Use of plasma human herpesvirus-8 viral load measurement: evaluation of practice in three UK HIV treatment centres

DB Nugent[1], D Webster[2*], D Mabayoje[2], E Chung[1], K El Bouzidi[3,5], A O'Sullivan[4], J Ainsworth[4] and RF Miller[1,3,5]

[1]Mortimer Market Centre, Central and North West London NHS Foundation Trust

[2]Royal Free London NHS Foundation Trust

[3]University College London Hospitals NHS Foundation Trust

[4]North Middlesex University Hospital NHS Trust

[5]University College London

*Deceased

Key words: human herpesvirus-8, Kaposi sarcoma, Castleman, PCR

Word count: Abstract = 148 words

Manuscript = 849 words

Correspondence to: Dr DB Nugent, Department of Sexual Health, Mortimer Market Centre, Central and North West London NHS Foundation Trust, London WC1E 6JB, UK. Tel: +44 203 317 5253

Email: diarmuid.nugent@nhs.net

Abstract

A retrospective audit of plasma HHV-8 viral load testing was performed in three HIV treatment centres over 24 months. Reasons for testing (360 tests) were: symptoms of systemic inflammatory response syndrome (fever, lymphadenopathy and raised inflammatory markers); monitoring in known HHV-8 pathology other than Kaposi sarcoma (KS); known/suspected KS, and other/no reason. Of patients with multicentric Castleman disease (MCD) 14/16 (88%) had detectable plasma HHV-8, as did 27/45 (60%) with KS, and 6/19 (32%) with lymphoma. Neither of the two patients with MCD and no detectable HHV-8 had SIRS symptoms at the time of the test. There was wide variation between centres in the indications prompting HHV-8 testing, with a more conservative approach resulting in a higher proportion of positive results. Measuring plasma HHV-8 in the absence of SIRS symptoms, established HHV-8 disease monitoring, or confirmed/suspected KS is unlikely to yield detectable HHV-8 thus allowing potential cost savings.

Introduction

Human herpesvirus (HHV)-8-related diseases, including multicentric Castleman disease (MCD), Kaposi sarcoma (KS) and lymphoma cause significant morbidity in HIV-infected patients[1]. HHV-8 can be detected by PCR in plasma of patients with HHV-8-related pathology[2]. However, there is controversy regarding the clinical utility of plasma HHV-8 measurement in investigating patients with suspected HHV-8-related disease[3,4] and a lack of guidance on indications for testing.

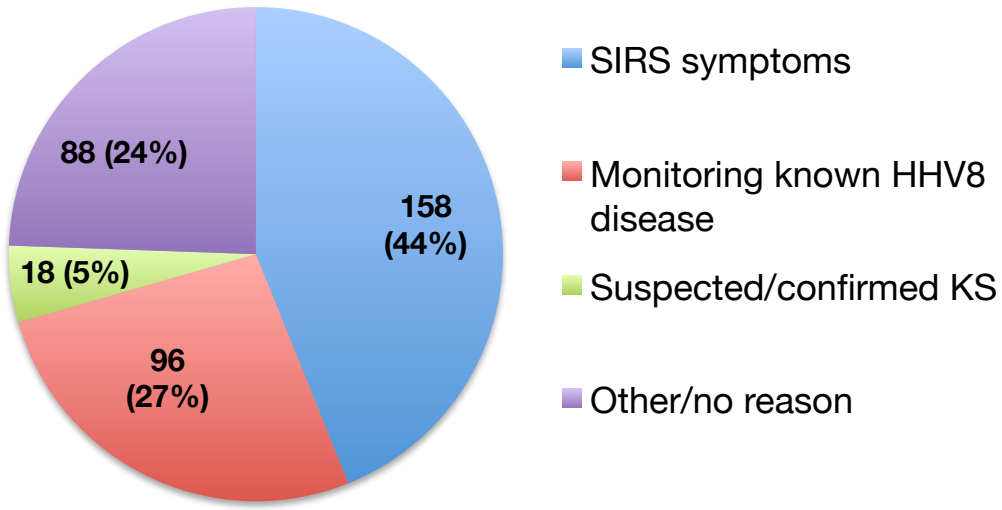
Methods

We performed a retrospective audit of plasma HHV-8 viral load testing across our network of three large UK HIV treatment centres from January 2012 to January 2013. We reviewed case notes and laboratory results and recorded plasma HHV-8 DNA quantitation, indications for testing, patient demographics, antiretroviral therapy (ART) use and concurrent HIV viral load and CD4 measurements. Confirmed HHV-8-related diagnoses were also recorded. Case notes of patients with detectable HHV-8 and without an HHV-8-related diagnosis were reviewed again 24 months after the audit period to ascertain if HHV-8-associated diagnoses had been made subsequently.

Results

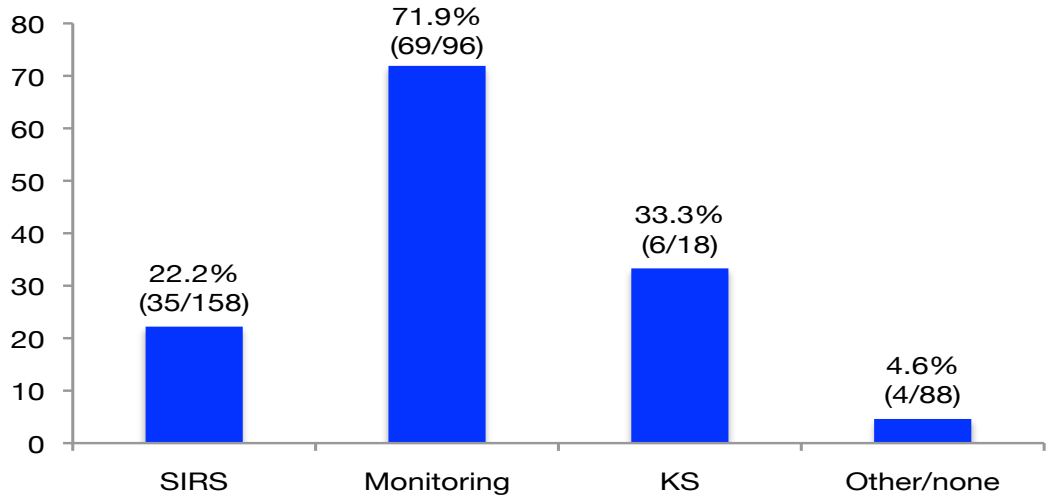
A total of 360 tests were requested across the three centres in the 24 month period. Reasons for testing were: symptoms of systemic inflammatory response syndrome (SIRS) such as fever, lymphadenopathy and raised inflammatory markers; monitoring in known HHV-8 pathology other than KS; investigation of known/suspected KS, and other/no reason (Figure 1a).

Figure 1a: Number of plasma HHV-8 DNA viral load tests by indication



Plasma HHV-8 was detectable by PCR in 114/360 (31.7%) tests. The proportion of samples with detectable HHV-8 according to the reason for the test is shown in Figure 1b.

Figure 1b**:** Proportion of samples with detectable HHV-8 by indication



Patients with detectable HHV-8 were more likely to be male (94% vs 68%, p<0.002 two tailed Fisher exact test), 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 cell count was 280 cells/mm^3 in those with detectable HHV-8 compared with 285 cells/mm^3 in those without. Of patients with MCD 14/16 (88%) had detectable plasma HHV-8, as did 27/45 (60%) with biopsy proven or clinically confirmed KS, and 6/19 (32%) with lymphoma (primary effusion lymphoma (n=4) and plasmablastic lymphoma (n=2)). Neither of the two patients with MCD and no detectable HHV-8 had SIRS symptoms at the time of the test.

Reasons for ordering plasma HHV-8 DNA quantitation varied between centres (Table 1).

Table 1: HHV-8 viral load testing: indication and yield by study centre

Centre No	Total number of HIV patients attending centre	Reason for test	Tests ordered	Detectable HHV-8
1	4200	SIRS	85	18 (21%)
		Monitoring	46	32 (70%)
		KS	15	6 (40%)
		Other	24	0 (0%)
2	3203	SIRS	16	7 (44%)
		Monitoring	33	23 (69%)
		KS	0	-
		Other	8	1 (13%)
3	1148	SIRS	57	10 (18%)
		Monitoring	17	14 (82%)
		KS	3	0 (0%)
		Other	56	3 (5%)

Eighteen patients had detectable plasma HHV-8 DNA in the absence of any HHV-8-related diagnosis during the audit period of whom sixteen had SIRS symptoms which prompted the test and four had no clear indication recorded. Their case notes were reviewed again 24 months later. Eleven patients had HHV-8 DNA levels of <10,000 copies/ml and had no subsequent HHV8-related diagnosis. Two patients had levels of 30,920 and 22,000 copies/ml but with no subsequent relevant diagnoses or HHV-8 levels requested. One patient had a level of 43 copies/ml in the absence of SIRS symptoms, but MCD was subsequently diagnosed in the context of SIRS symptoms and an HHV-8 DNA level of 13,000 copies/ml. Two patients with SIRS symptoms had very high plasma HHV-8 DNA levels (825,000 and 3,300,000 copies/ml) and died soon after the tests were sent. One patient with SIRS symptoms and an HHV-8 DNA level of 167,100 copies/ml was later diagnosed MCD after two non-diagnostic biopsies. One patient, with newly diagnosed HIV infection, had SIRS symptoms and a plasma HHV-8 DNA level of 577,400 copies/ml, which became undetectable with ART.

Discussion

There is wide variation between our centres in the indications prompting HHV-8 testing, with a more conservative approach resulting in a higher proportion of positive results. The audit suggests that measuring plasma HHV-8 in the absence of SIRS symptoms, established HHV-8 disease monitoring or confirmed/suspected KS is unlikely to yield detectable HHV-8 thus allowing potential cost savings. The higher likelihood of HHV-8 viraemic patients to be on suppressive ART is of interest given the well-documented phenomenon of MCD and HHV-8 viraemia as an immune reconstitution inflammatory syndome [5,6] in contrast to KS which usually improves or resolves with ART[7].

We found a high prevalence of HHV-8 viraemia in patients with MCD. There were two confirmed MCD patients with undetectable plasma HHV-8 levels but neither had SIRS symptoms at the time of testing suggesting the MCD was in remission. This implies that in patients presenting with SIRS symptoms, an undetectable plasma HHV-8 level makes active MCD unlikely in consistent with longitudinal cohort data[8] and with conclusions from a recent evaluation of the use of the test as a tumour biomarker[4].

The detection of HHV-8 in plasma of patients without a confirmed HHV8-related diagnosis can provoke uncertainty. Our data suggest that low HHV8 levelsin the absence of SIRS symptoms or known HHV-8 related disease are

unlikely to be of clinical significance. Nonetheless, in view of the low plasma HHV8 levels seen in some HHV8-related conditions, notably KS[3], these patients should be closely monitored for symptoms. Conversely, persistent high levels of HHV-8 viraemia in a symptomatic patient, when tissue biopsy is non-diagnostic or unavailable should arouse suspicion of undiagnosed HHV-8 related pathology and prompt further investigation.

While histological diagnosis remains the gold standard for diagnosing MCD[9,10], the condition is relapsing and remitting in nature and confirmation by tissue biopsy can be problematic. The introduction of effective therapies for MCD, particularly rituximab, has dramatically improved survival and prognosis[11], hence more attention is needed to determine whether to proceed with treatment in the absence of a histological diagnosis when clinical features suggestive of MCD are accompanied by a high plasma HHV-8 level.

This audit adds to the current understanding of the relationship between HHV-8 viraemia and disease and highlights the need for clinical guidance in the use of HHV-8 quantitation.

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