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Impact of cytomegalovirus infection on the progression of TB disease in people with HIV on ART

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BACKGROUND

- Emerging evidence from epidemiological and immunological studies suggest there is a relationship between human cytomegalovirus (HCMV) infection and progression to tuberculosis (TB) disease.
- This study aimed to evaluate the temporal relationship of HCMV infection on TB progression in people with HIV (PWH).

METHODS

- We conducted a matched nested case-control study within the HIV-NAT 006 (HN006) prospective, clinic-based cohort that has enrolled adults PWH aged ≥ 18 years.
- In this cohort, participants were seen every 6 months at HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand.
- The stored plasma samples from PWH who developed active TB after stable ART (cases) were assessed for HCMV infection.
- For controls, we selected stored samples from PWH in the same cohort who did not develop TB disease, matched in a 1:2 ratio by ART duration.
- HCMV DNA, HCMV IgM, and IgG were measured at 3 timepoints: (1) 6-24 months before TB diagnosis (pre-TB visit) (2) at TB diagnosis (TB visit), and (3) 6-24 months after TB diagnosis (post-TB visit)
- HCMV viremia was defined as detectable CMV DNA in plasma.

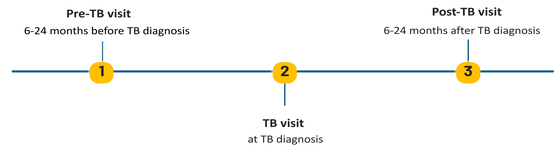
Table 1. Characteristics of TB case and control participants at the matched visit (TB diagnosis visit)

Clinical characteristics	TB patients (N=34)	Controls (N=68)
Age (years), median (IQR)	41.7 (33.8-51.4)	44.3 (37.5-52.2)
Males, N (%)	19 (56)	41 (60)
BMI (kg/m^2), median (IQR)	19.8 (17.7-21.6)	23.7 (21.7-26.4)
CD4 cell count (cells/mm^3), median (IQR)	427 (213-611)	606 (449-864)
Duration of ART (years), median (IQR)	11.1 (6.2-17.6)	10.6 (6.7-17.2)

CONCLUSIONS

- **We found no evidence suggesting HCMV viremia and HCMV serology were associated with the progression of TB disease over a period of 6-24 months.**
- **At TB diagnosis, PWH with TB had higher prevalence of HCMV viremia and higher GMC of HCMV IgM, possibly reflecting HCMV reactivation due to TB disease.**

The stored samples were measured for HCMV DNA, HCMV IgM, and IgG at 3 timepoints



RESULTS

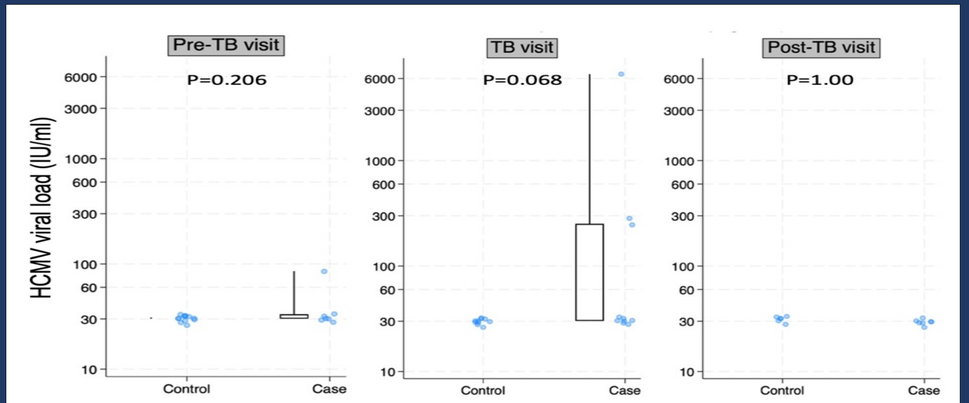
- A total of 34 TB cases and 68 control PWH were enrolled.
- 100% of participants were HCMV IgG seropositive.
- All of the TB cases had drug-susceptible pulmonary TB and received the standard 6-month treatment regimen.
- At the pre-TB visit, we observed no significant differences in the proportion of HCMV viremia (21% vs18%; p=0.719), HCMV IgM geometric mean concentration (GMC) (0.13 (95%CI 0.10-0.16) vs 0.12 (95%CI 0.10-0.13), p=0.402), and HCMV IgG GMC (225.6 (95%CI 210.2-242.1) vs 206.6 (95%CI 190.2-224.6), p=0.179) among TB cases and controls.
- At TB visit, we found the proportion of HCMV viremia was higher among TB cases (35% vs 14%, p= 0.028), median HCMV viral titer was 30 IU/ml (IQR 30-251, range 30-6,606) in the cases vs 30 IU/ml (IQR 30-30, range 30-30 IU/mL) in the controls (p=0.068) (Figure 1.)
- The HCMV IgM GMC at the TB visit was higher in the TB group than control (0.17 (95%CI 0.12-0.23) vs 0.12 (95%CI 0.10-0.14) AU/ml, geometric mean ratio (GMR)=1.38 (95%CI 1.01-1.87, p=0.039).

Table 2. Summary of HCMV viremia, HCMV serology in participants by visit

Visit	Group	HCMV viremia, n/N (%)	p-value	HCMV viral load if detectable Median (IQR) IU/mL	p-value[c]	HCMV IgM GMCs (95%CI) AU/ml	GMR (95%CI)	p-value[d]	HCMV IgG GMCs (95%CI) AU/ml	GMR (95%CI)	p-value[d]
Pre-TB	TB	7/34 (21%)	0.719[a]	30 (30-33)	0.206	0.13 (0.10-0.16)	1.11 (0.86-1.44)	0.402	225.58 (210.16-242.12)	1.09 (0.96-1.24)	0.179
	Control	12/68 (18%)		30 (30-30)		0.12 (0.10-0.13)			206.6 (190.15-224.62)		
TB-Dx	TB	10/29 (35%)	0.028[a]	30 (30-251)	0.068	0.17 (0.12-0.23)	1.38 (1.01-1.87)	0.039	232.00 (216.64-248.45)	1.13 (0.98-1.29)	0.081
	Control	8/58 (14%)		30 (30-30)		0.12 (0.10-0.14)			205.47 (188.04-224.50)		
Post-TB	TB	7/22 (32%)	0.006[b]	30 (30-30)	1.000	0.15 (0.11-0.21)	1.20 (0.83-1.73)	0.317	234.49 (218.37-251.81)	1.12 (0.98-1.27)	0.078
	Control	2/44 (5%)		30 (30-30)		0.12 (0.10-0.15)			209.24 (193.00-226.85)		

[a] Chi-square test, [b] Fisher's exact test, [c] Mann-Whitney-U test, [d] t-test
GMC: Geometric mean concentrations, GMR: Geometric mean ratio

Figure 1. Level of detectable HCMV viral load by visit and study group



When any HCMV DNA values are above detection limit, boxes represent median and 75th percentile, whiskers represent maximum values

ACKNOWLEDGEMENTS

The authors would like to thank the HIV-NAT 006 study participants and the study team for their contribution to this cohort.

FUNDING

This study was supported by a grant from the Mr. Willem Bakhuys Roozeboomstichting, Amsterdam, Netherlands.

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