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

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BACKGROUND

The risk of opportunistic infections (OIs) increases substantially with increasing immunodeficiency i.e. at declining level of CD_4 cell count. Some patients, however, develop OIs at "higher than expected" CD_4 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 CD_4 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 CD_4 counts.

METHODS

The EuroSIDA study is a prospective observational cohort study of HIV-1 infected patients from 80 centres in 30 countries across Europe including Israel and Argentina. Patients were divided into three groups according to the development of three categories of OIs and CD_4 count threshold above which these OIs are traditionally considered infrequent :

- **Group 1:** CD_4 threshold › 100 cells/µL; OIs constituting end-points were defined as disease from: *Cytomegalovirus* (retinitis), *Mycobacterium avium* complex, and *Toxoplasma gondii* (cerebral) (CMV/MAC/TOXO);
- **Group 2:** CD_4 threshold › 200 cells/µL; OIs constituting end-points were defined as disease from: *Pneumocystis jiroveci* (pneumonia) and *Candidia albicans* (oesophageal) (PCP/OC);
- **Group 3:** CD_4 threshold › 300 cells/µL; OIs constituting end-points were defined as (extra)pulmonary tuberculosis (TB).

Patient follow-up began at the first prospective CD_4 count above the given threshold in the three groups (baseline). At each CD_4 count, follow-up since the last CD_4 count was calculated; person years of follow-up (PYFU) accrued in 2 categories: above or below the CD_4 count threshold, and OIs were categorised 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 CD_4 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), one 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 CD_4 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 11,229 EuroSIDA patients were available for analyses. Of those, 8.396 were eligible for inclusion in Group 1; 7.189 in Group 2; and 7.063 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 67, 112 and 33 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) CD_4 count at the time of diagnosis was 175 (120-230), 303(253-383) and 460 (394-573) cells/µL respectively, which is ‹ 2 times the predefined threshold.

Figure 1

Description of patients included

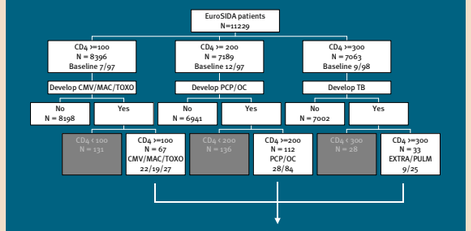

Table 1

Baseline characteristics of patients at risk of developing OIs at high CD_4 counts

		Group 1 N= 8396	Group 2 N= 7189	Group 3 N= 7063
Median (IQR)				
CD_4 count		300 (189-429)	333 (249-451)	380 (331-480)
CD_4 count Nadir		180 (87-290)	205 (100-307)	194 (81-308)
pVL log_{10}		2,75 (2,0-4,01)	2,7 (1,9-4,0)	2,6 (1,7-3,9)
Age		37 (32-44)	37 (31-44)	38 (32-45)
N (%)				
On cART		3350 (40)	2832 (39)	2922 (41)
Naïve to ART		1584 (19)	1466 (20)	1378 (20)
DSP*		2816 (33.5)	2363 (33)	97 (1)
Prior AIDS		1881 (22)	1080 (15)	1517 (22)
Exposure group	IDU	1937 (23)	1642 (23)	1494 (21)
	Other	6459(77)	5547 (77)	5569 (79)

DSP – Disease Specific Prophylaxis

Figure 2

Incidence of OIs above CD_4 threshold

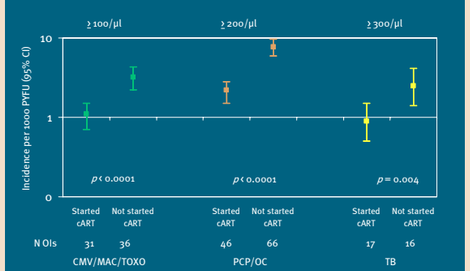

Figure 3

Incidence of OIs and latest CD_4 count

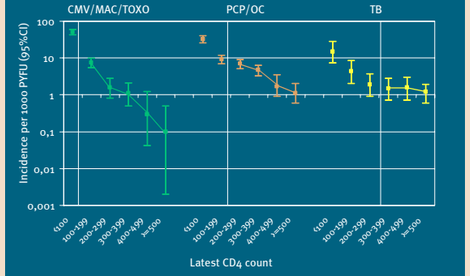

Table 2

Incidence rate ratios (IRR) for specific OIs above the given threshold

	Univariate analysis		Multivariate analysis	
Risk factors	IRR (95% CI)	p	IRR (95% CI)	p
Group 1				
Age*	0.8 (0.6-1.0)	.082	0.7 (0.5-0.9)	.016
Nadir CD_4*	0.9 (0.8-1.0)	.061	0.95 (0.8-1.1)	.531
Time from Nadir CD_4*	0.7 (0.5-0.9)	.0095	0.7 (0.6-1.0)	.042
Time with CD_4 ‹ threshold*	1.3 (1.0-1.6)	.025	0.9 (0.65-1.2)	.346
Current CD_4*	8.9 (4.2-9.1)	‹.0001	5.6 (3.9-8.3)	‹.0001
Prior AIDS	3.2 (2.0-5.2)	‹.0001	3.0 (1.8-5.0)	‹.0001
Started cART	0.4 (0.2-0.6)	‹.0001	0.5 (0.3-0.8)	.003
Group 2				
Current CD_4*	4.5 (3.1-6.7)	‹.0001	4.0 (2.7-5.9)	‹.0001
Started cART	0.3 (0.2-0.4)	‹.0001	0.5 (0.3-0.7)	.0004
Started some ART	0.2 (0.1-2.9)	‹.0001	0.4 (0.2-0.7)	.0002
IDU	2.0 (1.3-2.9)	.0008	1.6 (1.1-2.4)	.016
Group 3				
Nadir CD_4*	1.7 (1.1-2.42)	.0085	1.3 (0.8-1.9)	.280
Time from Nadir CD_4*	0.6 (0.4-0.9)	.011	0.8 (0.5-1.1)	.680
Time with CD_4 ‹ threshold*	0.8 (0.6-1.0)	.094	1.0 (0.8-1.4)	.950
Prior AIDS	0.3 (0.07-1.2)	.080	0.6 (0.13-2.6)	.460
Started cART	0.4 (0.2-0.7)	.0039	0.6 (0.2-1.2)	.130
Started some ART	0.3 (0.1-0.6)	.0023	0.7 (0.2-2.0)	.480
IDU	2.4 (1.2-5.0)	.015	2.1 (1.0-4.3)	.045

* **Age** per 10 years older; **Nadir** per 50% higher; **Current CD_4** per 50% lower; **Time from Nadir CD_4** and **with CD_4 ‹ threshold** per 12 months extra

Incidence of OIs

The incidence rate of OIs in the three groups was 1.7, 3.8, and 1.3 per 1000 PYFU, respectively. Figure 2 illustrates the incidence of OIs above the CD_4 threshold according to whether patients did or did not start cART prior to the diagnosis. In all three groups, it is clear that incidence of OIs is higher in patients not starting cART compared to those that did, regardless of CD_4 threshold.

Figure 3 shows the incidence of OIs in each group according to the latest CD_4 count. In Groups 1 and 2 there was a clear increase of the incidence of the OIs when the CD_4 count decreases below the threshold. For Group 3, the incidence of TB was significantly higher when the CD_4 count decreased below 100 cells/mm3. However, as the current CD_4 count increases above this level, there were few changes in the incidence of TB.

Predictors of development of an OI

In multivariate analyses (Table 2), the strongest predictors of OIs in groups 1 and 2 were the latest CD_4 count [Incidence Rate Ratio (IRR) per 50% lower latest CD_4 count: 5.6 (95% Confidence Interval (CI) 3.9–8.3) and 4.0 (2.7–5.9) respectively] and initiation of cART 0.5 (0.3–0.8) and 0.5 (0.3–0.7), respectively, whereas nadir and baseline CD_4 as well as duration of prior severe immunodeficiency were not predictors. The sole predictor in Group 3 was intravenous drug use [2.1 (1.0–4.3)].

In the subgroup of follow-up with available HIV-RNA (pVL), most recent values of pVL were categorised as ‹/› 3 log10 copies/ml. In group 1, after adjustment, patients with a current pVL › 3 log10 copies/ml had a 4.4 times higher incidence of CMV/MAC/TOXO compared to the patients with current pVL ‹ 3 log10 copies/ml (95% CI 1. 87 – 10.41, p = 0.0007). Similar results were observed for Group 2 (IRR = 2.63, 95% CI 1.55 – 4.48, p = 0.0004). In Group 3 results were not significant. Of note, the other multivariate factors presented in Table 2 did not change considerably after adjustment for pVL (data not shown).

CONCLUSION

The studied OIs were rare at high CD_4 count, but may nevertheless be seen. OIs other than TB may be present in patients with clinically suggestive symptoms if the latest CD_4 count is ‹ 2 fold above the usual CD_4 threshold for that OI, and even more so if the patient has not initiated cART. TB at a CD_4 count above 300 cells/µL should in particular be suspected in case of compatible symptoms in a person using intravenous drugs.

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