Use of plasma human herpesvirus 8 (HHV8) viral load measurement: a joint evaluation of practice in 3 HIV units

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Background

HHV8-related diseases, including multicentric Castleman disease (MCD), Kaposi sarcoma (KS) and lymphoma cause significant morbidity in HIV-infected patients. HHV8 is known to be detectable by PCR in the plasma of patients with HHV8-related pathology. However there is controversy regarding the clinical utility of plasma HHV8 measurement[1,2] and a lack of guidance on the indications for testing.

Methods

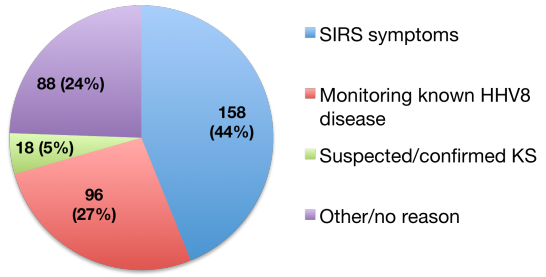
We performed a retrospective audit of all plasma HHV8 viral load tests across our network of 3 large UK HIV treatment centres from 01/01/2012 to 01/01/2014. We reviewed case notes and laboratory results and recorded HHV8 DNA quantitation, indications for testing, patient demographics, ART use and concurrent HIV viral load and CD4 measurements. Confirmed HHV8-related diagnoses were also recorded. Case notes of patients with detectable HHV8 without a HHV8-related diagnosis were reviewed again 24 months after the audit period for subsequent relevant diagnoses.

Results

Reasons for testing plasma HHV8

- A total of 360 tests were requested across our 3 sites in the 24 months for which records were examined
- Reasons for testing were (i) symptoms of systemic inflammatory response syndrome (SIRS) such as fever, lymphadenopathy and raised inflammatory markers; (ii) monitoring in known HHV8 pathology other than KS; (iii) known/suspected KS and (iv) other/no reason:

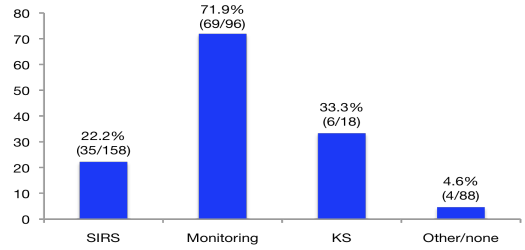
Illustration 1: *Number of HHV8 viral load tests according to reason ordered*



Incidence of detectable HHV8 in plasma

- 114/360 (31.7%) of tests ordered had detectable HHV8 levels
- The proportion of samples with detectable HHV8 according to the reason for the test is shown below:

Illustration 2: *% samples with detectable HHV8 by reason ordered*



Characteristics of patients with detectable HHV8 levels

- Patients with detectable HHV8 were more likely to be male (94% vs 68%, p<0.002 two tailed Fisher exact tests), MSM (48% vs 29%, p=0.016), be receiving ART (79% vs 64%, p=0.006) and to have an undetectable HIV viral load (59% vs 45%, p=0.0024)
- Median CD4 was 280 in those with detectable HHV8 vs 285 in those without.
- Of patients with MCD 14/16 (88%) had detectable plasma HHV8, as did 6/19 (32%) with lymphoma and 27/45 (60%) with KS. The 6 patients with lymphoma and detectable HHV8 had either primary effusion lymphoma (n=4) or plasmablastic lymphoma (n=2). Of the 2 patients with diagnosed MCD and no detectable HHV8, neither were recorded as having SIRS symptoms at the time of the test.

Variation in clinical practice between sites

Table 1: *Number of HHV8 tests ordered and number with detectable HHV 8 levels according to reason ordered broken down by site*

Site	Total patient cohort	Reason for test	Tests ordered	Detectable HHV8
Mortimer Market Centre	4200	*SIRS*	85	18 (21%)
		Monitoring	46	32 (70%)
		KS	15	6 (40%)
		Other	24	0 (0%)
Royal Free Hospital	3203	*SIRS*	16	7 (44%)
		Monitoring	33	23 (69%)
		KS	0	-
		Other	8	1 (13%)
North Middlesex Hospital	1148	*SIRS*	57	10 (18%)
		Monitoring	17	14 (82%)
		KS	3	0 (0%)
		Other	56	3 (5%)

Review at 24 months

- 18 patients had detectable HHV8 levels in the absence of any HHV8-related diagnosis during the audit period.
- 11 patients had levels of <10000 copies HHV8 DNA/ml and had no subsequent HHV8-related diagnosis
- 2 patients had levels of 30,920 and 22,000 but with no subsequent relevant diagnoses or HHV8 levels requested
- 1 patient had a level of 43 copies/ml in the absence of SIRS symptoms but was subsequently diagnosed with MCD with SIRS symptoms and a HHV8 level of 13,000
- 2 patients had very high levels (825,000 and 3,300,000) and SIRS symptoms and died soon after the tests were sent
- 1 patient with SIRS symptoms and a HHV8 level of 167,100 was later diagnosed MCD after 2 non-diagnostic biopsies during the audit period
- 1 patient, newly diagnosed with HIV, had SIRS symptoms and a HHV8 level of 577,400 which became undetectable with ART

Discussion

There is wide variation between our sites in the indications prompting HHV8 testing with a more conservative approach resulting in a higher proportion of positive results. Plasma HHV8 requests in the absence of SIRS symptoms, established HHV8 disease monitoring or confirmed/suspected KS are unlikely to yield detectable HHV8 thus allowing potential cost savings. The higher likelihood of HHV8 viraemic patients to be on suppressive ART may indicate the occurrence of HHV8 viraemia as an IRIS phenomenon[3]. Our data shows a high incidence of HHV8 viraemia in patients with MCD suggesting an undetectable HHV8 can exclude this diagnosis in patients with SIRS symptoms. Low levels (<10000) of detectable HHV8 in the absence of SIRS symptoms or known HHV8 related disease, including KS, are unlikely to be of clinical significance. Conversely, persistent high levels of symptomatic HHV8 viraemia when tissue biopsy is non-diagnostic or unavailable should prompt high suspicion of undiagnosed HHV8 related pathology. Our data add to the current understanding of the relationship between HHV8 viraemia and disease and highlight the need for clinical guidance in the use of HHV8 quantitation.

References: 1. Sayer *et al*, "Can plasma HHV8 viral load be used to differentiate multicentric Castleman disease from Kaposi sarcoma" Int J STD AIDS 2011 22: 585-589. 2. Haq *et al*, "The clinical application of plasma Kaposi sarcoma herpesvirus viral load as a tumour biomarker: results from 704 patients" HIV Medicine 2016 Jan 17(1): 56-61. 3. Lumley *et al*, "High level human herpesvirus-8 viraemia and multicentric Castleman disease following initiation of highly active antiretroviral therapy" AIDS 2014, 28: 1693-1700.