17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

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Imperial College London

6-8 April 2011, Bournemouth International Centre

SSAT ST STEPHEN'S AIDS TRUST

Imperial College London

Increased incidence of multicentric Castleman's disease in KSHV$^+$ HIV-1$^+$ individuals of black African ethnicity may result from the higher frequency of the TLR4 SNP A299G

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Kaposi's Sarcoma

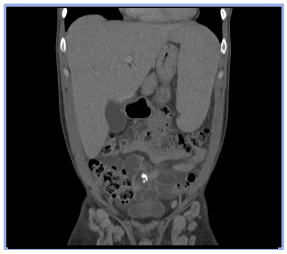
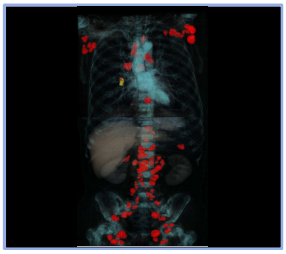
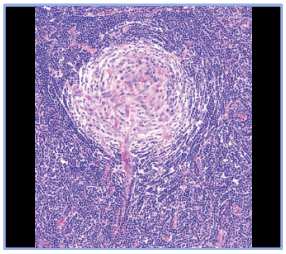
Kaposi's sarcoma herpesvirus (KSHV)

- Oncogenic human γ-herpesvirus (HHV8)
- Kaposi's sarcoma (KS)
  - Abnormal growth of lymphatic endothelial-type cells

Multicentric Castleman's Disease

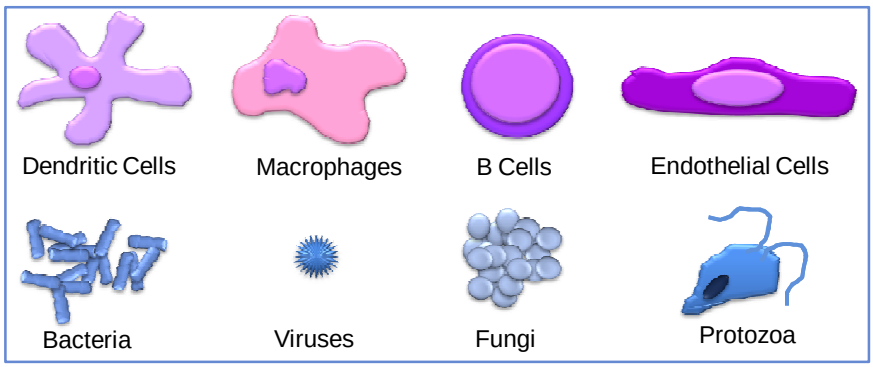
Kaposi's sarcoma herpesvirus (KSHV)

- Oncogenic human γ-herpesvirus (HHV8)
- Multicentric Castleman's disease (MCD)
  - Abnormal proliferation of lymphocytes
  - high KSHV plasma level

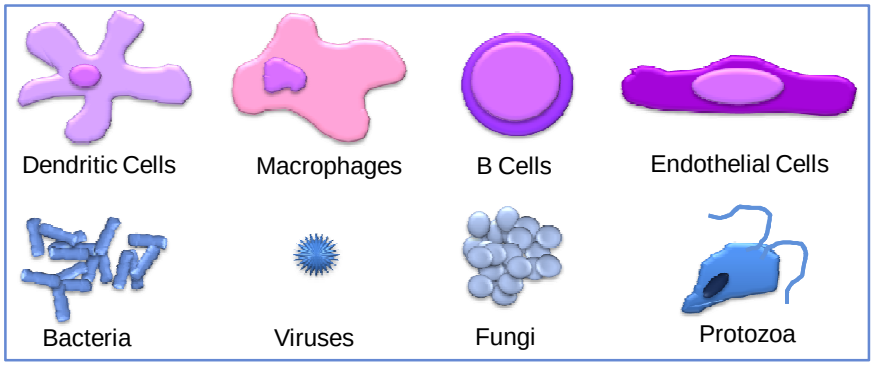
Toll-like Receptor (TLR)4

- Ten TLR in humans
  - Membrane receptors that recognise PAMP



Toll-like Receptor (TLR)4

- Innate immune response to KSHV
  - KSHV^{+} endothelial cells down-regulate TLR4
    (Lagos *et al.*, 2008)



A299G SNP

- Single nucleotide polymorphism in *TLR4*
  - Down-regulation of TLR4
  - Associated with increased incidence of MCD in HIV-1^{+} KSHV^{+} patients (Lagos *et al*., 2008)

GAT

299

A299G SNP

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GGT

299

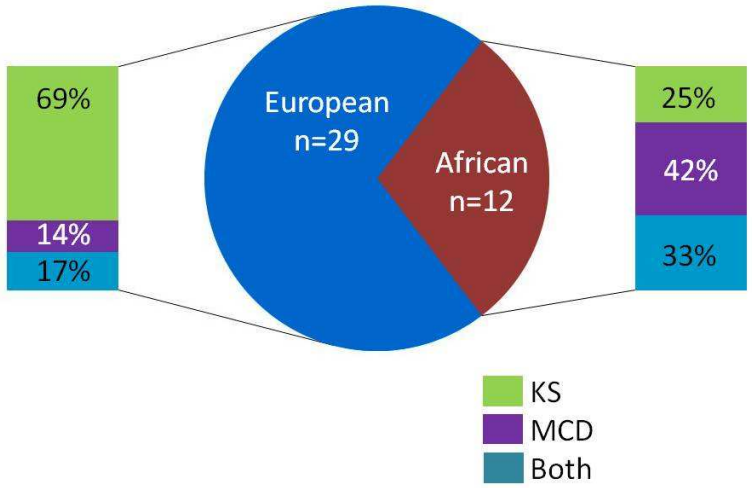
Patient Cohort and Methods

- 107 HIV-1^{+} patients from the Chelsea and Westminster cohort
  - KSHV related malignancies (n=41)
    - KS (n=23); MCD (n=9); both (n=9)
  - KSHV unrelated malignancies (n=66)
    - Including non-Hodgkin's lymphoma, Hodgkin's Disease, Anal, Lung and Thyroid cancer
- DNA was extracted from peripheral blood

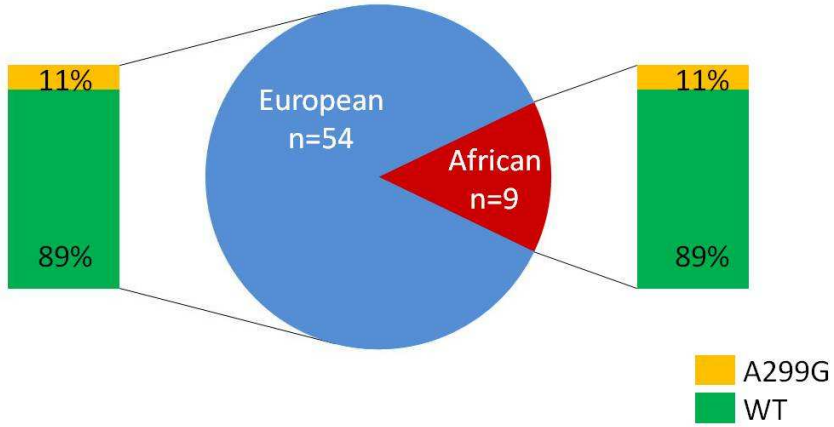
Patient Cohort and Methods

- Genotyped for the presence of A299G SNP
- Analysed according to ethnicity
  - African ancestry (n=21)
  - European ancestry (n=83)
  - Other/not stated (n=3)

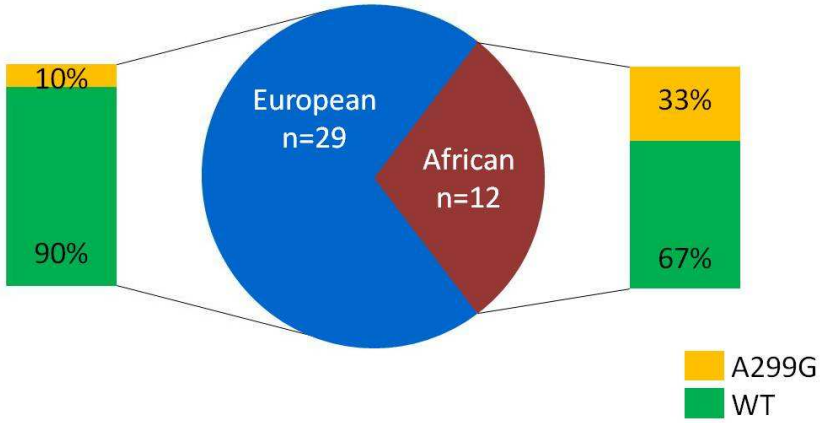
Patients with KSHV-related malignancies



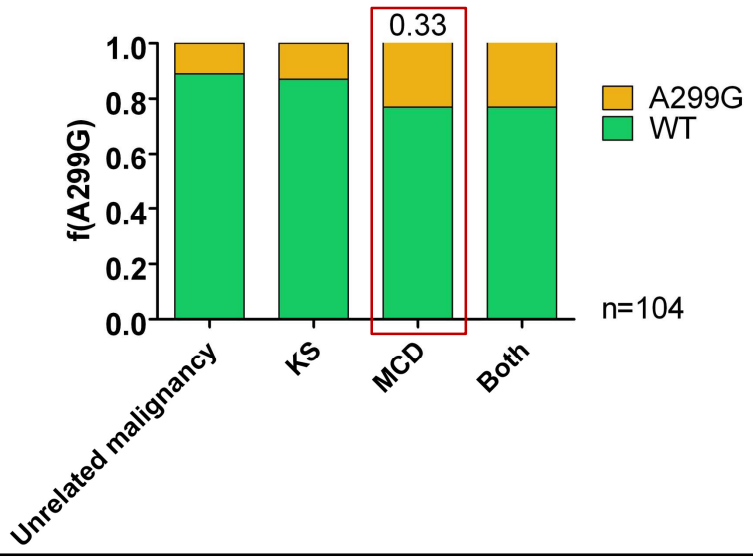
TLR4 SNP in patients with KSHV-unrelated malignancies



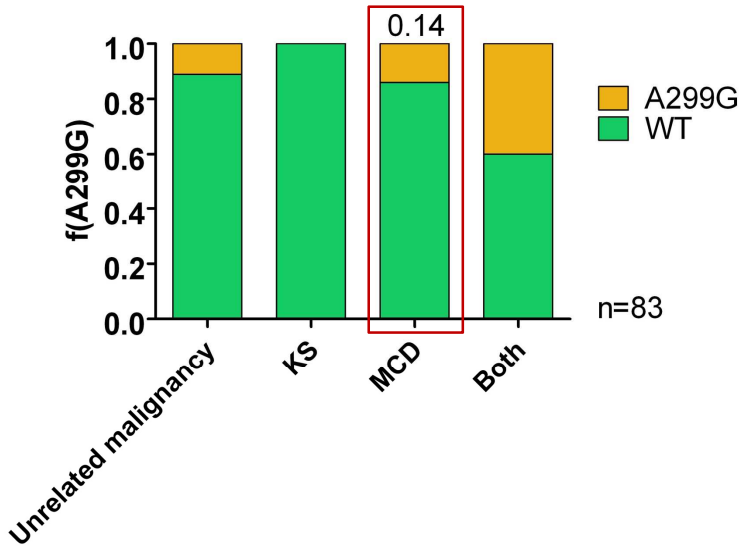
TLR4 SNP in patients with KSHV-related malignancies



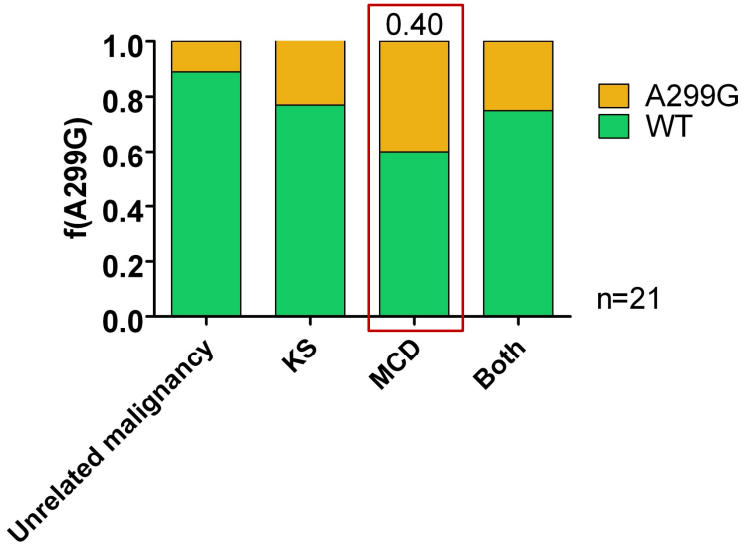
TLR4 SNP in all individuals



TLR4 SNP in individuals of European ancestry



TLR4 SNP in individuals of African ancestry



Conclusions

- >3 times higher frequency of the TLR4 A299G SNP in HIV-1$^+$ KSHV$^+$ patients of African ancestry
  - Associated with protection from malaria mortality in sub Saharan Africa (Ferwerda *et al.*, 2007)
- 2.4 fold increased incidence of MCD in individuals of African ancestry with KSHV-related malignancies compared to individuals of European ancestry
  - Order of infection
- Variation in risk of MCD may prove to be a clinically relevant consideration in HIV-1$^+$ KSHV$^+$ patients

Acknowledgements

Dr Nesrina Imami
Prof F Gotch

Department of Medicine
Imperial College London

Prof M Bower

Department of Oncology
Imperial College London

Dr D Lagos
Prof C Boshoff

University College London
Cancer Institute

Prof B Gazzard
Dr Mark Nelson

St Stephen's AIDS Trust

Patients and Staff of the St Stephen's Centre and Kobler day care unit