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

W Bannister[1], A Mocroft[1], O Kirk[2], P Reiss[3], A d'Arminio-Monforte[4], J Gatell[5], M Fisher[6], H Trocha[7], A Rakhmanova[8] and JD Lundgren[2,9] for the EuroSIDA study group

[1]UCL Medical School, London, United Kingdom; [2]Copenhagen HIV Programme, Panum Institute, Copenhagen, Denmark; [3]Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam, The Netherlands; [4]Istituto Di Clinica Malattie Infettive e Tropicale, Milan, Italy; [5]Hospital Clinic i Provincial, Barcelona, Spain; [6]Royal Sussex County Hospital, Brighton, United Kingdom; [7]Medical University, Gdansk, Poland; [8]Medical Academy Botkin Hospital, St Petersburg, Russia; [9]Centre for Viral Disease KMA, Rigshospitalet, Copenhagen, Denmark

Wendy Bannister
w.bannister@pcps.ucl.ac.uk
Research Dept of Infection & Population Health
UCL Medical School
Royal Free Campus
Rowland Hill St
LONDON
NW3 2PF
Tel: 44 (0)2078302239

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 ≤ 200 cells/mm³ between those with:

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

INCLUSION CRITERIA

Patients were included who had:

- ≥ 1 month's prospective follow-up with a CD4 count ≤ 200 cells/mm³ 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 ≤ 200 cells/mm³ 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

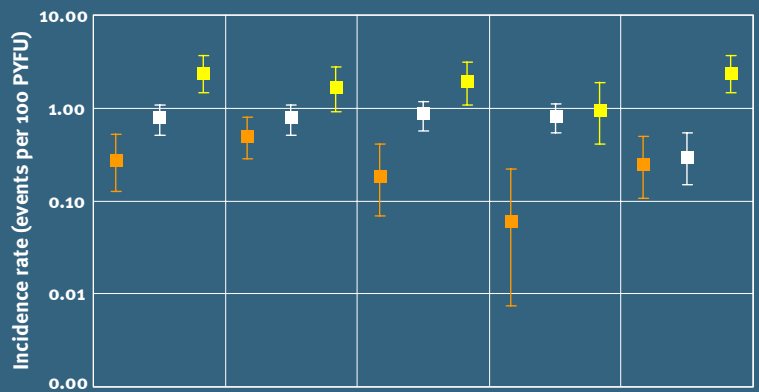
- 4,924 patients were included: 3,164 patients with VL<500 on cART, 3,537 with VL≥500 on cART and 1,601 with VL≥500 no ART
- 7,686 PYFU were included: 3,225 PYFU with VL<500 on cART, 3,624 with VL≥500 on cART and 837 with VL≥500 no ART
- 70% of PYFU were from white males, 41% homosexual, 25% injecting 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≥500 no ART (46% < 100 cells/mm³) and highest in VL<500 on cART (80% ≥ 100 cells/mm³)
- Viral loads were highest in VL≥500 no ART (83% ≥ 10000 copies/mL compared to 63% in VL≥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≥500 on cART
- Of 3,624 patients with VL≥500 on cART, 1,345 (38%) had previously had VL suppression a median time of 8 (IQR: 4-19) months before first VL≥500 on cART
- 462 patients (29%) with VL≥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≥500 on cART and 53 events per 100 PYFU in VL≥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≥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≥500 no ART were nearly 10 times that of the rate in VL<500 on cART. However, the rate in VL≥500 on cART was slightly lower
- **Figure 3** shows that it was a lower rate of non HIV-related deaths in VL≥500 on cART that had resulted in the unexpected lower overall death rate ratio. The rate of HIV-related deaths in VL≥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≥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≥500 on cART and VL≥500 no ART taking only PYFU where the viral load assays used had a limit of detection ≤ 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≥500 on cART

CONCLUSIONS

- Achieving full VL suppression in immunocompromised patients with a CD4 count ≤ 200 cells/mm³ 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

Figure 1

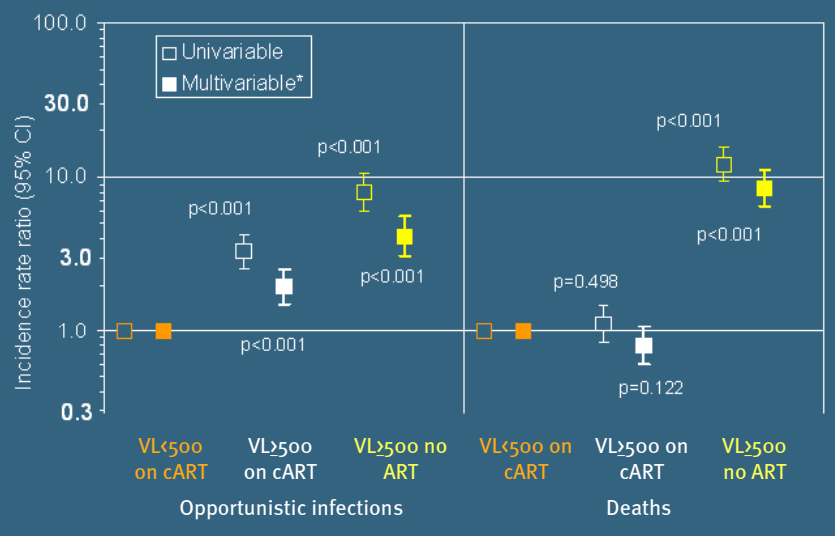
Rates of most common OIs



n (%)	Mycobact TB	NH lymphoma	HIV wasting	CMV	PCP	Total OI events
VL<500 on cART	9 (11%)	16 (20%)	6 (8%)	2 (3%)	8 (10%)	80
VL≥500 on cART	29 (10%)	29 (10%)	32 (11%)	30 (10%)	11 (4%)	295
VL≥500 no ART	20 (12%)	14 (8%)	16 (10%)	8 (5%)	20 (12%)	165

Figure 2

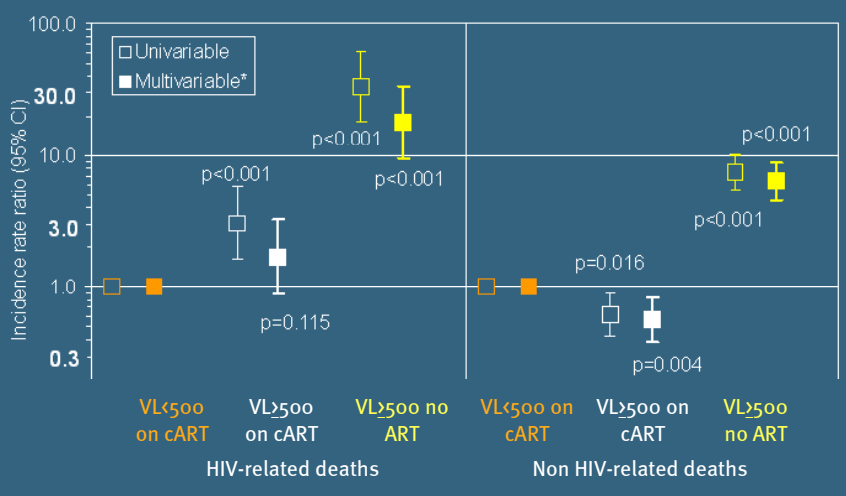
Incidence rate ratios of OIs and deaths



*Multivariable analyses adjusted for current CD4 count, VL, calendar time of follow-up, age, whether or not ART-naive, 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-naive, 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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