KAPOSI SARCOMA IN ART-TREATED PLWH: DISTINCT VIRAL AND IMMUNE CHARACTERISTICS

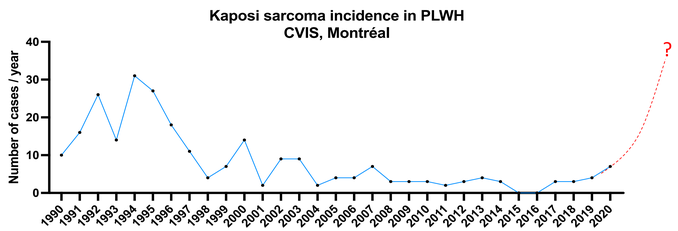
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BACKGROUND

- Incidence of HHV8-induced Kaposi sarcoma (KS) decreased in PLWH with ART
- Reemergence of cases in ART-treated PLWH with restored CD4 T-cells and HIV control



- Mostly arise in middle-age men, with cutaneous lesions similar to classic KS lesions arising in elderly men *(Royston L et al., AIDS, 2021)*

Hypothesis: HIV-induced immunosenescence is associated with a progressive decrease in HHV-8 immune control.

METHODS

Objective of the study:

- Compare virological and immunological determinants of KS in ART-treated PLWH (KS HIV+) and in HIV-uninfected people (KS HIV-)

Prospective cohort study including:

- ART-treated PLWH with undetectable HIV viral load with KS (KS HIV+, n=11)
- Age-matched ART-treated PLWH without KS (HIV+, n=11)
- HIV-uninfected people with classical KS (KS HIV-, n=11)
- Age-matched HIV-uninfected controls without KS (HIV-, n=11)

Collection of blood (PBMC/plasma) +/- skin samples.

We assessed CD4/CD8 ratios, circulating cytokines by ELISA multiplex, anti-HHV-8 IgG levels with an in-house cell-based assay, anti-HHV-8 specific T-cells by ELISPOT, and circulating and skin T-cells phenotypes by flow cytometry.
HHV-8 viral loads were quantified by digital-droplet PCR and next-generation sequencing was performed.

PLWH on ART can still develop Kaposi sarcoma despite immune reconstitution and viral control
→ immune and viral determinants

RESULTS

1) Clinical results

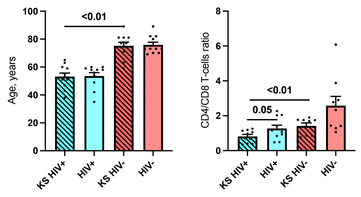
KS HIV+



KS HIV-



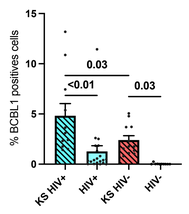
Characteristics	KS HIV+ (n=11)	HIV+ (n=11)	KS HIV- (n=11)	HIV- (n=11)
Age, years (range)	**53.0** (38-65)	53.5 (35-60)	**78.3** (71-89)	76.5 (70-89)
Sex, % males	100%	100%	80%	80%
CD4 T-cells/µL (range)	579 (234, 1099)	509 (346, 1172)	437 (46-730)	929 (517, 1271)
CD8 T-cells/µL (range)	608 (357, 1919)	473 (224, 1488)	394 (200, 582)	373 (186-948)
CD4:CD8 ratio (range)	**0.73** (0.3, 1.2)	0.91 (0.4, 2.3)	**1.31** (0.2-1.9)	2.33 (1.1, 6.1)
HIV VL, log10 copies/mL	<1.7	<1.7	N/A	N/A
HIV RNA/int DNA (range)	5.4 (0.5-32)	3.1 (0.4-5.7)	N/A	N/A



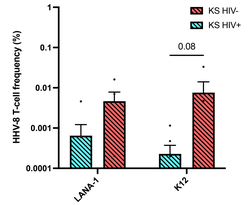
- Only skin lesions
- KS HIV+ younger than KS HIV-
- CD4/CD8 ratios ↘ in KS HIV+ compared to KS HIV- and to HIV+
- Tendency for larger transcriptionally active HIV reservoir in KS HIV+

2) Immunological results

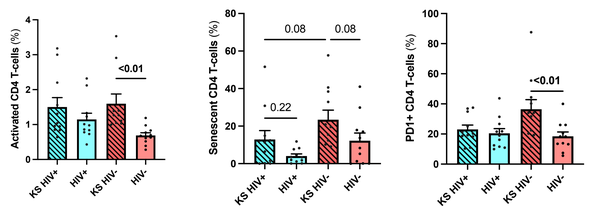
A. Anti-HHV-8 IgGs



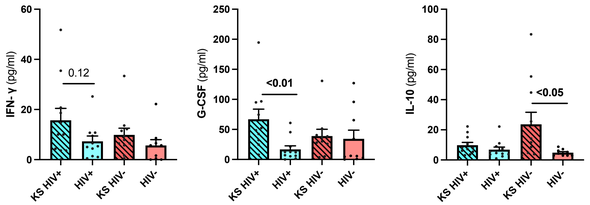
B. Anti-HHV8 T-cell response



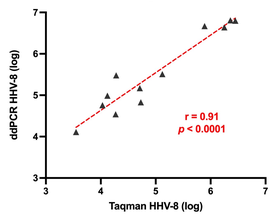
C. T-cell phenotype in skin biopsies



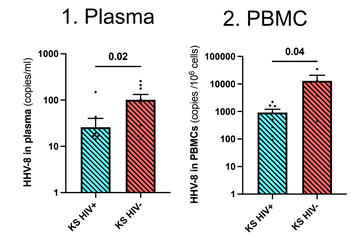
D. Circulating cytokines



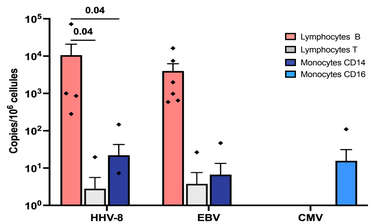
A. HHV-8 ddPCR assay development



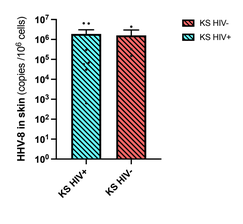
B. HHV-8 quantification in samples



3. Cell types

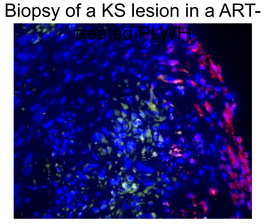


4. Skin lesions



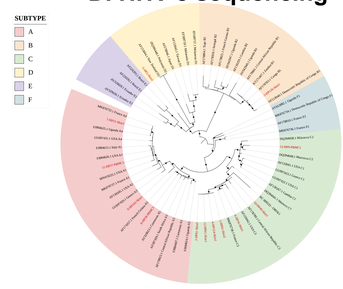
C. HHV-8 detection in tissues

Biopsy of a KS lesion in a ART-treated PLWH



Green: HHV-8 Pink: CD3 Red: CD8

D. HHV-8 sequencing



KS HIV+: genotypes A (3) & C (4)
KS HIV-: genotypes A (2) & C (2)
+ **1 new subtype (2 inuit patients)**

CONCLUSIONS

- KS in ART-treated PLWH compared to classic KS: younger age, decreased CD4/CD8 ratio
- Compared to age-matched PLWH, KS HIV+ exhibited features of early immune senescence, with a ↘ CD4/CD8 ratio and ↗ frequency of CD57+/CD28- T-cells.
- HHV-8 viral control differs between KS HIV+ and KS HIV-:
  - KS HIV+ vs HIV-: ↘ HHV-8 VL in plasma/PBMC, ↘ anti-HHV-8 T-cell response but ↗ anti-HHV-8 IgG.
  - Genotypes of HHV-8 strains: subtypes A and C + 1 new subtype.

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