Kaposi's sarcoma-associate herpesvirus (KSHV) is recognized as the etiologic agent of all epidemiological forms of Kaposi's sarcoma (KS), including classic, endemic, iatrogenic, and epidemics (associated to HIV-infection) forms. This virus is also involved in the development of lymphoid malignancies, particularly primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD). In individuals of Western countries, KS prevalence is low in general population (<5%), whereas a significantly higher prevalence has been described in men who have sex with men (MSM). Among them, KSHV-acquisition was mainly linked to sexual behavior.

At the end of left KSHV genome, the open reading frame K1 (ORF-K1) encodes a transmembrane glycoprotein whose amino acid sequences varies from 20% to 40% between KSHV subtype and from about 10% within subtype.

The distribution of KSHV subtype was mainly related to geographic region and ethnicity: subtype A and C were found in Europe, North America, Middle East, Mediterranean basin and Asia, subtype B and A5 predominately in Sub-Saharan Africa, subtype D in the Pacific Island and Taiwan, subtype E in Brazilian Indians, subtype Z as a small cohort of Cuban children and subtype F in individuals from Uganda.

However, there has been suggested that subtypes differed according to clinical presentation or progression, but this remains to be clarified, results from different studies studies were conflicting.

Objectives
- Patients were included retrospectively in 4 infectious diseases department (Bichat, Pitié-Salpétreire, Saint-Antoine and Tenon hospitals), Paris, France.
- 57 MSM were positive with KSHV-associated diseases diagnosed between 2010 and 2017
- 8 samples under HIV Pre-exposure prophylaxis (PrEP) with positive KSHV-association.

Methods
- **Materials and methods**

  **1. ORF-K1 phylogenetic analysis**
  **Among the 65 patients included, KSHV-typing was contributions for 1984 (46%) with KSHV, 11/129 (92%) with MCD, 64/1005 (10%) with PEL and 58/252 (23%) under HIV-PEP**
  - Overall, KSHV subtype C was the most prevalent (20/9), of whom 17/19 (94%) fell in variant C, followed by subtype A (11/30), subtype B from 7/19 (38%) in variant A. Subtype B was identified in only one patient [Fig 1].
  - Genetic distances (GD) calculated between subtypes B and A or C were respectively 34% and 39% whereas ORF-K1 amino acid sequences of subtype A and C differed from each other by 19%.

  **2. KSHV subtype according to patients’ origin**
  **Most of patients came from France (29/39) 15/29 (52%) fell in subtype C whereas variant F was only in subtype A. 29/39 (29%) in subtype B and 42/49 (44%) in subtype F.**
  - From Mediterranean basin, 3 belong to subtype A and one to subtype C. Patients from Asia fell in subtype C and from South American patients, one fell in subtype A, one in subtype C and one in subtype F [Fig 2A].

  **3. Relationship between subtype and clinical presentation**
  **Preparation of KSHV and MCD subtype were not significantly different (26% of KS and 53% of MCD to subtype A and 63% of KS and 55% of MCD to subtype C) suggesting that subtype associated with KSHV pathologies may related to the prevalence of each subtype in this population (2B)**
  - Among patients with KS
    - KSHV-DNA viral load tended to be higher among patient with subtype A and C with those with subtype B and F regarding the immunological status [Fig 2C].
    - Variant C was more associated with one common and/or oral mucous involvement than other subtypes (Odd ratio = 11.3 95% CI 1.1 – 214.2, p = 0,002) regarding of the immunological status (CD4 count cells p = 0.776, HIV RNA viral load p = 0.495) [Fig 2D].

  **4. New variant characteristics**
  - ORF-K1 phylogenetic analysis was confirmed by KSHV-WG sequencing of our “subtype F” (P073, P075 and P076) and compared to P072 identified as “African F” (KSHV-WG reference sequence not available in NCBI database).

**Results**

### Conclusion

Our study showed that subtype C, and specifically variant C3, was the most prevalent in KSHV smoking in France and tended to be associated with less severe epidemiological forms. We also reported for the first time, 5 new “subtype F” isolated only in MSM and associated with severe diseases. We suggest that, in view of phylogenetic (ORF-K1 and KSHV-WG analysis) and epidemiological (Caucasian Vs African - subtype) finding, subtype F could be subdivided in two genotypes variant (F1 and F2).

### Background

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