

# HLA alleles and KIR genes frequencies in HIV-2 infected individuals from two cohorts in West Africa

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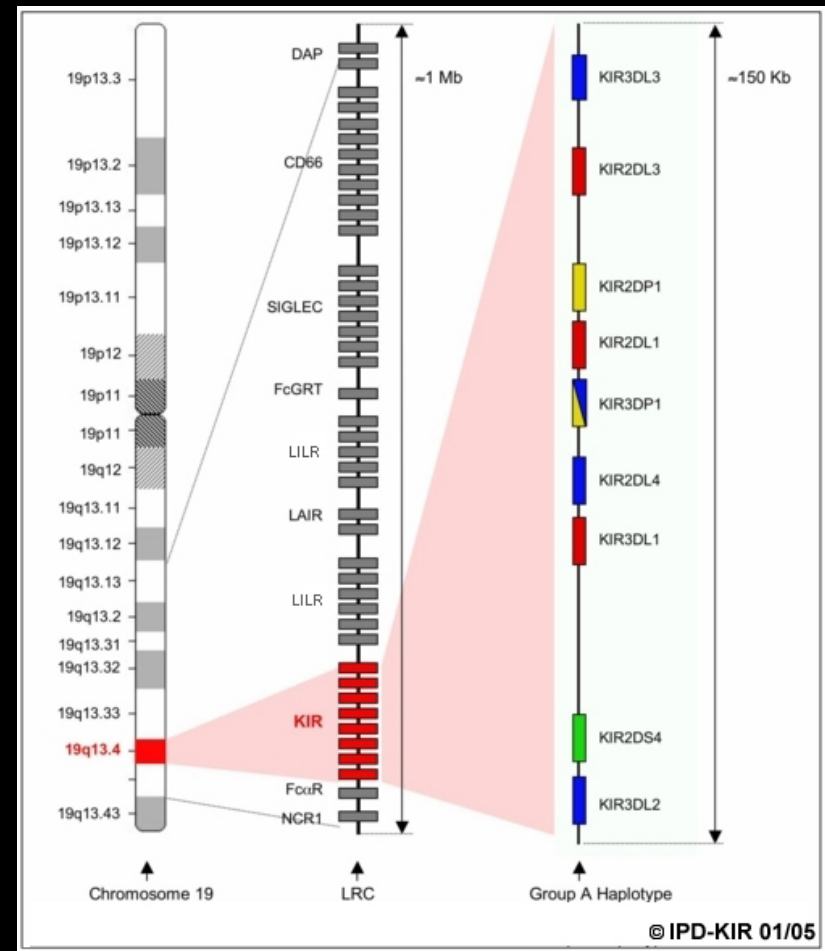


# Natural Killer cells and the immune system

- NK cells are effector lymphocytes
- First line of defence against viral infections and transformed cells (tumours)
- Cells are killed by direct cytotoxicity and release of cytokines
- NK cell surface receptors are of two types
  - C type lectin - 12p13.1 (rodents)
  - KIR – LRC - 19q13.4 (humans)

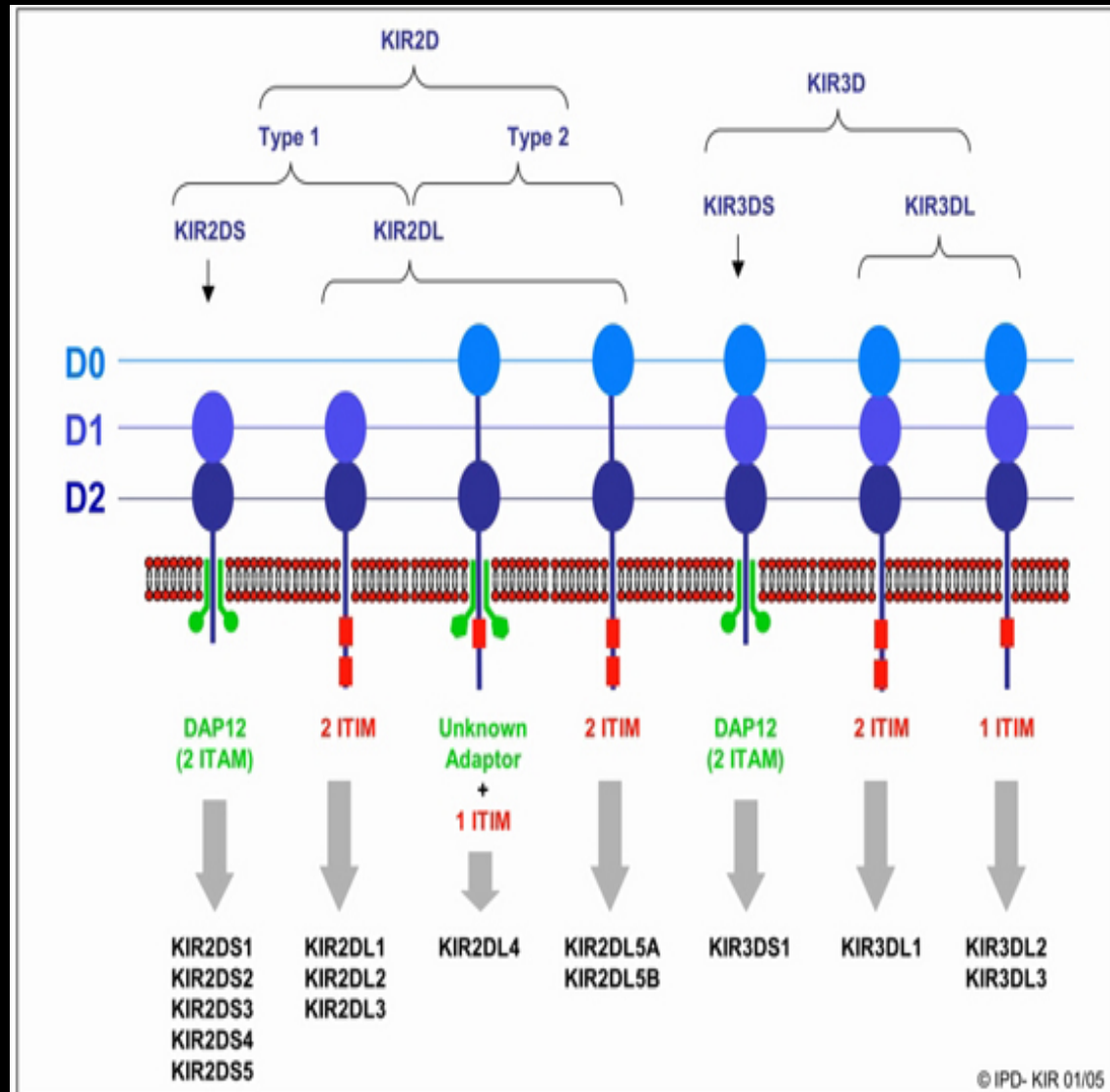
# Killer immunoglobulin-like receptors (KIR)

- KIRs are type I transmembrane glycoproteins with 2-3 extracellular domains
- A group of regulatory molecules expressed by NK cells, a subpopulation of  $\gamma\delta$  T cells, and some memory  $\alpha\beta$  T cells
- They were first identified by their ability to impart some specificity on natural killer cytotoxicity
- They are specific for allelic forms of HLA class I molecules
- Their interaction with HLA class I molecules modulate the cytotoxic activity of NK cells
- Different populations have different KIR patterns



# KIR structure

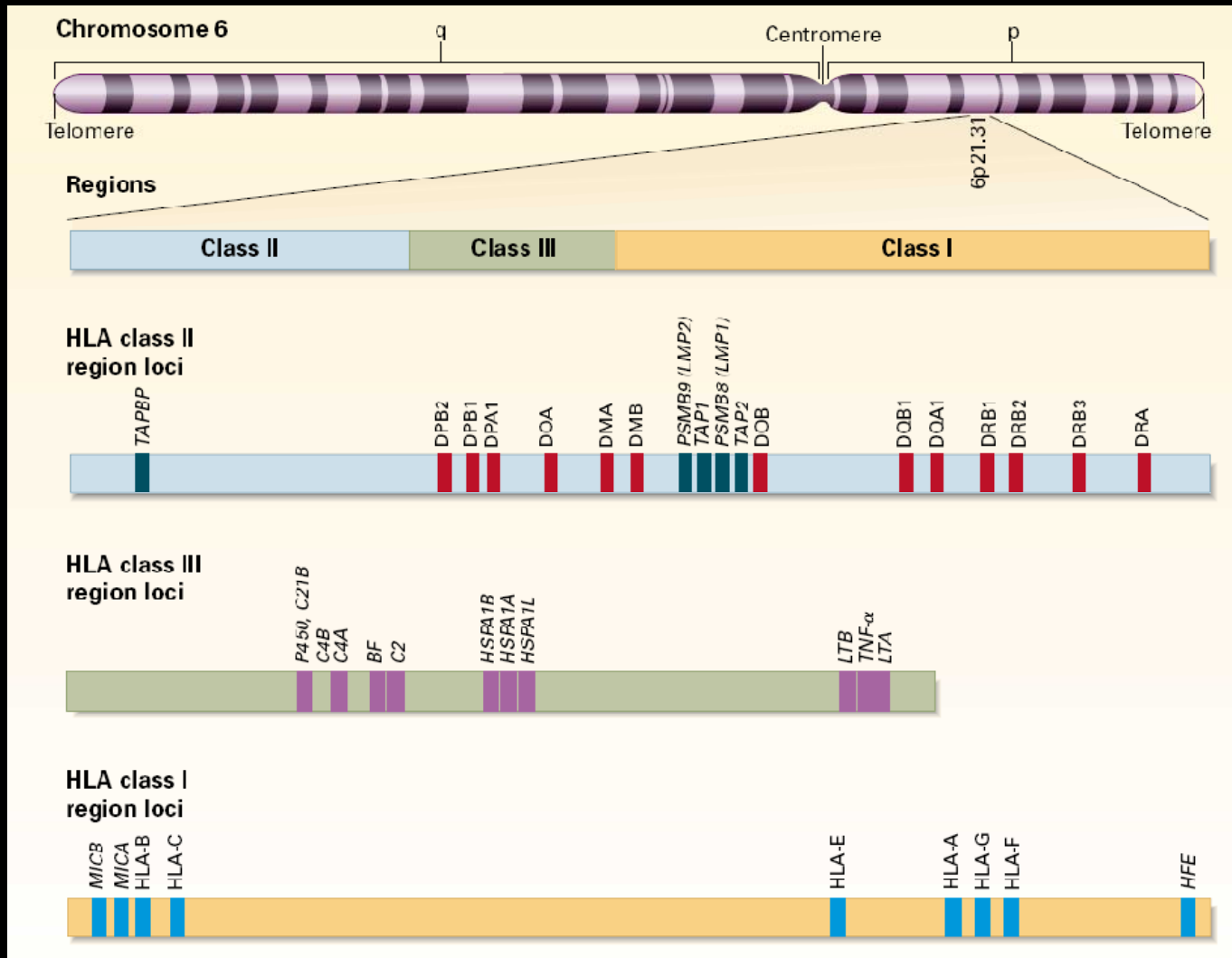
- Functionally KIR molecules have been classified as either inhibitory or activating receptors
- Activating KIR have short (S) cytoplasmic tail with a positively charged residue in the transmembrane region
- Inhibitory KIR have a long (L) cytoplasmic tail containing ITIM<sup>s</sup>
- Their transmembrane and cytoplasmic regions are functionally relevant as they define the type of signal transduced to NK cells
- KIR proteins possess Ig-like domains (D0, D1 & D2) which interact with HLA class I ligands to initiate or inhibit NK cell activity



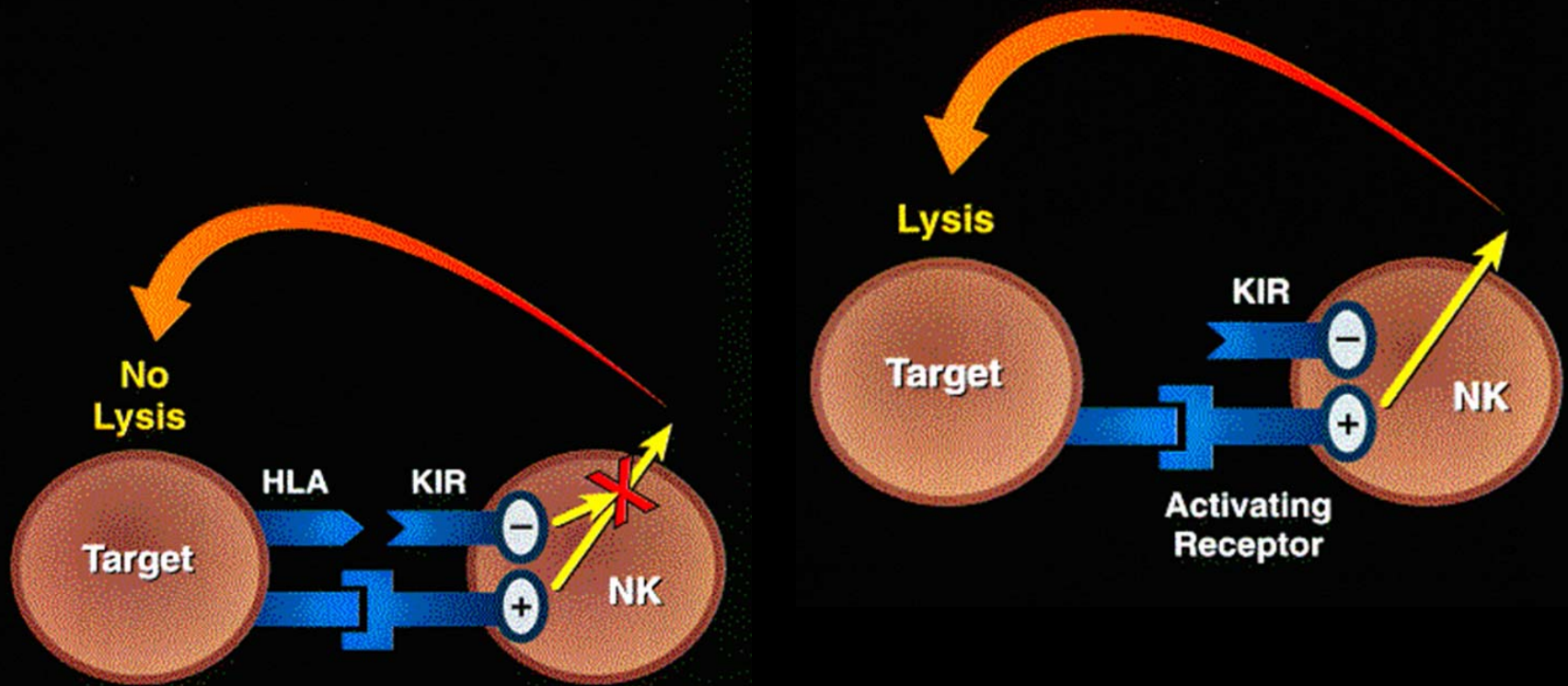
# HLA

- The human major histocompatibility complex (MHC)
- The most polymorphic genes known to human
- HLA genes are located within the short arm of human chromosome 6 (6p21.3)
- There are 3 main HLA classes (I, II, and III)

# Genes of the HLA region



# HLA-KIR and NK cell function



**NK cells kill targets that do not express HLA class I**

# KIR3DS1/Bw4-80I in HIV infection

- a) **protects against AIDS progression** (Nat Gen 2005 31: 429)
- b) **protects against OI independent of CD4+ T cell decline** (PLoS Pathog 2006 2(8): 741)
- c) **associates with lower virus load set point** (PLoS Pathog 2006 2(8): 741)

# Why this project?

- The burden of HIV epidemic rest in Sub-Saharan Africa (2/3 of all affected people)
- An effective vaccine is yet to be found
- Mechanism(s) of protective immunity poorly understood
- HIV-2 (West Africa) is a naturally attenuated form of HIV
  - Less transmissible and less pathogenic
  - Offers opportunity for longitudinal studies
- There is a paucity of information from HIV-2 research
- Understanding the reason why most HIV-2 infected people do not develop immune deficiency could provide unique insights into protective immunity in HIV infection and pave the way for design of vaccines against the virus

# HYPOTHESIS

- Main hypothesis
  - Specific *HLA* and *KIR* genes/alleles and/or *KIR* gene profiles associate with relative protection against HIV-2 infection in some people and/or progression to AIDS in others

# Specific objectives

- To determine the KIR genes pool in a community based cohort in Caio (Guinea-Bissau)
- To study the effect of individual KIR genes and haplotypes on susceptibility or resistance to HIV-2 infection
- To determine the haplotype diversity and its role in long-term non-progression status observed in HIV-2 infection

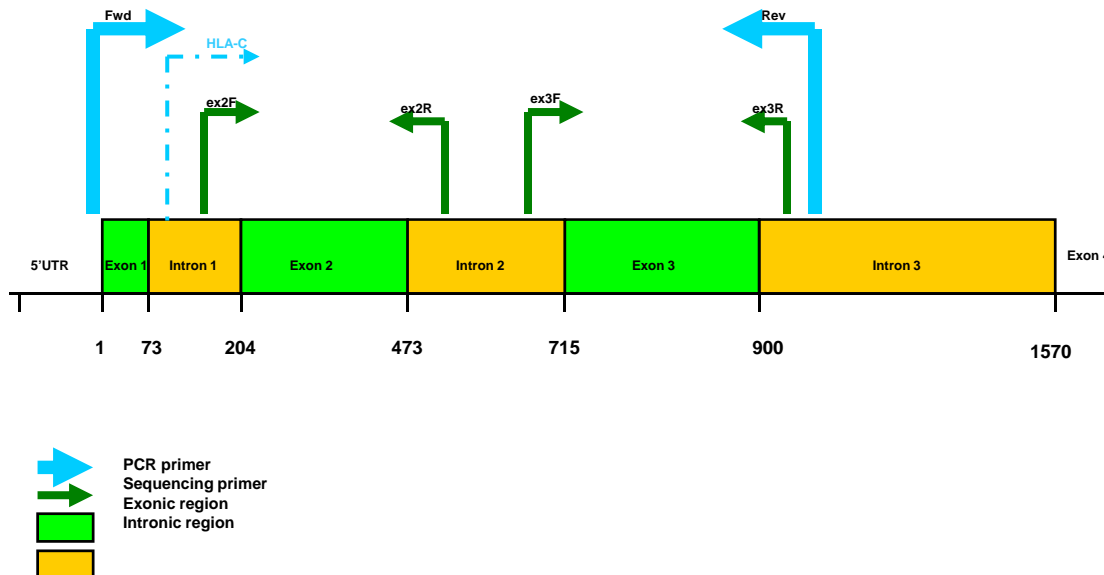
# Design and subjects

- Cohort study
  - Clinical cohort >> Fajara, The Gambia
    - Established in May 1986
    - good follow up data
    - Several time points clinical data
    - 600 samples
  - Community based cohort >> Caio, Guinea Bissau
    - Established in 1989
    - Good follow up data
    - 513 samples



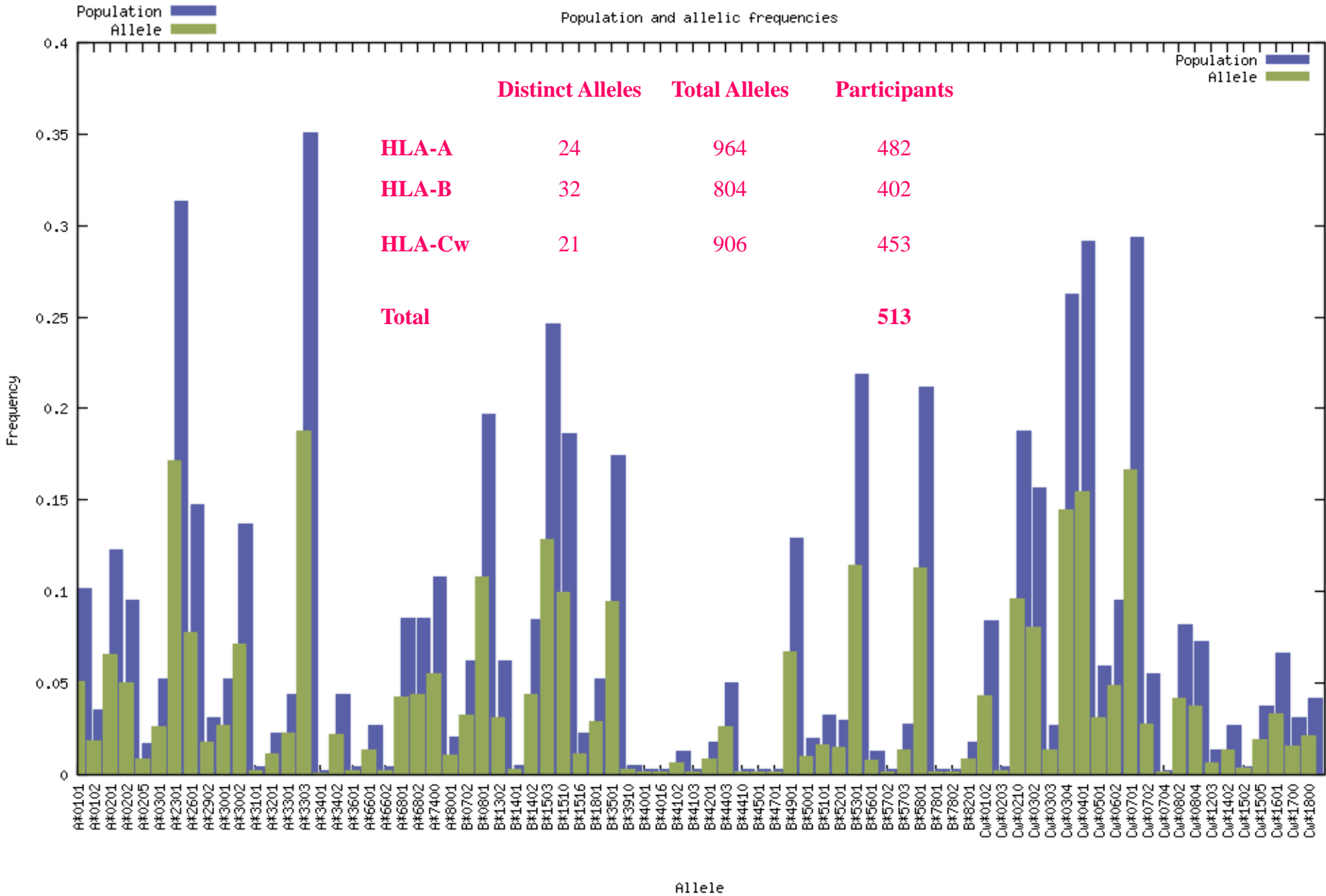
# Methods (1)

- KIR typing by PCR-SSP using a panel of 60 reactions mixes to detect 15 KIR genes
- HLA typing was done by sequence-based techniques (SBT) for HLA class I (A, B, C)



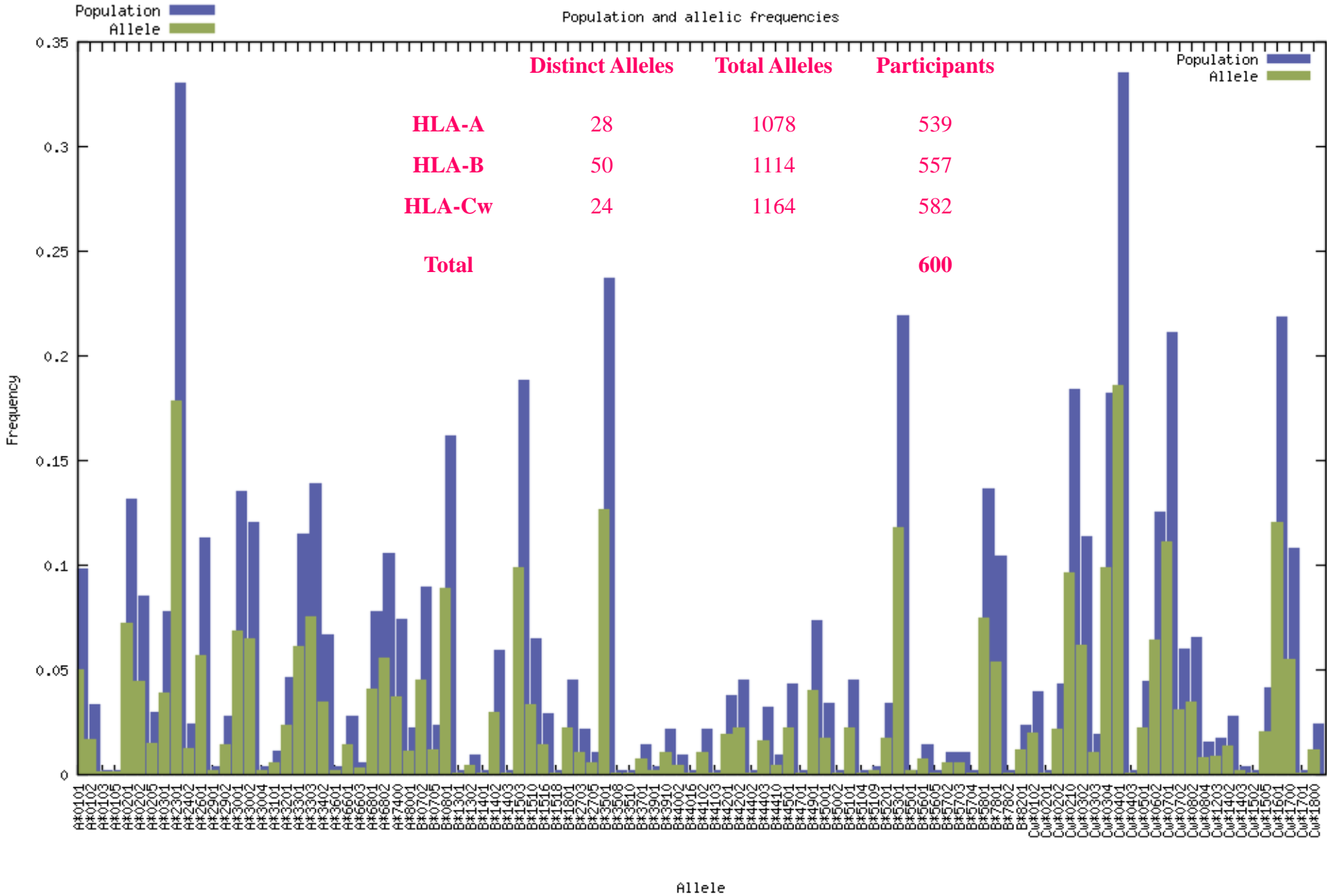
# HLA frequencies Caio

Population and allelic frequencies



# HLA frequencies Fajara

Population and allelic frequencies

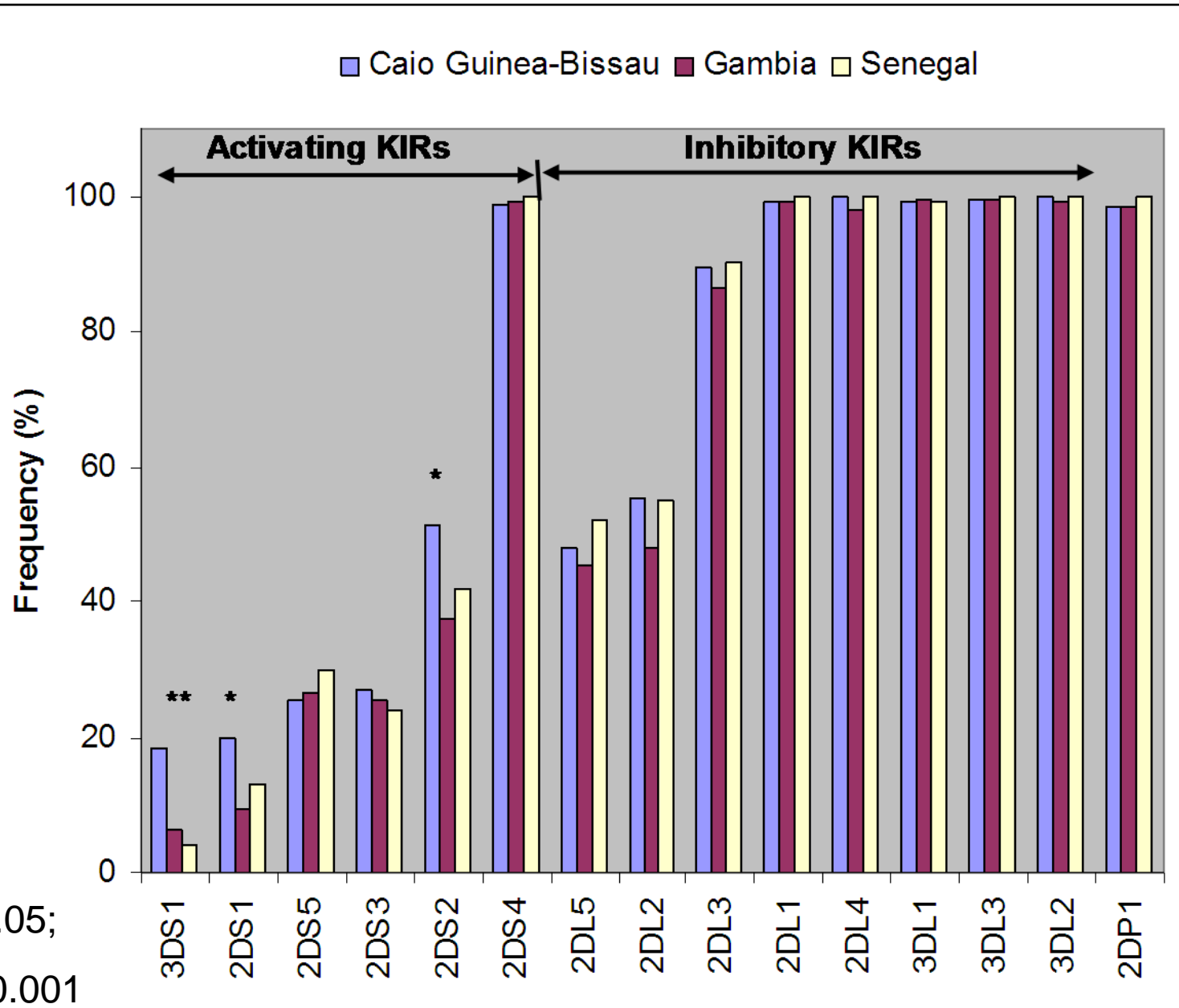


## Effects of *HLA-B* and *HLA-C* on CD4+ T lymphocyte counts and viral load

HLA (n=135)	Mean sqrt CD4 (n)	SE	p	Mean logHIV-2 VL (n)	SE	p
<i>B*14</i> (P)	26.81 (14)	1.71	0.23	2.39 (14)	0.29	<b>0.02</b>
<i>B*15</i> (S <sup>+</sup> )	22.61 (51)	0.86	<b>0.001</b>	3.41 (52)	0.14	<b>0.001</b>
<i>B*1503</i> (S <sup>+</sup> )	21.18 (26)	1.20	<b>0.001</b>	3.48 (28)	0.20	<b>0.02</b>
<i>B*1510</i>	24.78 (24)	1.31	0.96	3.22 (25)	0.22	0.36
<i>B*1516</i>	19.75 (3)	3.68	0.16	3.55 (2)	0.78	0.51
<i>B*44</i> (P)	27.01 (7)	2.42	0.36	2.27 (8)	0.38	<b>0.04</b>
<i>B*49</i> (S <sup>+</sup> )	21.51 (17)	1.53	<b>0.02</b>	3.39 (20)	0.24	0.12
<i>B*57</i> (P)	29.82 (7)	2.37	<b>0.03</b>	3.30 (7)	3.30	0.51
<i>B*82</i> (P)	27.71 (3)	3.68	0.43	1.70 (3)	0.61	<b>0.03</b>
<i>Cw*02</i> (S <sup>+</sup> )	20.43 (19)	1.46	<b>0.002</b>	3.41 (20)	0.24	0.14
<i>Cw*07</i> (S <sup>+</sup> )	24.39 (47)	0.96	0.73	3.35 (50)	0.15	<b>0.03</b>

Average mean sqrtCD4+ T cell counts = 24.7; Average mean logHIV-2 VL = 3.1

# KIR genes



## Effects of KIR and HLA compound genotypes on HIV-2 antibody status

	HIV-2+		HIV-negative			OR	95% CI	p
	N	%	N	%				
<i>B*0801</i>	39	27.27	34	14.53	<i>B*0801</i> vs. others	2.20	1.31-3.70	<b>0.003</b>
Others	104	72.73	200	85.47				
<i>A*8001</i>	8	5.37	2	0.65	<i>A*8001</i> vs. others	8.90	1.86-42.53	<b>0.01</b>
Others	141	94.63	307	99.35				
<i>2DS2</i>	66	44.00	178	54.27	<i>2DS2</i> vs. others	0.67	0.45-0.98	<b>0.04</b>
Others	84	56.00	150	45.73				
<i>2DL2</i>	72	48.00	195	59.45	<i>2DL2</i> vs. others	0.63	0.43-0.93	<b>0.02</b>
Others	78	52.00	133	40.55				
<i>2DS2+/CI+</i>	49	33.79	124	44.93	<i>2DS2+ / CI+</i> vs. others	0.63	0.41-0.95	<b>0.03</b>
Others	96	66.21	152	55.07				
<i>2DL2+/CI+</i>	56	38.62	135	48.91	<i>2DL2+ / CI+</i> vs. others	0.66	0.44-0.99	<b>0.04</b>
Others	89	61.38	141	51.09				

# Summary (1)

- HLA class I frequencies differed between the two populations
- HLA B\*0801 and A\*8001 was associated with susceptibility to HIV-2 infection
- HLA-B\*1503 carriers are predicted to progress to AIDS much faster
- Inhibitory KIR genes are ubiquitously expressed in these populations while most of the activating KIR genes are expressed by only 1/3 of the study subjects

## Summary (2)

- However, the frequencies of most activating KIR genes are significantly higher in Caio than other West African population (KIR3DS1)
- KIR2DS2 and KIR2DL2 when present in the same individual with their corresponding ligands HLA-C group 1 offer some degree of protection against HIV-2 acquisition
- KIR gene profile A predominated in the study population

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