

Delayed disease progression in HIV-2: The importance of  
TRIM5 $\alpha$  and the retroviral capsid

Short title: Interaction of TRIM5 $\alpha$  and HIV-2 CA

Dear editor

Thank you for agreeing to review this manuscript for publication as per my  
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Author 1:

Dr Michael Terence Boswell

Nuffield Department of Medicine, University of Oxford

Author 2:

Prof Sarah Rowland-Jones

Nuffield Department of Medicine, University of Oxford

Corresponding author:

Prof Sarah Rowland-Jones

Postal address: Nuffield Department of Medicine Research Building, Old Road  
Campus, Headington, Oxford, OX3 7FZ

Email address: [sarah.rowland-jones@ndm.ox.ac.uk](mailto:sarah.rowland-jones@ndm.ox.ac.uk)

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## Abbreviations

AIDS - Acquired Immune Deficiency Syndrome

ART – Antiretroviral therapy

CA - Capsid

CC – Coiled Coil

CCR5 - C-C chemokine receptor type 5

CD - Cluster of differentiation

cDNA – Complementary Deoxyribonucleic Acid

cGAS-STING - cyclic GMP–AMP synthase and stimulator of interferon genes

CTD – C terminal domain

CTL – Cytotoxic T lymphocyte

CRISPR - clustered regularly interspaced short palindromic repeats

DC-SIGN - dendritic cell-specific ICAM3-grabbing nonintegrin

DNA – Deoxyribonucleic Acid

*env* - envelope

*gag* – group antigen

gp125 – glycoprotein 125

HIV - Human Immunodeficiency Virus

HLA – Human Leucocyte Antigen

IFN - interferon

IL-2 - interleukin-2

KIR - Killer-cell immunoglobulin-like receptor

LAV – Lymphadenopathy Associated Virus

LPS - lipopolysaccharide

LTNP – long term non-progressor

MA - matrix

NC - nucleocapsid

NFKB - nuclear factor kappa-light-chain-enhancer of activated B cells

NONO - Non-POU domain-containing octamer-binding protein

NTD – N terminal domain

OWM – old world monkey

RC – replicative capacity

RING – Really Interesting New Gene

RTC – reverse transcriptase/capsid complex

SAMHD1 - SAM domain and HD domain-containing protein 1

T/f – transmitted/founder

TNF- $\alpha$  - tumor necrosis factor- $\alpha$

TREX1 - three prime repair exonuclease 1

TRIM – tripartite motif

*Vpu* – viral protein U

*Vpx* – viral protein X

## **Abstract**

**HIV-2 is thought to have entered the human population in the 1930s through cross-species transmission of SIV from sooty mangabeys in West Africa. Unlike HIV-1, HIV-2 has not led to a global pandemic and recent data suggest that HIV-2 prevalence is declining in some West African states where it was formerly endemic. Although many early isolates of HIV-2 were derived from patients presenting with AIDS-defining illnesses, it was noted that a much larger proportion of HIV-2-infected subjects behaved as long-term non-progressors (LTNP) than their HIV-1-infected counterparts. Many HIV-2-infected adults are asymptomatic, maintaining an undetectable viral load for over a decade. However, despite lower viral loads, HIV-2 does progress to clinical AIDS without therapeutic intervention in most patients. In addition, successful treatment with antiretroviral therapy (ART), is more challenging than for HIV-1.**

**HIV-2 is significantly more sensitive to restriction by host restriction factor TRIM5 $\alpha$  than HIV-1, and this difference in sensitivity is linked to differences in capsid structure. In this review we discuss the determinants of HIV-2 disease progression and focus on the important interactions between TRIM5 $\alpha$  and HIV-2 capsid in long term viral control.**

## Introduction

HIV-2 was first isolated in 1986 from healthy commercial sex workers in Senegal and named HTLV-IV. Shortly afterwards a similar virus (named LAV-II) was isolated from two West African patients with AIDS and renamed HIV-2 (1). Subsequent molecular characterisation showed that HIV-2 was related to HIV-1 but was closer to SIV derived from macaques displaying an AIDS-like syndrome (1). It has since been established that HIV-2 entered the human population in approximately 1938 from a virus infecting sooty mangabeys (SIVmm) in West Africa (2).

An estimate of HIV-2 prevalence of 1-2 million infected people worldwide is widely cited (3). However, as HIV-2 is not regularly included in national testing strategies and requires specialist laboratory facilities for accurate diagnosis (4) the current prevalence is unknown. The recent falls in national HIV-2 prevalence in some West African countries (5) have led to predictions that the epidemic will reach extinction around 2068 (3,6).

In contrast to untreated HIV-1 infection, longitudinal follow-up of a rural community cohort with HIV-2 infection demonstrated that 30 - 40% of infected people exhibit low or undetectable viral loads with AIDS-free survival for up to ten years (7). These HIV-2 LTNPs had mortality rates equivalent to the uninfected population, although most people infected with HIV-2 have moderately higher mortality rates than the HIV-negative population (7,8). After 8 years of follow up, the mortality rate for HIV-1 infection is approximately double that of HIV-2 infection without treatment (7,9). This distinction between HIV-1 and HIV-2 mortality was highlighted in recent report from a cohort in Bissau with an unusually high proportion of subjects with known dates of infection, in which the median survival time for HIV-1 was 8.2 years and for HIV-2 it

was 15.6 years (10). In this study it was also noted that HIV-2-infected people developed clinical AIDS with a higher mean CD4<sup>+</sup> T-cell % than seen for HIV-1. The risk of HIV-2 disease progression is dependent on viral load - people with viral loads >10 000 copies/mL are likely to progress to AIDS at the same rate as those with HIV-1 (7). The differential effect of plasma viral load on mortality in HIV-2 infection is illustrated in figure 1 below. Furthermore, when matched for low CD4<sup>+</sup> counts (< 100 cells/mL), mortality in HIV-2 infection is equivalent to that of HIV-1 (8). Spontaneous undetectable viraemia and an indolent disease course in HIV-1 is rare (11), whereas this is a common feature of HIV-2 infection.

In this review we discuss the relative contributions to HIV-2 disease progression of viral, immunological and host factors. We focus on the potential importance of the interaction between HIV-2 capsid and human tripartite motif containing protein, TRIM5 $\alpha$ , and discuss how these viral and host factors may contribute to delayed disease progression in HIV-2 infection.

## TRIM5 $\alpha$ and HIV-2

TRIM5 $\alpha$  is a host restriction factor, one of a group of intracellular antiviral proteins which act as the effector arm of the Interferon response to disrupt the HIV life cycle at multiple points (13). The structure of TRIM proteins is characterised by a conserved modular tripartite motif consisting of a Really Interesting New Gene (RING) domain followed by one or two zinc binding areas named B-box, a coiled coil (CC) region and in some cases a PRY-SPRY domain (14). *TRIM5* is transcribed into 5 isoforms and its antiviral activity is mediated by isoform TRIM5 $\alpha$ . The other isoforms result in truncated proteins lacking a PRY-SPRY domain and inhibit TRIM5 $\alpha$  activity, therefore the proportion of TRIM5 $\alpha$  amongst total *TRIM5* transcripts may influence HIV restriction (15). Although TRIM proteins are structurally similar, their functions are diverse: here we will focus on the anti-retroviral mechanisms of TRIM5 $\alpha$ .

Host restriction factors play a key role in the prevention of cross-species movement of lentiviruses: for example, the orthologue TRIM5 $\alpha$  derived from rhesus macaques potently restricts HIV-1, whereas the human equivalent does not (16). *TRIM5* is one of the fastest evolving genes in the human genome (17). *TRIM5* has evolved under positive selection pressure, probably due to various pathogens exerting selection pressure at different periods of human evolution (18). Positive selection on residues in the PRY-SPRY domain is prominent in *TRIM5*, particularly in an amino acid motif which determines viral capsid specificity and hence viral restriction (18). TRIM5 $\alpha$  monomers bind at the interface of three capsid hexamers. This binding site was shown for rhesus TRIM5 $\alpha$  and HIV-1 and is associated with high affinity binding and determines species-specific restriction of TRIM5 $\alpha$  orthologues (19).



TRIM5 $\alpha$ 's ability to restrict HIV-1 in old world monkey (OWM) cells by targeting viral capsid was reported in 2004 (20). The sensitivity of HIV-2 to TRIM5 $\alpha$  is determined by a region of the capsid which corresponds to the cyclophilin binding loop in HIV-1 (21). Depletion of cyclophilin A enhances TRIM5 $\alpha$  mediated restriction and reduces infectivity of HIV-2 (22). The anti-retroviral mechanism of TRIM5 $\alpha$  acts at the pre-integration phase of the HIV life-cycle and is summarised in figure 2. TRIM5 $\alpha$  in rhesus macaques is also capable of late viral restriction by incorporation into nascent HIV-2 virions, thereby decreasing the production of functional new virus particles. This late restriction is a saturable process as increased virion production may overwhelm it (23). In feline cell lines permissive to HIV-2 infection, experimentally-induced expression of human TRIM5 $\alpha$  restricts viral replication and TRIM5 $\alpha$ -specific short interfering RNA rescues infectivity in resistant cells (21). Additional antiretroviral mechanisms include that TRIM5 binding to the incoming capsid prevents nuclear entry via nucleoporin channels (24) and also stimulates TAK-1 phosphorylation, which activates the NF $\kappa$ B transcription pathway (25). This capsid-specific recognition then stimulates further downstream transcription of inflammatory cytokines, which enhances the antiviral response against HIV.

Despite high *TRIM* diversity, *TRIM5* genotype has minimal impact on HIV-1 disease progression (26). Moreover, TRIM5 $\alpha$  does not appear to drive evolutionary change in HIV-1 capsid sequences from clade B (27). HIV infected patients who are homozygous for the H43Y substitution develop AIDS more quickly than heterozygotes or H43 homozygotes (28) and this substitution modestly impairs the restrictive capacity of TRIM5 $\alpha$  (28). Furthermore, the appearance of putative TRIM5 $\alpha$  viral escape variants has been found to precede rapid immunological decline in HIV-1 infection (29). Increased expression of TRIM5 $\alpha$  in peripheral blood mononuclear

cells is associated with a reduced risk of incident HIV-1 infection (30). The impact of *TRIM5* genotype and expression on HIV-2 disease outcomes has not been reported. A primate model of human HIV-2 infection using SIVsm-infected Indian Macaques showed that certain *TRIM5* variants were associated with increased memory CD4<sup>+</sup> cells and longer AIDS-free survival. This longitudinal study also demonstrated the development of escape mutants to TRIM5 $\alpha$ , which could accelerate immunological decline, resulting in simian AIDS in the test subjects (31).

## Viral factors associated with HIV-2 progression

### Contribution to disease progression by viral replicative capacity, diversity, fitness

The HIV genome consists of several genes in an open reading frame, represented in figure 3. Differences between the HIV-1 and HIV-2 genomes are shown in figure 3.

Viral replicative capacity, genetic diversity and intra-host evolution rates have all been linked to differences in disease outcomes in HIV infection and are discussed in turn.

Measuring virion production in cell cultures with a radio-labelled reverse transcriptase assay, it has been shown in HIV-1 infected patients that a greater viral replicative capacity (RC) in the Transmitted/founder (T/f) strain is associated with greater immune activation, higher viral load set-points and faster disease progression (37). The RC of Gag-MJ4 chimeric viruses correlates closely with that of full-length T/f molecular clones. This suggests that the *gag* sequences of the T/f strains influence replicative capacity. In an epidemiologically-linked transmission cohort, CTL pressure on *gag* in transmitted viruses negatively influenced viral RC (38). Residue substitutions in all *gag* regions influenced RC, although only a few mutations occurred in capsid, which is a highly conserved region (38). Further studies did not support the sole importance of *gag* and have suggested that multiple genes interact to determine RC (39).

An alternative approach to measuring replicative capacity is to use competition assays with different viral strains. Using this method, Arien *et al* showed that most HIV-2 isolates had lower RC than HIV-1 (40) and additional studies demonstrated that clinical HIV-2 isolates from aviraemic patients had a lower RC than those from viraemic patients (41). This indicates that viral RC is probably also an important contributor to disease progression in HIV-2 infection.

HIV-1 diversity shows a strong correlation with viral load, fitness and disease progression but less is known about HIV-2 diversity and divergence influence disease outcomes (42). Skar *et al* reported that HIV-2 had a greater evolutionary rate than HIV-1, specifically in the gp125 region that contains the V3 loop (43). This region binds to CD4<sup>+</sup> receptors and thereby exposes the V3 loop to neutralising antibodies. Mutations were more likely to be synonymous and therefore due to viral factors (purifying selection) as opposed to immunological (positive selection) pressure - escape mutants to neutralising antibodies were notably rare. In contrast, findings from a Senegalese cohort showed limited divergence of *env* (44). One possible reason for the disparity in the results of these studies is that the two patient profiles were different. The Senegalese cohort were ART-naïve, with limited disease progression, and had a long follow-up time. Skar *et al* reported on *env* divergence in patients with mostly progressive HIV-2 infection. Many of these patients displayed X4 tropism with high viral loads and low CD4<sup>+</sup> counts. In addition, slow disease progression has been associated with lower *env* diversity and *vice versa* (45). A recent study stratified HIV-2 infected patients into fast and slow progressors and showed that HIV-2 *env* evolutionary rates in fast progressors are approximately double that of slow-progressors (46). Furthermore, stronger positive selection pressure on conserved residues in the envelope was associated with slower disease progression. The following trends emerge: individuals with controlled HIV-2 infection have viruses with a low replicative rate, low viral loads and diversity. Those that develop progressive disease have higher viral loads and greater diversity, with prominent negative selection pressure.

A study of *env* and *gag* sequences showed that viral loads in phylogenetically linked HIV-2 infection clusters were discordant (47). Therefore, viral genetic factors, at least

in *gag* and *env*, probably do not account for the full spectrum of disease progression in HIV-2 infection. This finding strengthens the hypothesis that interaction between viral and immunological factors are collective determinants of disease outcomes in HIV-2.

### The importance of *gag*

The viral *gag* gene encodes structural proteins capsid (CA/p26), nucleocapsid (NC) and matrix (MA). After an HIV virion enters a cell the capsid houses the viral RNA and facilitates reverse transcription during transit to the nucleus. HIV-1 capsids prevent both innate immune sensing of viral cDNA by the cGAS-STING (cyclic GMP–AMP synthase and stimulator of interferon genes) pathway as well as cDNA degradation and sensing by endogenous DNase enzymes such as TREX1 (three prime repair exonuclease 1) (48,49). In contrast to HIV-1, HIV-2 is able to replicate in dendritic cells and stimulates innate immune sensing via its capsid in a cyclophilin A-dependent manner (35). Capsid structures are highly conserved amongst retroviruses and mutations in their sequence may either reduce viral infectivity or increase the virus' susceptibility to host immune responses (50,51). It was recently reported that HIV-2 capsid binds more strongly than HIV-1 to the NONO protein in the nucleus, promoting DNA sensing by cGAS and stimulating a potent interferon response (52). The capsid residues involved in NONO binding are highly conserved in primate lentiviruses (52). Capsid sequences also determine the pathway for nuclear import and influence the choice of integration sites for viral DNA (53). The choice of integration site can then influence viral load depending on how transcriptionally active the site is.

Polymorphisms in HIV-2 capsid sequences have been implicated in multiple aspects of disease progression. Capsid sequences differ between patients with low and high HIV-2 viral loads, a key determinant of immune activation and disease progression. Specifically, patients with low viral loads often displayed prolines in capsid at positions 119, 159 and 178. Prolines in these positions had an additive effect on decreasing viraemia (54). In addition, prolines in these positions are associated with enhanced proteasomal processing of a CD8+ T-cell gag epitope 165-DRFYKSLRA-173. This epitope is associated with greater gag-specific T-cell responses as determined by ELISpot and is a frequent target for T-cell responses in patients with low viral loads (55). Therefore, it is possible that capsid sequences directly influence adaptive immune responses. HIV-2 capsid sequences with a proline at position 119 are more sensitive to restriction by the antiviral protein TRIM5 $\alpha$  (rhesus macaque) than sequences with alternative amino acids at this position. This enhanced sensitivity to TRIM5 $\alpha$  may be linked to conformational changes in the capsid protein (56,57). HIV-1 NL4-3 chimeras which contain HIV-2 capsid sequences are more susceptible to restriction by human TRIM5 $\alpha$  than the wildtype virus, though proline substitutions at position 119 do not correlate with TRIM5 $\alpha$  restriction (58). Furthermore, HIV-2 CA sequences derived from rapid progressors and LTNP do not differ in their sensitivity to TRIM5 $\alpha$  – though they are all more sensitive than HIV-1 (22).

Despite the increased sensitivity of HIV-2 capsid to TRIM5 $\alpha$  restriction, as well as the strong cytotoxic T-cell response directed towards gag, there is no evidence of positive selection pressure on *gag* divergence in a cross-sectional analysis of viral sequences from the Caio community cohort (59). Purifying selection pressure

predominates in interhost evolution, and this reflects the constrained evolution of this gene.

## HLA/KIR and other host genetic associations with HIV-2 disease outcomes

The most robust immunogenetic associations with LTNP in HIV-1 are found in *HLA* alleles and *CCR5* polymorphisms (60). Few studies have reported on the impact of *HLA* genotypes on HIV-2 infection outcomes. This reflects the paucity of well-characterised cohorts in West Africa, compounded by the variability of *HLA* repertoires present in different ethnic groups (61).

Yindom *et al* noted that *HLA* class I associations were strongest for *HLA* B\*1503, which correlated with high viral loads and low CD4<sup>+</sup> counts. Surprisingly *HLA* B\*5703 did not correlate with low viral load, despite its strong association with LTNP in HIV-1 infection (62). In Senegalese female sex workers *HLA*-B35, together with the *HLA*-B35-Cw4 and *HLA*-A23-C7 haplotypes, were associated with increased risk of disease progression (63). Three additional *HLA* types have been associated with lower odds of having a detectable viral load in HIV-2 infection, *HLA*-B\*58:01, *HLA*-DPB1\*10:01 and *HLA*-DRB1\*11:01 (64).

Many associations between compound *HLA*/*KIR* genotypes and outcomes in HIV-1 infection have been reported, but in the Caió cohort there were no significant associations between individual *KIR* alleles or *HLA*/*KIR* genotypes and either the risk of infection with HIV-2 or HIV-2 disease progression (62).

An additional study from the Caió cohort reported that a haplotype for polymorphisms rs11575097-rs10849523 in the *CD4* gene was associated with high viral loads in HIV-2 (65). In the same study, no correlations were found between polymorphisms in the *CD209* gene, encoding the dendritic cell-specific ICAM3-grabbing nonintegrin, and HIV-2 susceptibility or progression.



There is clear potential for further genetic studies to shed light on the mechanisms of HIV-2 disease progression.

#### CD4<sup>+</sup> T cell responses and HIV-2 disease outcomes

One of the hallmarks of HIV-1 infection is the progressive loss of CD4<sup>+</sup> T helper cells. Strikingly, the subset of HIV-1-specific CD4<sup>+</sup> cells is particularly susceptible to HIV-1 infection (66). However, despite the fact that the HIV-2-specific CD4<sup>+</sup> cell response is relatively well-preserved in most patients, HIV-2-specific CD4<sup>+</sup> T-cells are as vulnerable to HIV-2 infection as their HIV-1 specific counterparts are to HIV-1 infection (66,67). The relative proportion of infected virus-specific CD4<sup>+</sup> T-cells between HIV-2 controllers and progressors has not been investigated.

CD4<sup>+</sup> cells from aviraemic HIV-2 infected patients show preserved proliferative and cytokine-releasing functions, IFN- $\gamma$  and interleukin-2 (IL-2) being the dominant cytokines released (67,68). Aviraemic patients' CD4<sup>+</sup> cells have a broader cytokine profile, they release IFN- $\gamma$ , IL-2, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), macrophage inflammatory protein-1 $\beta$ , and CD107 (69), whereas in HIV-2 viraemic progressors the functional profiles of HIV-specific CD4<sup>+</sup> T-cells are similar to those seen in HIV-1 infection. This could suggest that HIV-2 disease progression is associated with greater infection of HIV-2-specific CD4<sup>+</sup> populations, leading to reduced T helper cell activity. A greater CD4<sup>+</sup> response against homologous gag proteins correlates positively with immune activation and negatively with HIV-2 proviral load, suggesting that the host responses promoting immune activation limits HIV-2 viral replication (70). Expanded T regulatory populations coupled with increasing PD1-PDL1 expression on T cells have been observed in patients with advanced HIV-2 disease and low CD4<sup>+</sup> counts, but these findings did not correlate with viraemia. This

observation may indicate that aberrant immune tolerance mechanisms in the face of longstanding immune activation can drive HIV-2 disease progression (71–73).

#### Cytotoxic T cell responses and disease outcomes

Many studies have implicated the HIV-1-specific CD8<sup>+</sup> cytotoxic T lymphocyte (CTL) response as the major factor controlling viral replication from acute infection through the asymptomatic stage of infection (74). In HIV-1 the CTL response tends to be broad, targeting a wide variety of epitopes, but is largely undermined by escape mutants that evade CTL recognition (75). Despite the importance of the CTL response in HIV-1 control, progressors cannot be distinguished from non-progressors based on the magnitude or breadth of their HIV-1-specific CTL response. There are characteristics of CTL found in non-progressors, including restriction by “protective” HLA molecules such as HLA-B27 or B57, polyfunctionality, proliferative capacity, levels of cytolytic molecules and the ability potentially to suppress HIV replication *in vitro* (76). In addition, greater targeting of HIV-1 Gag is associated with lower viral loads (77).

The CTL response in HIV-2 is characterised as being narrow, consistently targeting a smaller number of epitopes than HIV-1 (78). CTL from HIV-2 infected subjects produce a wider range of cytokines, as well as greater quantities of individual cytokines per cell, compared to those from HIV-1 infected individuals (69). This is linked with the high functional avidity reported for some HIV-2-specific CTL responses (78). Using ELISpot to measure CTL responses to gag peptides, aviraemic patients showed higher magnitude T-cell responses than viraemic patients (79). Gag specific CTL responses were shown to correlate strongly and inversely with viral load in HIV-2 infected subjects, with most viraemic patients lacking gag-

specific responses (which would be rare in HIV-1 infection) (80). CD8<sup>+</sup> cells from aviraemic patients can potently suppress viral replication in CD4<sup>+</sup> cells; these CD8<sup>+</sup> cells have an early differentiation phenotype and are potent effectors (81). Therefore, there are both quantitative and qualitative differences between CTL responses in HIV-2-infected subjects with and without detectable viraemia, suggesting that the generation of a potent and effective CTL response is central to limiting HIV-2 replication. Robust gag-specific CD8<sup>+</sup> T cell responses are common in subjects with undetectable viral load, raising the question of how these CTL populations are maintained in the absence of detectable viraemia. HIV-2 replication is detectable in gut mucosa in patients who are otherwise aviraemic, and this may offer an explanation if CTL are stimulated through persistent HIV-2 replication in gut-associated lymphoid tissue (82).

It is unclear why some HIV-2 infected patients do not generate effective gag-specific CTL responses, although we hypothesise that this may be related to a relatively weak interaction between TRIM5α and HIV-2 capsid (see below).

### Immune activation

Many of the characteristic features of HIV-1 disease progression are thought to be a consequence of prolonged immune activation. Immune activation also appears to be driving HIV-2 disease progression: the soluble activation marker beta-2 microglobulin predicts HIV-2 disease progression as accurately as plasma viral load in untreated subjects (83). T-cell activation markers closely correlate with plasma viral load in viraemic patients – however, there is a subgroup of patients with undetectable viraemia who exhibit elevated T-cell activation (78). There has been speculation that the lower levels of immune activation in the many aviraemic HIV-2 infected patients

constitute the key factor explaining their slower rates of disease progression (84).

Levels of biomarkers associated with enhanced immune activation are equivalent in HIV-1 and HIV-2 infection and when viral load is taken into account, HIV-2 appears to elicit greater immune activation per unit of viral load than does HIV-1 (85).

Moreover, immune activation in patients with HIV-1 and HIV-2 infection is equivalent when matched for CD4<sup>+</sup> count (86).

A key driver of immune activation in HIV-1-infected subjects is the increased translocation into the blood of microbial products from the gut, including lipopolysaccharide (LPS), which promotes macrophage activation (87). LPS levels were elevated in an African cohort with HIV-2 infection and correlated with disease progression (88). However, this was not observed in a European cohort, even though there was evidence of significant T-cell and monocyte activation (89). In marked contrast to HIV-1 infection, mucosal integrity and gut-associated lymphocyte numbers are preserved in aviraemic HIV-2 infection (with or without ART), despite the presence of replicating virus in the gut mucosa (82). These findings suggest that there is a significant difference in HIV-associated gut mucosal pathology between HIV-1 and HIV-2 infection, although how this might link with HIV-2 progression is not entirely clear.

### Other Host factors associated with HIV-2 progression

Disease progression in HIV reflects a complex interplay between social factors and biological factors which influence how rapidly a person will develop AIDS after HIV infection. Age at infection and sex are important determinants in this dynamic process.

Being male is an important determining factor in disease outcomes for both HIV-1 and HIV-2 (90). These findings may be explained, in part, by social behaviour of men resulting in poor adherence to ART and health-seeking behaviour later in infection (91). In addition, baseline mortality rates due to non-infectious causes are higher in males and this contributes to the observed higher mortality rates in HIV-infected men (92).

Social factors do not fully account for the discrepancy in disease progression rates between males and females. Plasmacytoid dendritic cells from females produce higher transcription levels of several interferon stimulated genes in response to IFN $\alpha$  than those from males (93). This enhanced response may be beneficial in acute infection - limiting viral set point and initial CD4<sup>+</sup> count decline (94). Females on average have lower viral load set points coupled with an enhanced Type I IFN response and greater CD8<sup>+</sup> T cell activation – this may favour rapid CD4<sup>+</sup> recovery, and improved outcomes after ART initiation (95,96). Statistical modelling of transmitted viral sequences indicates that transmission bottlenecks in heterosexuals exist, and that they favour the transmission of viruses with greater fitness from females to males (97). It has been postulated that because women have a large population of cells in the vaginal mucosa which are susceptible to HIV infection, they therefore have a lower barrier to infection than men. This bottleneck selects viruses

infecting men with greater predicted replicative capacity based on the presence of specific amino acid residues. The viruses which infect men may therefore predispose them to accelerated disease progression.

HIV-1 infected males in Cameroon had an elevated risk of virological failure after ART initiation which was not linked to pre-existing viral resistance or poor adherence. Furthermore, females in this study showed greater CD4<sup>+</sup> count recovery after 24 months of ART (98). Most African HIV-2 cohorts contain more women than men and here male sex has been associated with higher mortality as well (99).

In HIV-1 advanced age at infection is a powerful co-factor for accelerated disease progression – this is probably due to immunological senescence (100). Males are often older than females when they initiate ART which may therefore explain their diminished immunological reconstitution (101). HIV-2 prevalence in Guinea-Bissau was highest amongst females in the 45-60-year age group (102) and in the pre-ART era older HIV-2-infected adults had mortality rates equivalent to the HIV negative population, suggesting that age was not a risk factor for progression in HIV-2 infection (103). In contrast, data from the ANRS cohort showed that age greater than 40 years was a significant risk factor for HIV-2 disease progression after ART initiation (104).

## Conclusion - Possible Causal Factors Which Promote HIV-2 Disease

### Progression

We believe that greater priority should be given to HIV-2 research because of the unique insights this human model can provide about the pathophysiology of HIV-1, particularly a better understanding of host and viral factors associated with long-term viral control. The interaction between the viral capsid, host restriction factors and the cellular immune response may be central to maintaining durable control of viral replication in HIV-2 infection. Multiple lines of evidence indicate that TRIM5 $\alpha$  may, soon after initiating viral uncoating, target the viral capsid for proteasomal degradation (32). During this process HIV-2 capsids enriched in proline residues may favour the efficient processing of CTL epitopes that are associated with a long lasting, protective gag-specific CTL response. The strength of the capsid/TRIM5 $\alpha$  interaction is also related to the extent to which the Type I IFN responses are triggered (105), combinations of capsid and TRIM5 $\alpha$  that bind with high affinity could lead to a potent CTL response targeting gag epitopes. In aviraemic patients this CTL response may potentially be maintained by ongoing, low-level mucosal replication in the gut. HIV-2-specific CTL may be able to control viral replication and maintain a low level of immune activation for many years, without the emergence of viral escape mutants (59). A caveat to the search for a functional cure is that therapies which maintain a low viral load may not always result in a reversal of immunodeficiency if immune activation remains high (106).

Given HIV's unparalleled ability to adapt to its host, future therapies which aim to induce a state of prolonged clinical latency in the absence of regular therapeutic intervention (either ART or infusions of monoclonal antibodies) will need to target

multiple aspects of viral replication. TRIM5 $\alpha$  restriction acts at the pre-integration phase of the life-cycle, displays cross-talk with the adaptive immune response and may negatively affect viral RC. There is evidence to support this proposition as HIV-1 CTL escape variants display increased sensitivity to restriction by TRIM5 $\alpha$  (107). The RC of these escape variants may be further reduced given the functional constraints on capsid structure (108).

*TRIM5* has been successfully edited using the CRISPR-Cas 9 system to effect single nucleotide polymorphisms which augment HIV-1 restriction (109) and recent advances in CRISPR technology may allow for multiple specific edits to the human genome with greater accuracy and lower risk of off-site effects (110). It is possible to envisage *ex vivo* editing of *TRIM5* to generate a patient specific pool of HIV-resistant CD4<sup>+</sup> T cells in the future. Understanding how HIV-2 replication is durably controlled by TRIM5 $\alpha$  may provide valuable insights into working toward this future scenario.



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### Conflict of interest

We report no conflict of interest

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## Figure legends

**Figure 1:** Mortality after years of follow up based on HIV-2 viral load. HIV-2 VL = HIV-2 viral load measured in copies/mL. These survival curves are adapted from Kaplan-Meier survival curves for HIV-2 when stratified for viral load published in (12). Increasing viral load level has a strong association with decreasing survival probability (12).

**Figure 2:** Mechanism of retroviral restriction by TRIM5 $\alpha$ : a) after viral entry TRIM5 $\alpha$  monomers binds to the capsid and oligomerise with additional TRIM5 $\alpha$  molecules. b) these are then poly-ubiquitinated via TRIM's E3 ligase activity. This prematurely uncoats the capsid, disrupting the reverse transcription/capsid complex (RTC). c) The RTC is then recruited to the cellular proteasome for degradation. d) We hypothesise that enhanced proteasomal processing selects for epitopes which are associated with protective gag specific CD8<sup>+</sup> T cell responses presented on HLA class I molecules (32,33).

**Figure 3:** Differences in the HIV-1 and HIV-2 genomes. *Gag* genes display approximately 60% protein sequence similarity between HIV-1 and 2, whereas *env* has approximately 40% similarity (34). HIV-1 possesses the accessory protein Vpu which degrades both surface CD4 receptors and tetherin, thereby enhancing virion release. HIV-2 contains *vpx*: this protein counteracts restriction factor SAMHD1, which is present in myeloid cell lines (figure adapted from (36)).