Factors associated with development of opportunistic infections in HIV-1 infected adults with high CD4 cell counts: a EuroSIDA study

Amanda Mocroft1, UB Dragsted1, A Mocroft2, B Ledergerber3, M Beniowski4, A Lazzarin5, J Weber6, N Clumeck7, N Vetter8, A Phillips2, and JD Lundgren1 for the EuroSIDA study group

BACKGROUND
The risk of opportunistic infections (OIs) increases substantially with increasing immunodeficiency i.e. at declining level of CD4 cell count. Some patients, however, develop OIs at “higher than expected” CD4 levels, where the immune function would appear to be acceptable or only moderately affected. Limited data exists on factors predicting the development of OIs at high CD4 counts and the role of combination antiretroviral therapy (cART) in this situation.

OBJECTIVE
To investigate the incidence of and predictors for the development of OIs at high CD4 counts.

METHODS
The EuroSIDA study is a prospective observational cohort study of HIV-1 infected patients from 30 centres in 15 countries across Europe including Israel and Argentina. Patients were divided into three groups according to the development of OIs and latest CD4 count threshold above which these OIs are traditionally considered relevant:

- **Group 1**: CD4 threshold > 100 cells/µL; OIs constituting endpoints were defined as disease from Cytomegalovirus (CMV), Mycobacterium avium complex, and Toxoplasma gondii (Costello) (CMV/MAC/TOXO);
- **Group 2**: CD4 threshold > 200 cells/µL; OIs constituting endpoints were defined as disease from Pneumocystis jiroveci (pneumonia) and **Toxoplasma gondii (cerebral)*** (PCP/OC);
- **Group 3**: CD4 threshold > 300 cells/µL; OIs constituting endpoints were defined as extrapulmonary tuberculosis (TB).

Patient followup began at the first prospective CD4 count above the given threshold in the three groups. At each CD4 count, follow-up since the last CD4 count was calculated; person-years of follow-up (PYFU) occurred in 2 categories: above or below the CD4 count threshold, and OIs were categorized in the same way. Of note, a patient could be included in one or more of Group 1-3. Only follow-up time that occurred while the latest CD4 count was above the indicated threshold was used in these analyses (except data presented in Figure 3). The follow-up period was from January 1994 until Spring 2004. cART was defined as any combination of ≥ 3 antiretroviral drugs including at least one protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or abacavir.

The incidence of clinical disease within each of the three groups was calculated. Person-years of follow-up began at the baseline date and ended at the diagnosis of the clinical event, or last CD4 count for those who were not diagnosed with the relevant event.

Further, three multivariate Poisson regression models were developed to determine factors related to the development of either of three categories of OIs. Factors that were significant (p < 0.1) in any of the univariate models for each group were included in the multivariate models for this particular group.

RESULTS
A total of 12,197 EuroSIDA patients were available for analyses. Of those, 8,581 were eligible for inclusion in Group 1: 7,489 in Group 2, and 7,006 in Group 3. Figure 1 shows the distribution of patients in each group and the number of OIs below and above the chosen threshold.

A total of 671, 733, and 793 patients, in each group respectively, experienced one of the OIs. Baseline characteristics of patients in each of the three groups are presented in Table 1. The median (IQR) CD4 count at the time of diagnosis was 175 (120-250), 333 (249-451) and 491 (394-673) cells/µL respectively, which is in 2.1 times the predicted threshold.

CONCLUSION
The studied OIs were rare at high CD4 count, but may nevertheless be seen. OIs other than TB may be present in patients with clinically suggestive symptoms if the latest CD4 count is ≥ 2 fold above the usual CD4 threshold for that OI, and even more so if the patient has not started cART. TB at a CD4 count above 300 cells/µL should in particular be suspected in case of compatible symptoms in a person using intravenous drugs.