issues related to the HIV/TB co-infection.

Further, EuroSIDA is the first clinical study to document a pronounced regional difference in patients' characteristics across Europe. Our data emphasises a more recent HIV epidemic in EE: 50% of the HIV-infected population have a history of injection drug use and are co-infected with hepatitis C. A low usage of cART in HIV-infected patients in EE was also documented.

One of the reasons for low usage of cART and high mortality rate of HIV/TB co-infected patients in EE could be a suboptimal management of these patients. Compliance with current HIV-guidelines (when to start cART, what regimen to use, frequency of laboratory monitoring) and ability to maintain maximum virological suppression were assessed and compared across the European regions using the EuroSIDA database. The analysis showed, that a high proportion of EE patients with low CD4 cell count had not initiated cART, and among patients who had initiated cART, their ability to maintain maximal virological suppression was considerably lower when compared to patients from the rest of the Europe. In addition, the HIV-RNA and CD4 cell counts of patients in this region are less frequently monitored than in other regions. Countries from Northern Europe archived the best results in terms of virological response to cART and results of this region can be used to benchmark HIV-care.

Thus, this study introduces a benchmark of HIV care and a set of health care indicators, which can be used for assessment of clinical management of HIV-infected patients. It can be further adjusted and implemented elsewhere.

The new knowledge obtained during the current PhD project is applicable for the enhancement of surveillance efforts and the establishment of targeted interventions in the specific regions and population groups, and for specific diseases. This may help to identify patients in greatest need and ultimately improve the clinical management of these patients and thereby also their prognosis.