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Opportunistic diseases among HIV+ persons with CD4 counts ≥ 500 cells/µL: a EuroSIDA study

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INTRODUCTION

- In the START study,[1] immediate cART initiation reduced the risk of AIDS-related events by 72% when compared to cART deferral until CD4 counts dropped below 350 cells/µL.
- These were unexpected findings because START enrolled young participants with early HIV infection (CD4 >500 cells/µL at entry)
- cART reduces the risk of opportunistic diseases by recovering CD4 counts and improving immune function. However, a non-negligible number of HIV+ persons still develop opportunistic diseases after immune recovery.[2,3]

AIM

- To investigate factors associated with the development of opportunistic diseases among EuroSIDA participants with current CD4 counts >500 cells/µL.

METHODS

- EuroSIDA participants were followed from the latest of 1/1/2001 or recruitment to last visit or death (Figure 1). Participant follow-up and events were censored when current CD4 count was < 500 cells/µL.
- 3 treatment categories were defined using time-updated cART and VL:

Treatment category	Definition
Off cART	
Suboptimal response	on cART, VL > 400 copies/mL
Good response	on cART, VL < 400 copies/mL

- Opportunistic diseases were classified[4] as:

Opportunistic Diseases	Definition
Cancer	non-Hodgkin lymphomas, Kaposi sarcoma and invasive cervical cancer
Viral	CMV disease, disseminated herpes simplex, progressive multifocal encephalopathy, HIV-related encephalopathy
Bacterial	recurrent bacterial pneumonia, pulmonary and extra-pulmonary tuberculosis, nontuberculous mycobacteriosis and recurrent salmonellosis
Fungal	oesophageal candidiasis, cryptococcal meningitis, *Pneumocystis jirovecii* pneumonia
Protozoal	brain or disseminated toxoplasmosis, isosporiasis, cryptosporidiosis, visceral leishmaniasis and Chagas disease reactivation
Other	wasting syndrome and AIDS events with undetermined aetiology
Fatal AIDS	Fatal AIDS events with unknown aetiology and not classified elsewhere

- Poisson regression determined factors associated with opportunistic diseases. Generalised estimating equation models allowed multiple events per participant. Recurrences of the same event were not included.

RESULTS

- Of 11,378 persons (median age 40y, median CD4 589 cells/µL, 73.3% male, 87.7% on cART and 77.1% VL < 400 at baseline), 336 persons developed 360 opportunistic diseases during 64,716 PYFU (Figure 1) (incidence 5.6/1,000 PYFU [95% CI 5.0 - 6.1]).
- Cancer was the most common event, followed by fungal, fatal AIDS, bacterial, viral and protozoal infections (Figure 2).
- After adjustment, those with any previous opportunistic disease had an overall increased incidence of a new opportunistic disease (aIRR: 1.96[1.54-2.50]), as did those off cART (2.19[1.65-2.90] *vs* good response) and with suboptimal response to cART (2.93[2.13-4.04] *vs* good response), anaemia (2.78 [2.21-3.49]), and current smokers (1.60[1.22-2.10]).
- After adjustment, a higher nadir CD4 was associated with a marginally significantly increased incidence of cancer and a lower incidence of viral infections (Figure 3).
- Other than viral or protozoal infections, prior history of all types of opportunistic diseases was significantly associated with a new opportunistic disease after immune recovery (Figure 4).

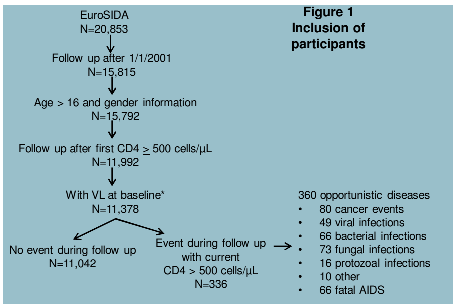
CONCLUSIONS

- A subset of HIV+ persons with CD4 ≥ 500 cells/µL, particularly those with prior history of opportunistic disease and without good response to cART, remains at subsequent risk of new opportunistic diseases.
- Clinical scores to quantify individual risk of developing opportunistic diseases after immune recovery are needed.

REFERENCES

1.Lundgren *et al* NEJM 2015; 2.Mocroft *et al* CID 2009; 3. Mocroft *et al* CID 2013; 4. d'Arminio Monforte *et al* AIM 2005

Figure 1
Inclusion of participants


EuroSIDA
N=20,853
Follow up after 1/1/2001
N=15,815
Age > 16 and gender information
N=15,792
Follow up after first CD4 ≥ 500 cells/µL
N=11,992
With VL at baseline*
N=11,378
No event during follow up
N=11,042
Event during follow up with current CD4 > 500 cells/µL
N=336
360 opportunistic diseases
80 cancer events
49 viral infections
66 bacterial infections
73 fungal infections
16 protozoal infections
10 other
66 fatal AIDS

*in 12 months prior to baseline, defined as first CD4 ≥ 500 cells/µL after 1.1.2001 and during prospective follow up

Figure 2
Crude incidence of opportunistic diseases with CD4 ≥ 500 cells/µL

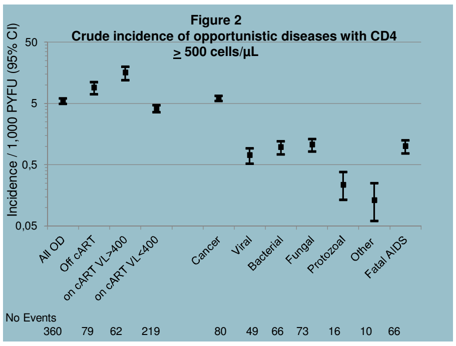
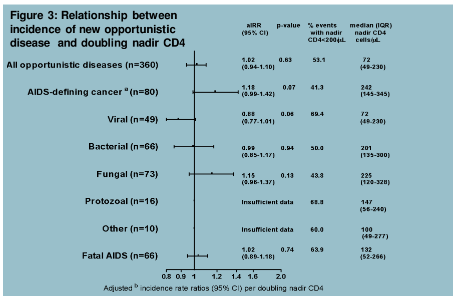
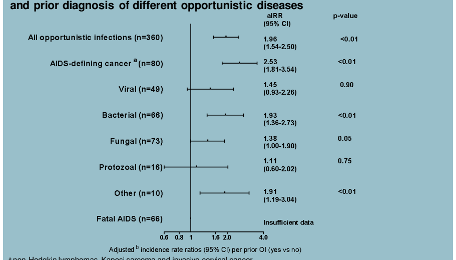


Figure 3: Relationship between incidence of new opportunistic disease and doubling nadir CD4


aIRR (95% CI)
p-value
% events with nadir CD4<200/µL
median (IQR) nadir CD4 cells/µL
All opportunistic diseases (n=360)
1.02 (0.94-1.10) 0.63 53.1 72 (49-230)
AIDS-defining cancer a (n=80)
1.18 (0.99-1.42) 0.07 41.3 242 (145-345)
Viral (n=49)
0.88 (0.77-1.01) 0.06 69.4 72 (49-230)
Bacterial (n=66)
0.99 (0.85-1.17) 0.94 50.0 201 (135-300)
Fungal (n=73)
1.15 (0.96-1.37) 0.13 43.8 225 (120-328)
Protozoal (n=16)
Insufficient data 68.8 147 (56-240)
Other (n=10)
Insufficient data 60.0 100 (49-277)
Fatal AIDS (n=66)
1.02 (0.89-1.18) 0.74 63.9 132 (52-266)
0.8 0.9 1 1.2 1.4 1.6 2.0
Adjusted b incidence rate ratios (95% CI) per doubling nadir CD4

[a] non-Hodgkin lymphomas, Kaposi sarcoma and invasive cervical cancer
[b] Models adjusted for treatment category, current CD4 count, prior OI, prior non-AIDS event, anaemia and smoking status as time dependent variables. Anaemia was defined as a haemoglobin <14 mg/dl for males and <12 mg/dl for females. Treatment categories were defined as off cART; on cART, VL < 400 (good response); on cART, VL > 400 (intermediate response)

Figure 4: Relationship between a new diagnosis of opportunistic disease and prior diagnosis of different opportunistic diseases


aIRR (95% CI)
p-value
All opportunistic infections (n=360)
1.96 (1.54-2.50) <0.01
AIDS-defining cancer a (n=80)
2.53 (1.81-3.54) <0.01
Viral (n=49)
1.45 (0.93-2.26) 0.90
Bacterial (n=66)
1.93 (1.36-2.73) <0.01
Fungal (n=73)
1.38 (1.00-1.90) 0.05
Protozoal (n=16)
1.11 (0.60-2.02) 0.75
Other (n=10)
1.91 (1.19-3.04) <0.01
Fatal AIDS (n=66)
Insufficient data
0.6 0.8 1 1.6 2.0 4.0
Adjusted b incidence rate ratios (95% CI) per prior OI (yes vs no)

[a] non-Hodgkin lymphomas, Kaposi sarcoma and invasive cervical cancer
[b] Models adjusted for treatment category, current CD4 count, prior OI, prior non-AIDS event, anaemia and smoking status as time dependent variables. Anaemia was defined as a haemoglobin <14 mg/dl for males and <12 mg/dl for females. Treatment categories were defined as off cART; on cART, VL < 400 (good response); on cART, VL > 400 (intermediate response)

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