

## Opportunistic infections in immunocompromised but virologically suppressed HIV-1 infected patients

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for the EuroSIDA study group

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### BACKGROUND

- A low CD4 count and a high viral load (VL) are associated with clinical progression to AIDS or death.
- Limited knowledge of the relative risk in patients with a low CD4 count and a suppressed VL
- There may be different predictors of disease progression and death specific to these particular patients compared to those with unsuppressed VL

### AIMS

To compare the incidence of opportunistic infections (OIs) and death in immunocompromised patients with a CD4 count  $\leq$  200 cells/mm<sup>3</sup> between those with:

- VL < 500 copies/mL whilst on combination antiretroviral therapy (cART): VL<500 on cART
- VL  $\geq$  500 copies/mL whilst on cART: VL $\geq$ 500 on cART
- VL  $\geq$  500 copies/mL whilst off all ART: VL $\geq$ 500 no ART (including ART-naïve patients and those who had discontinued treatment)

### INCLUSION CRITERIA

Patients were included who had:

- $\geq$  1 month's prospective follow-up with a CD4 count  $\leq$  200 cells/mm<sup>3</sup> after Jan 1997
- a VL measured within 6 months before the CD4 count

A given month for a given patient contributed to the person-years of follow-up (PYFU) if the most recent CD4 count measured was  $\leq$  200 cells/mm<sup>3</sup> with a VL measured within the previous 6 months.

### METHODS

- cART was defined as at least 3 drugs including a PI, NNRTI or abacavir
- PYFU were split into the 3 groups according to most recent VL and treatment
- PYFU contributed by a patient were not necessarily consecutive and a patient could be included in more than one group
- Incidence rates of OIs and death were calculated as number of events per 100 PYFU
- Multivariable Poisson regression models were used to determine the predictors of OIs and death, adjusted for repeated events per patient

### RESULTS

- 4,924 patients were included: 3,164 patients with VL<500 on cART, 3,537 with VL $\geq$ 500 on cART and 1,601 with VL $\geq$ 500 no ART
- 7,686 PYFU were included: 3,225 PYFU with VL<500 on cART, 3,624 with VL $\geq$ 500 on cART and 837 with VL $\geq$ 500 no ART
- 70% of PYFU were from white males, 41% homosexual, 25% injecting drug users and 25% heterosexual
- 53% of PYFU were after an AIDS diagnosis. PCP prophylaxis had been previously used in 90%
- CD4 counts were lowest in PYFU with VL $\geq$ 500 no ART (46% < 100 cells/mm<sup>3</sup>) and highest in VL<500 on cART (80%  $\geq$  100 cells/mm<sup>3</sup>)
- Viral loads were highest in VL $\geq$ 500 no ART (83%  $\geq$  10000 copies/mL compared to 63% in VL $\geq$ 500 on cART)
- Patients started cART a median time of 1.7 (IQR: 0.7-4.2) years prior to first VL<500 on cART and 1.0 (IQR: 0.3-2.6) years prior to first VL $\geq$ 500 on cART
- Of 3,624 patients with VL $\geq$ 500 on cART, 1,345 (38%) had previously had VL suppression a median time of 8 (IQR: 4-19) months before first VL $\geq$ 500 on cART
- 462 patients (29%) with VL $\geq$ 500 no ART had never started cART and 265 (17%) had never started any ART. Among those that had, the median time since stopping cART was 1.0 (IQR: 0.5-5.2) months
- The overall incidence of OIs and death was found to be lowest in the VL<500 on cART group: 5 events per 100 PYFU compared to 13 events per 100 PYFU in VL $\geq$ 500 on cART and 53 events per 100 PYFU in VL $\geq$ 500 no ART. The 5 most common OIs that occurred are displayed in Figure 1
- Figure 2 shows the incidence rate ratios of OIs and deaths. After adjustment for the variables listed in the figure, the rate of OIs in VL $\geq$ 500 on cART was significantly higher and almost twice that of VL<500 on cART. The patients off treatment had a rate 4 times that of VL<500 on cART. Overall death rates in VL $\geq$ 500 no ART were nearly 10 times that of the rate in VL<500 on cART. However, the rate in VL $\geq$ 500 on cART was slightly lower
- Figure 3 shows that it was a lower rate of non HIV-related deaths in VL $\geq$ 500 on cART that had resulted in the unexpected lower overall death rate ratio. The rate of HIV-related deaths in VL $\geq$ 500 on cART was higher than that in VL<500 on cART after adjustment, although not significantly
- A sensitivity analysis was carried out excluding deaths that occurred within 3 months of stopping treatment. In VL $\geq$ 500 no ART this reduced the HIV-related death rate ratio to 11.8 and the non HIV-related death rate ratio to 3.4
- A further sensitivity analysis defined 4 groups VL<50 on cART, VL50-499 on cART, VL $\geq$ 500 on cART and VL $\geq$ 500 no ART taking only PYFU where the viral load assays used had a limit of detection  $\leq$  50, leaving a total of 6655 PYFU. Similar patterns were observed with VL<50 on cART having the lowest rate of OIs. HIV death rates were similar between the first three groups all on cART. The non HIV death rate was lowest in VL $\geq$ 500 on cART

### CONCLUSIONS

- Achieving full VL suppression in immunocompromised patients with a CD4 count  $\leq$  200 cells/mm<sup>3</sup> is important for reducing the risk of OIs
- Use of cART in patients with unsuppressed VLs also reduces the risk, suggesting a beneficial effect over and above what can be explained by suppression of VL and increases in CD4 count
- Patients on cART have a much lower risk of death than those not receiving cART, regardless of VL suppression
- Part of this difference in risk of death was due to terminally ill patients being taken off cART and part was due to non HIV-related deaths
- Non HIV-related death rate was lower in those with an unsuppressed VL on cART compared to a suppressed VL - further investigation into competing risks and specific causes of death is needed to explain this

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Figure 1

### Rates of most common OIs

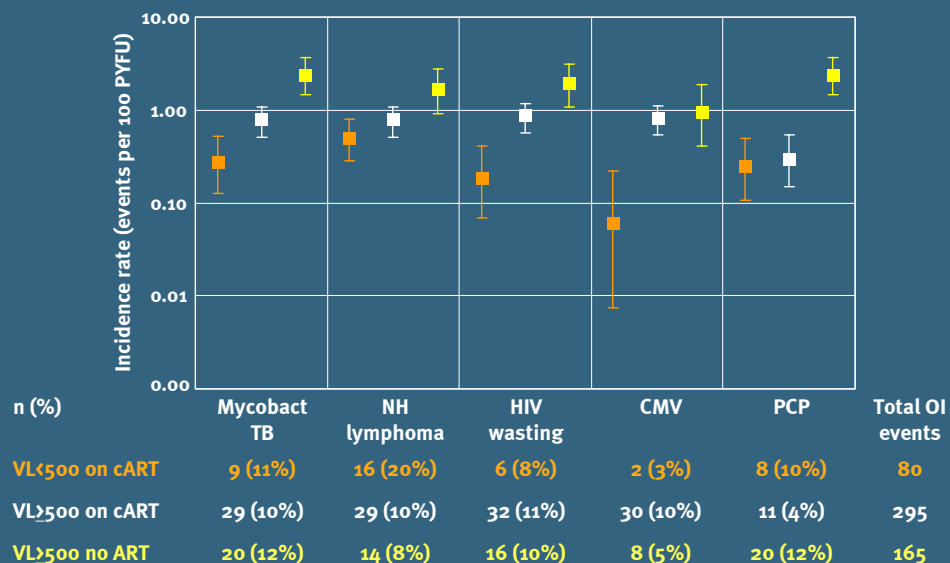
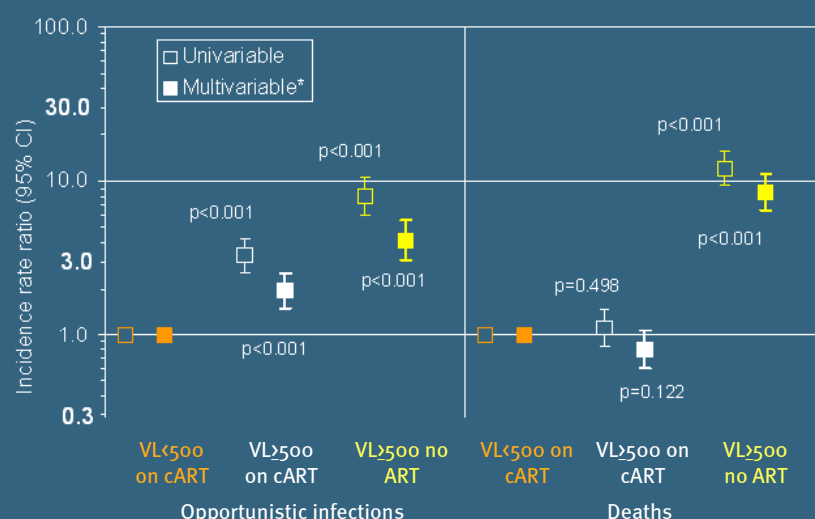


Figure 2

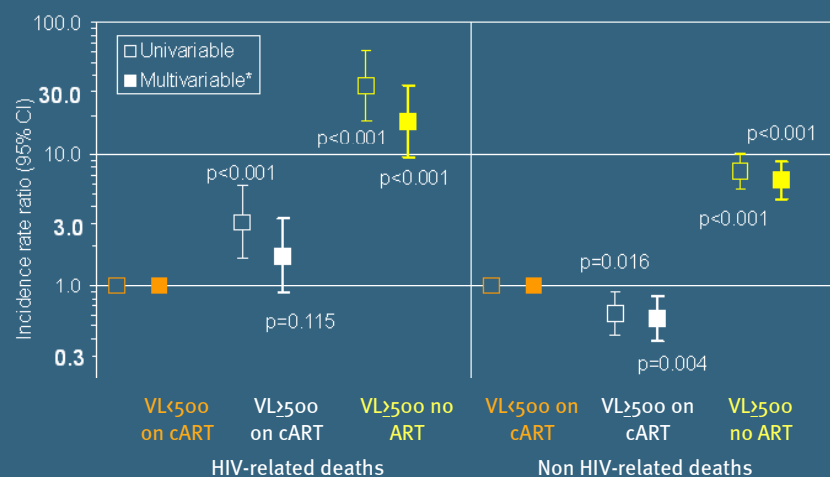
### Incidence rate ratios of OIs and deaths



\*Multivariable analyses adjusted for current CD4 count, VL, calendar time of follow-up, age, whether or not ART-naïve, ethnicity, risk group, hepatitis B and C status, whether or not received OI prophylaxis, and for death rates, prior AIDS diagnosis.

Figure 3

### Incidence rate ratios of HIV and non HIV-related deaths



\*Multivariable analyses adjusted for current CD4 count, VL, calendar time of follow-up, age, whether or not ART-naïve, ethnicity, risk group, hepatitis B and C status, whether or not received OI prophylaxis, and for death rates, prior AIDS diagnosis.

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