

# Differential Reduction of Human Herpesvirus 8 (HHV-8) Oropharyngeal Shedding Rates with Specific Antiretroviral Agents

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## BACKGROUND

- Antiretroviral therapy (ART) has been associated with a dramatic decline in Kaposi's sarcoma (KS) cases among persons with HIV.
- The mechanism responsible for the reduction in incidence remains undefined, but may be attributable to immune reconstitution<sup>1</sup>, anti-angiogenic factors<sup>2,3</sup>, or a direct antiviral effect on human herpesvirus 8 (HHV-8)<sup>4,5</sup>.
- Replicating HHV-8, as evidenced by viremia, has been associated with a significantly elevated risk of developing KS<sup>6,7</sup>.
- The use of ART decreases HHV-8 levels in plasma<sup>1</sup>.
- Only a small proportion of persons with KS will have HHV-8 detectable in the peripheral blood, while oropharyngeal viral shedding is far more common<sup>8</sup>. The effect of specific ART on HHV-8 oropharyngeal shedding has not been described.

## RESEARCH QUESTION

- What is the effect of ART on HHV-8 oropharyngeal shedding?

## METHODS

- Participants: 54 HIV and HHV-8 seropositive MSM from Seattle participating in studies of HHV-8 mucosal shedding from 1994-2002.
- Data Collected
  - Demographic characteristics and information on the use of antiviral / ART therapy
  - HIV plasma RNA by Roche Amplicor Monitor assay, CD4 count
  - Saliva was collected daily at home on consecutive days with the use of Dacron swabs as described previously<sup>9</sup>
  - HHV-8 quantitative DNA PCR by TaqMan<sup>10</sup> was performed on all salivary specimens
- Statistical Analysis
  - Definitions
    - HHV-8 shedding: the detection of HHV-8 DNA in saliva
    - HHV-8 shedding frequency: number of days with HHV-8 DNA detected from oral swabs / the total number of days that oral swabs were collected X 100
  - Highly active antiretroviral therapy (HAART) was defined as two nucleoside reverse transcriptase inhibitors plus either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor, while ART was defined as all other combinations of antiretroviral therapy

## RESULTS

- Participants
  - Most participants were male (94%), white (78%), and reported engaging in sex with other men (89%)
  - The median duration of HIV infection was 8.3 years since the time of first diagnosis (range 0.2-18.2 years)
  - The median CD4 count was 335 cells per mL (range 1-1122), with a moderate median HIV plasma RNA level of 6,388 copies per mL (range 7-376057)
  - 44% of participants had never used HAART, while 48% had shedding sessions collected while on HAART regimens
- Collection Sessions
  - The 54 participants collected a total of 6007 days of oral swabs over 114 sessions
    - The median number of consecutive days of swabs collected per session was 49 (range 15-208)
    - 23 participants (42.6%) collected only one session, 14 (25.9%) collected 2, 12 (22.2%) collected 3, one collected 4, 6 or 7 sessions (1.9% each), and 2 (3.7%) collected 5 sessions
- HAART Use and HHV-8 Oropharyngeal Shedding
  - Overall, HHV-8 DNA was detected in 1745 of 6007 (29%) samples. 22 of 54 (41%) participants had at least 1 positive oropharyngeal sample for HHV-8 DNA
  - Specific ART and HHV-8 Shedding Rates (Figure 1)
    - HHV-8 shedding was lowest on days with tenofovir (HHV-8 detected 0% of 123 days with tenofovir vs. 29% of 6012 days without), amprenavir (0% of 306 vs. 30% of 5829), indinavir (0% of 339 vs. 30% of 5796), lopinavir / ritonavir (0% of 295 vs. 30% of 5840) and efavirenz (0% of 613 vs. 32% of 5522).
    - Other protease inhibitors (PIs) (regimens with nelfinavir 16% vs. 31% without, saquinavir 15% vs. 30%), and nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir 10% vs. 31%, didanosine 18% vs. 30%, lamivudine 16% vs. 38% and zidovudine 26% vs. 29%) were associated with smaller differences in shedding.
    - Stavudine, zalcitabine, or nevirapine use was not associated with lower HHV-8 shedding rates.
  - Classes of ART and HHV-8 Shedding Rates
    - Shedding rates were lower on days when any PI (11% with PI vs. 40% without), NRTI (25% vs. 34%) or non-nucleoside reverse transcriptase inhibitor (NNRTI) (23% vs. 30%) were used.
    - Regimens with ≥1 drug in each class were associated with the lowest HHV-8 shedding rates (0% of 393 days), followed by the combination of NRTI and PI (13% of 1956), NRTI and NNRTI (35% of 791), and NRTI only (65% of 676). Use of >3 ART was not associated with greater reductions in HHV-8 shedding (Tables 1 and 2)

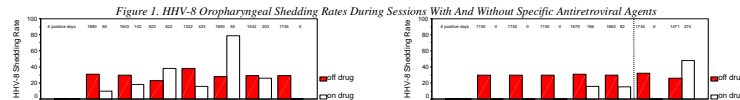


Table 1. HHV-8 Oropharyngeal Shedding Rates By Combination of ART

Drug	On Regimen			Off Regimen			Difference On vs. Off Drug (%)
	Participants (n)	Sessions (n)	HHV-8 Shedding Rate (%)	Participants (n)	Sessions (n)	HHV-8 Shedding Rate (%)	
Only NRTI	4	8	441/676 (65)	52	115	1311/5776 (23)	42
No PI, Use of 3 ARTs	7	13	209/636 (33)	49	110	1543/5816 (27)	6
> 3 ART Regimen	7	13	68/580 (12)	50	110	1684/5872 (29)	-17

Table 2. HHV-8 Oropharyngeal Shedding Rates by ART Class

Class Combinations	Participants (N)	Sessions (n)	HHV-8 Shedding Rate (%)	Median Shedding Rate (IGR)
No drugs	29	46	702/2319 (30%)	10.6 (0-77.8)
PI, NRTI, and NNRTI	7	8	0/393 (0%)	0 (0-0)
1 PI, 1 NRTI, 1 NNRTI	3	3	0/137 (0%)	
1 PI, 2 NRTI, 1 NNRTI	3	3	0/135 (0%)	
2 PI, 1 NRTI, 1 NNRTI	1	1	0/54 (0%)	
2 PI, 2 NRTI, 1 NNRTI	1	1	0/87 (0%)	
PI, NRTI	20	37	248/1956 (13%)	0 (0-7.9)
1 PI, 2 NRTI	18	24	248/1648 (15%)	
1 PI, 3 NRTI	1	1	0/58 (0%)	
2 PI, 1 NRTI	1	2	0/10 (0%)	
NRTI, NNRTI	9	17	274/1919 (14%)	0 (0-0)
2 NRTI, 1 NNRTI	7	13	209/636 (33%)	
4 NRTI, 1 NNRTI	2	4	0/153 (0%)	
NRTI only	4	8	441/676 (65%)	44 (0-94.1)
1 NRTI	2	6	388/606 (64%)	
2 NRTI	2	2	55/70 (79%)	

## LIMITATIONS

- This initial descriptive analysis does not account for factors which may confound the relationship between HHV-8 shedding and use of specific ARTs, including CD4 count and plasma HIV RNA level. Future analyses will include the construction of generalized linear-mixed models to examine these relationships, and to examine within-person effects of ART on HHV-8 shedding

## CONCLUSIONS

- The use of certain antiretroviral agents is associated with low rates of HHV-8 oropharyngeal shedding. Tenofovir, indinavir, amprenavir, lopinavir/ritonavir, and efavirenz containing-regimens result in the lowest rates of HHV-8 shedding.
- HHV-8 oropharyngeal shedding is infrequently observed on days when PI-containing regimens are used.
- The choice of ART regimen may effect HHV-8 replication, transmission, and the development of KS.

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