CMV VIREMIA AND DISEASE IN VERY ADVANCED LATE PRESENTERS: AN ADVANZ-4 TRIAL SUBSTUDY

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BACKGROUND

The incidence of cytomegalovirus (CMV) end-organ disease (EOD) in patients with advanced HIV infection has dropped dramatically since the introduction of antiretroviral treatment (ART). In early studies CMV viremia was identified as a predictor of worse prognosis. Data regarding the clinical and immunological significance of CMV viremia with current ART options are still missing.

METHODS

-The Advanz-4 trial (NCT02337322) is a multicenter, randomized clinical trial that included 104 ART-naïve HIV-1 infected patients with <100 CD4+ T-lymphocytes (TL)/mm3 randomly assigned 1:1 to receive DTG or DRV/r plus ABC+3TC (data presented in CROI 2021, abstract number: 412).

-Patients were followed up for 48 weeks.

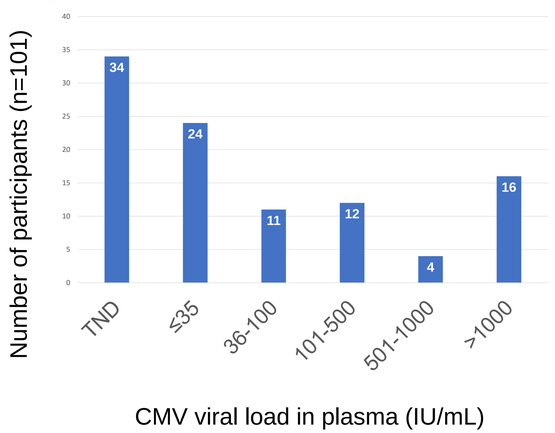
-We measured plasma CMV viral load (VL) by qPCR and CMV-specific IgG/IgM at baseline (BL).

-Endpoints: The primary endpoint was the incidence of CMV EOD. Secondary endpoints were the proportion of patients with undetectable HIV VL, IRIS, inflammation markers, immune activation, HIV disease progression and death. Anti-CMV treatment was left to the discretion of the treating physician.

-A mITT analysis was done (3 patients in the DRV/r arm were excluded, none started the study medication).

-Statistical analysis was performed using SAS v9.4.

Figure 1. CMV viral load in plasma at BL



Even though the prevalence of CMV viremia at baseline was high (42.4%) in ART-naïve patients with advanced HIV infection, the incidence of CMV end organ diseases was low (7.9%). ***CMV viremia seems to be a marker of severe immunosuppression***, as participants with detectable CMV viremia at baseline had lower CD4+ TL counts at baseline, a lower proportion of HIV virological suppression at week 48 and a higher rate of IRIS and AIDS events. Inflammation and immune activation markers were similar in patients with and without CMV viremia.

mITT analysis	Total (n=101)	Detectable CMV viremia (n=43)	Undetectable CMV viremia (n=58)	p-value
Age, years, median (IQR)	41 (31-47)	41 (32-52)	38.5 (31-47)	0.460
Sex, female, n (%)	14 (13.9)	6 (14.9)	8 (13.8)	1.000
Baseline AIDS-defining event, n (%)	42 (41.6)	22 (51.2)	20 (34.5)	0.100
Baseline HIV VL, copies/mL, median (IQR)	367643.5 (79146-1245000)	824869.5 (272000-2270000)	173100 (65702-804000)	0.001
Baseline CMV-specific IgG positive, n (%)	96 (95.05)	43 (100.00)	53 (91.38)	0.070
Baseline CD4+ TL, cells/mm3, median (IQR)	33.5 (10.5-67.5)	22 (10-48.3)	38 (17.4-74.1)	0.056
Week 48 CD4+ TL, cells/mm3, median (IQR)	226 (163-326)	282 (182-377)	200 (132-293)	0.004
Week 48 HIV VL <50 copies/mL, n (%)	71 (70.3)	24 (66.7)	47 (88.7)	0.016
CMV EOD, n (%)	8 (7.9)	8 (18.6)	0 (0)	<0.001
New AIDS event, n (%)	9 (8.9)	7 (16.3)	2 (3.5)	0.035
IRIS, n (%)	11 (10.9)	11 (25.6)	0 (0)	<0.001
CMV-related IRIS, n (%)	5 (4.9)	5 (11.6)	0 (0)	0.028

RESULTS

-At BL 43 (42.6%) patients had detectable CMV VL (DCV) (median:386 IU/mL, IQR:77-2130).

-There were no differences in BL CMV VL between ART arms (p=1.000).

-CMV disease: 8 (7.9%) patients developed CMV EOD (5 with unmasking CMV-related IRIS): 3 multiorgan involvement (including retinitis), 2 gastrointestinal infections, 1 myelitis, 1 pneumonitis, 1 CMV syndrome. All cases of CMV EOD occurred in participants with detectable CMV viremia at BL. 6/21 (30.0%) participants with CMV VL >500 IU/mL developed CMV EOD compared to 2/80 (2.5%) participants with CMV VL ≤500 IU/mL (p<0.001). Participants who developed CMV EOD had lower BL CD4+ TL counts (9 vs. 35 cells/mm3, p=0.018), but there were no differences in HIV VL at BL, proportion of patients with undetectable HIV VL at week 48 or CD4+ TL counts at week 48 (p>0.05 for all comparisons).

-Only 1 patient died (not CMV-related).

-BL HIV VL was higher in the DCV group, but there were no differences in BL CD4+TL values. At week 48, there was a lower proportion of patients with undetectable HIV VL in the DCV group but a greater increase in CD4+TL values.

-All the 11 cases of IRIS and most of the new AIDS events occurred in the DCV group.

-Inflammation (TNF-α, IL-6, hsCRP) and immune activation (CD8+CD38+TL, CD8+CD38+DR+) markers were similar at BL and declined similarly in both groups (p>0.05 for all comparisons).

CONCLUSIONS

Although the incidence of CMV EOD in patients with advanced HIV infection is low, CMV viremia seems to be associated with a worse immunovirological situation and a higher rate of IRIS and AIDS events, probably marking a deeper degree of immunosuppression. We found no association between CMV viremia and inflammation or immune activation.

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