

## Pure-AMC

### **Interplay between HIV-1 innate sensing and restriction in mucosal dendritic cells: balancing defense and viral transmission**

Hertoghs, Nina; Geijtenbeek, Teunis B. H.; Ribeiro, Carla M. S.

*Published in:*  
Current opinion in virology

*DOI:*  
[10.1016/j.coviro.2017.01.001](https://doi.org/10.1016/j.coviro.2017.01.001)

Published: 01/01/2017

*Document Version*  
Peer reviewed version

*Citation for published version (APA):*  
Hertoghs, N., Geijtenbeek, T. B. H., & Ribeiro, C. M. S. (2017). Interplay between HIV-1 innate sensing and restriction in mucosal dendritic cells: balancing defense and viral transmission. *Current opinion in virology*, 22, 112-119. <https://doi.org/10.1016/j.coviro.2017.01.001>

#### **General rights**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

#### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

**Interplay between HIV-1 innate sensing and restriction in mucosal dendritic cells:  
balancing defense and viral transmission**

*Nina Hertoghs, Teunis B.H. Geijtenbeek, Carla M.S. Ribeiro*

Department of Experimental Immunology, Academic Medical Center, University of  
Amsterdam, Amsterdam, the Netherlands

Corresponding Author: Teunis B. H. Geijtenbeek  
Department of Experimental Immunology  
Academic Medical Center (AMC)  
Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands  
Tel.: +31 20 566 60 63  
Fax: +31 20 697 71 92  
E-mail: [t.b.geijtenbeek@amc.uva.nl](mailto:t.b.geijtenbeek@amc.uva.nl)

2 **Abstract**

3 Innate sensing of HIV-1 by dendritic cells (DCs) initiates cell-intrinsic signalling programs  
4 that direct virus restriction and antiviral defences. These responses include the production of  
5 type I interferon (IFN) and a large number of IFN-stimulated genes (ISGs) with a broad  
6 spectrum of antiviral effector functions. Initial interactions of HIV-1 at the mucosal surfaces  
7 with DC-expressed innate immune factors including cGAS, TRIM5 $\alpha$  and SAMHD1 are  
8 predictive of viraemia, inflammation and disease pathogenesis. Here, we review the  
9 molecular basis of HIV-1 sensing in the two major mucosal DC subsets, i.e. epithelial  
10 Langerhans cells and subepithelial CD11c<sup>+</sup> conventional DCs. We discuss the concerted  
11 actions of the host restriction factors and innate sensors as well as viral evasion mechanisms  
12 in determining HIV-1 susceptibility to infection and directing antiviral adaptive immune  
13 responses.

## 14 **Introduction**

15 Innate antiviral defence is crucial for halting initial HIV-1 infection and dissemination,  
16 whereas adaptive immune responses are vital for elimination of virus-infected cells and long-  
17 term protection. Recent studies suggest that the initial events and the inflammatory profile  
18 during acute retroviral exposure across mucosal surfaces are predictive of the viral load set  
19 point and the rate of disease progression. Early inhibition of type I IFN responses by blocking  
20 the IFN $\alpha/\beta$  receptor in SIV-infected rhesus macaques results in increased SIV viraemia and  
21 accelerated CD4 T-cell depletion, suggesting that type I IFN responses direct anti-HIV-1  
22 responses [1]. However, high levels of the ISG IP-10 (interferon gamma-induced protein 10)  
23 and the cytokine TNF- $\alpha$  (tumor necrosis factor  $\alpha$ ) in the plasma during primary HIV-1  
24 infection in humans are associated with poor viral control and rapid disease progression [2,3].  
25 Thus, a tight regulation of the induction of inflammatory responses during HIV-1 infection is  
26 required to mount an effective early antiviral responses without deleterious effects.  
27 Remarkably, recent research in elite controllers, a subgroup of HIV-1-infected individuals  
28 able to control viral replication in the absence of antiretroviral therapy, underscores the *in*  
29 *vivo* relevance of dendritic cells (DCs) where it was shown that DC maturation and secretion  
30 of type I IFN rapidly after HIV-1 infection induces protective HIV-1 specific CD8<sup>+</sup> cytotoxic  
31 T cells [4]. In this review, we will focus on the innate intrinsic responses by mucosal DC  
32 subsets during primary HIV-1 infection and how components of the type I IFN system  
33 including innate sensors and restriction factors determine cell-intrinsic resistance to infection.  
34 Furthermore, we will discuss the implications of the interplay of these host effectors on DC  
35 activation and DC-mediated viral transmission.

36

### 37 **Many branches of DC functions at the crossroads of primary HIV-1 infection**

38 Among the different cellular components of mucosal immunity, DCs play a central role in  
39 orchestrating innate and adaptive T-cell mediated immune responses [5]. DCs are  
40 professional antigen-presenting cells, which reside in the mucosa (including vagina, foreskin,  
41 mouth and colorectal mucosal) and thereby proposed to be one of the first immune target  
42 cells to detect HIV-1 during sexual transmission [6–9]. Equipped with pattern-recognition  
43 receptors (PRRs), DCs sense viral pathogen-associated molecular patterns (PAMPs).  
44 Triggering of PRRs results in the production of Type I IFN and IFN-stimulated genes (ISGs)  
45 to control virus spread as well pro-inflammatory cytokines and chemokines necessary to  
46 recruit other immune cells and to initiate adaptive T-cell-mediated immune responses [10].  
47 PRRs mediate internalization and processing of pathogen-derived antigens for subsequent

48 antigen presentation to naïve T cells in the context of MHC molecules [11]. Optimal priming  
49 of naïve T cells into effector antiviral T cells depends on the maturation status of DCs, i.e., a  
50 cascade of phenotypical changes in DCs and secretion of DC-derived soluble mediators [5].  
51 A hallmark of DC maturation is the upregulation of MHC-I/II, co-stimulatory molecules  
52 CD80, CD86, CD70 and lymphoid tissue homing receptor CCR7. DC-mediated cytokine  
53 production including IL-12 and IL-27 are required to evoke CD4<sup>+</sup> TH1 responses and CD8<sup>+</sup>  
54 cytotoxic T cell response, respectively, to clear virus-infected cells and mount a memory T-  
55 cell-mediated immune response [12]. For the establishment of HIV-1 infection, the virus has  
56 to spread from the mucosal entry sites to the CD4<sup>+</sup> T cell-enriched areas in the lymphoid  
57 tissues. The ability of DCs to migrate from the periphery to lymph nodes supports also an  
58 important role for DCs not only in HIV-1 specific adaptive immune responses, but also in  
59 viral transmission and disease progression.

60

### 61 **Cell-intrinsic antiviral responses during mucosal HIV-1 transmission**

62 Two major DC subsets reside in human mucosal tissues, which can be distinguished by their  
63 specific location within mucosal surfaces as well as phenotypical and functional  
64 characteristics [13]. Langerhans cells (LCs) reside at mucosal epithelia and express C-type  
65 lectin receptor (CLR) langerin whereas myeloid CD11c<sup>+</sup> conventional DCs (myDCs) located  
66 at the subepithelia are characterized by the expression of the CLR DC-SIGN [14–16]. It has  
67 been suggested that myDCs are not productively infected by HIV-1 [17,18]. However,  
68 several other studies have shown that monocyte-derived DCs, an experimental model for  
69 myDCs, are efficiently infected by HIV-1 [19–22]. myDCs express PRRs that sense HIV-1  
70 but HIV-1 hijacks their signalling for replication as engagement of HIV-1 by the PRRs DC-  
71 SIGN and TLR8 promotes viral replication in myDCs [23]. Infected DCs act as virus  
72 producers that promote transmission of *de novo* HIV-1 particles to target T cells [24,25]. In  
73 addition, myDCs can transmit virus without the need for productive infection; DC-SIGN on  
74 myDCs acts as a *trans* receptor that binds to HIV-1 and transmits the virus to neighbouring  
75 target cells [15,26]. Strikingly, HIV-1 infected DCs do not undergo maturation and therefore  
76 have a diminished capacity to activate naïve T cells [18,19,22]. Furthermore, DCs are unable  
77 to produce type I and III interferon in response to HIV-1 [27,28]. The lack of DC maturation  
78 and type I IFN production, which are prerequisites for an effective antiviral immune  
79 response, might be due to either a lack of sensing by DC-expressed PRRs or the result of  
80 evasion mechanisms of the virus on PRR-induced antiviral signalling programs.

81 In contrast, primary immature LCs do not become infected and act as a natural barrier against  
82 HIV-1; LCs restrict HIV-1 infection [14,29–31]. LCs efficiently bind and internalize HIV-1  
83 via langerin. However, capture of HIV-1 via langerin does neither allow infection nor  
84 transmission but rather sequesters the virus into Birbeck granules [14,29,30]. These LC-  
85 specific organelles have a superior ability in viral degradation and contribute to the intrinsic  
86 antiviral function of langerin resulting in a post-entry restriction of HIV-1 infection in LCs  
87 [14,30,32]. Little is known about the innate sensing of HIV-1 in LCs and whether these cells  
88 become activated or produce type I IFN upon HIV-1 exposure[31].

89 The different roles of mucosal DCs on primary HIV-1 infection and viral transmission might  
90 represent a functional specialization of LCs and myDCs on antiviral responses or the result of  
91 the concerted action of innate sensors and restriction factors. Deciphering the molecular basis  
92 underlying the LC-intrinsic restriction mechanism and defective sensing in myDCs might  
93 provide rationale for novel strategies to provide both viral restriction and innate sensing by  
94 mucosal DCs and thus, mount a protective antiviral immune response early upon mucosal  
95 HIV-1 transmission.

96

### 97 **HIV-1 sensing and restriction in DCs: components of the IFN-I system**

98 Initially it was suggested that HIV-1 escapes immunosurveillance by not efficiently infecting  
99 DCs. Therefore, restriction of HIV-1 by these cells minimizes the capacity to mount a  
100 sufficient innate immune response, as cytosolic sensors are not triggered by HIV-1 DNA  
101 products. In 2013, cyclic GMP-AMP syntase (cGAS) was identified as the cytosolic DNA  
102 sensor that is triggered by HIV-1. In short, Polyglutamine binding protein 1 (PQBP1) binds to  
103 reverse transcribed cDNA, and mediates the interaction with, and activation of cGAS [33].  
104 Upon sensing of cDNA in the cytosol, cGAS synthesizes cyclic GMP-AMP (cGAMP) which  
105 binds and triggers the adapter molecule STING, which activates the transcription factor IRF3  
106 via TBK-1, leading to IFN-I production [34–36].

107 Type I IFN binding to cell surface IFN $\alpha/\beta$  receptor in an autocrine and paracrine manner and  
108 subsequent downstream signalling JAK/STAT cascade activation results in the induction of  
109 an array of ISGs, which enhances the cell-intrinsic resistance to infection. Among the ISG-  
110 encoded proteins are the so-called host restriction factors that have been shown to directly  
111 suppress retroviral replication and dissemination, such as TRIM5 $\alpha$  (tripartite motif-containing  
112 protein 5 $\alpha$ ), SAMHD1 (SAM-and HD domain-containing protein 1), APOBEC3  
113 (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3), Mx2 (Myxovirus  
114 resistance 2), tetherin and more recently IFITM (Interferon-induced transmembrane proteins)

115 and SLFN11 (Schlafen 11). The mechanisms of suppression of each of the restriction factors  
116 have been reviewed in detail elsewhere [37,38] and here we will focus on the antiviral  
117 effector functions of TRIM5 $\alpha$  and SAMHD1 in HIV-1 infected DCs.

118 TRIM5 $\alpha$  is an E3-ubiquitin ligase that suppresses retroviral replication early after viral fusion  
119 by targeting incoming viral capsid for degradation, which interferes with reverse-  
120 transcription processes [39–41]. Both proteosomal and autophagic-dependent TRIM5 $\alpha$   
121 mechanisms have been proposed to mediate HIV-1 capsid degradation [42,43]. In addition,  
122 TRIM5 $\alpha$  can also act as a PRR and trigger innate TAK-1 and NF- $\kappa$ B-dependent signaling  
123 pathways [44]. Furthermore, rhesus TRIM5 $\alpha$ -mediated heightened capsid-specific CD8<sup>+</sup> T  
124 cell activation suggests that TRIM5 $\alpha$  couples restriction to adaptive cellular immune  
125 responses [45]. Notably, non-human primate DCs lack TRIM5 $\alpha$ -mediated restriction, while  
126 still operative in other primary cell targets (macrophages and CD4<sup>+</sup> T cells) [46,47].  
127 Subcellular localization and the small ubiquitin-related modifier (SUMO) modification  
128 account for the lack of retroviral restriction [47–50]. DeSUMOylated TRIM5 $\alpha$  in DCs  
129 accumulates in the nucleus, which correlated with the lack of retroviral restriction and thus  
130 TRIM5 $\alpha$  nuclear sequestration allows innate sensing of viral DNA by cGAS in DCs and  
131 subsequent type I interferon production [47]. The current TRIM5 $\alpha$  restriction paradigm  
132 comprises that rhesus and other simian TRIM5 $\alpha$  proteins, but not human TRIM5 $\alpha$ , bind HIV-  
133 1 capsid and thereby efficiently block HIV-1 infection [51–55]. The findings that genetic  
134 variation in *trim5 $\alpha$*  genes are associated with differential clinical course of infection and that  
135 some primary HIV-1 isolates are 8-fold more sensitive to human TRIM5 $\alpha$  restriction than  
136 HIV-1 lab-adapted strains suggest that TRIM5 $\alpha$  antiviral activity may be underestimated in  
137 humans [56,57].

138 The restriction factor SAMHD1, is highly expressed in myeloid cells like DCs and  
139 macrophages and has been shown to limit HIV-1 cDNA synthesis in myDCs [58–61]. Both  
140 dNTPase and RNase activities of SAMHD1 have been implicated in the SAMHD1-mediated  
141 HIV-1 restriction in myDCs, resulting in limited reverse transcription processes [59,61].  
142 Interestingly, LC infection is restricted after viral fusion, but in contrast to myDCs, this post-  
143 entry restriction mechanism is independent of SAMHD1 antiviral activity [30,32]. Thus,  
144 differences in antiviral activity of SAMHD1 between LCs and myDCs not only suggest that  
145 SAMHD1 is a cell-specific restriction factor, but also strongly suggest that specific cell-  
146 intrinsic antiviral signature programs are initiated at the mucosal sites, which can determine  
147 the net outcome of HIV-1 infection and antiviral immunity.

149 The observed restriction by SAMHD1 in myDCs has been suggested to lead to a diminished  
150 induction of innate immunity, since active replication of HIV-1 is needed to activate the  
151 cGAS sensing mechanism. However, several studies do not support this model, as productive  
152 infection of DCs does not lead to activation and type I IFN responses, even when infection  
153 was enhanced by degradation of SAMHD1 [19,22,62]. Part of these differences might be due  
154 to use of different viruses as many studies use VSV-G pseudotyped HIV-1 [18], which  
155 triggers different receptors than HIV-1 [23]. Taken into account that the signalling via DC-  
156 SIGN and TLR8 leads to a favourable outcome for the virus illustrates that the mode of entry  
157 has an effect on infection and activation [23]. However, infection alone might also not  
158 enough for the induction of type I IFN responses as HIV-1 similar to other viruses might  
159 actively inhibit sensors via different mechanisms [63]. In recent years, several studies have  
160 aimed at identifying a putative sensor for HIV-1 in DCs. DCs are known not to be strongly  
161 reactive against HIV-1 even though several PRRs sense HIV-1, like TLR8 and DC-SIGN.  
162 This however, does not lead to a strong antiviral state, but rather induces and support  
163 transcription of the HIV-1 proviral genome [23]. Several studies have shown that DCs are  
164 capable of sensing HIV-1, but that there are many mechanisms that HIV-1 employs to escape  
165 immunosurveillance, often involving host factors that shield HIV-1 PAMPs. An interesting  
166 factor is TREX1 that eliminates reverse transcriptase-synthesized DNA products, thereby  
167 preventing triggering of cGAS and blocking TREX1 leads to a robust IFN production by DCs  
168 upon HIV-1 infection via cGAS [64].

169 Taken together, there are two separate ways of preventing immune activation by HIV-1; by  
170 preventing sensing in the cytosol, or by preventing infection at all. Which of the mechanisms  
171 is deemed the most crucial probably depends on differences in experimental models.  
172 Therefore, it is preferable to confirm experimental findings with models that accurately  
173 resemble the *in vivo* situation such as primary DC subsets isolated from tissues. Investigating  
174 the sensor mechanisms in primary DCs instead of cell-lines will resolve some of the  
175 controversial questions.

176 Apart from the production of newly synthesized cDNA, the replication cycle of HIV-1  
177 delivers several potential targets for cytosolic sensors. The ssRNA that enters the cytosol  
178 upon HIV-1 infection is not immunogenic, as these RNA strands are Poly-A-tailed and  
179 capped, similar to host mRNA molecules [65]. However, a study suggests that the triggering  
180 of RIG-I-like receptors (RLR) is prevented by SKIV2L, a host exonuclease that degrades and  
181 thereby shields incoming viral ssRNA [66]. Additionally, Cofactors cleavage and



182 polyadenylation specificity factor subunit 6 (CPSF6) and cyclophilins Nup358 and CypA are  
183 essential in preventing IFN production in macrophages [67].

184 Taken together, these studies show that HIV-1 employs many mechanisms via host factors to  
185 shield its PAMPs from the host immunosurveillance. The level and timing of IFN-I early  
186 upon retroviral have important consequences in viral transmission and disease progression.

187

### 188 **Dendritic cells mediate viral transmission: role for mucosal inflammation and type I** 189 **IFN production**

190 The early innate immune response that is elicited by invading viruses during HIV-1  
191 transmission is insufficient to protect against the invading virus. Many studies have shown  
192 that DCs contribute to HIV-1 transmission. There are several studies describing infection of  
193 DCs, but the general paradigm states that DCs bind HIV-1 but do not become infected  
194 themselves, and are therefore unable to sense the virus. As a Trojan horse, DCs transport  
195 HIV-1 to the lymph node where it transmits the virus to CD4 T-cells [15].

196 As mentioned before, LCs are not susceptible to HIV-1 infection, and the interaction with  
197 langerin leads to capture and degradation of the virus [14]. However, during co-infections  
198 with other pathogens, in the case of an STI for instance, restriction in LCs is abrogated,  
199 presumably because activation of LCs leads to downregulation of langerin, which renders the  
200 cells more susceptible to HIV-1 infection [14,29,68]. Thus, DC subsets and inflammation  
201 affect HIV-1 susceptibility during sexual transmission and it has been suggested that only  
202 viruses with specific attributes allowing them to overcome these barriers establish infection  
203 of the host.

204 Recently, methods have been devised to study the phenotype of HIV-1 just after  
205 transmission, as this can give insight into the factors contributing to successful transmission  
206 of HIV. In most of the cases, CCR5 using strains (R5) are transmitted, irrespective to the  
207 presence of CXCR4 (X4) using strains in the transmission fluid. Many studies have been  
208 devoted to unravel the mechanism behind this selection [69]. Recently, it has been shown that  
209 LCs exhibit a selective preference for transmitting R5 strains, even though both X4 and R5  
210 using strains were able to infect primary LCs, but only R5 strains were transmitted to target  
211 cells *in vitro* [29]. This study underscores that specific mechanisms exist that limit X4 virus  
212 transmission. Other studies suggest that target cells *in situ* do not express CXCR4 to the same  
213 level as CCR5, although conflicting findings have been published [29]. Furthermore, the R5  
214 selection occurs in all transmission routes, also via blood, suggesting that a single cell type is  
215 not the sole determinant of the R5 selection. Thus, detailed studies on the mechanisms of R5

216 selection will allow us to not only understand the important selection mechanisms but also to  
217 devise new strategies to prevent R5 transmission.

218 Indeed, recent studies have revealed specific characteristics for transmitted viruses, by  
219 investigating the transmitted viruses in depth, by employing a new technique called single  
220 genome sequencing (SGA) [70]. Here, limiting dilutions of cDNA are serially diluted in  
221 which each sample contains only one template of an HIV-variant from the plasma of an  
222 acutely infected individual. After amplification, each virus type is sequenced. This enables  
223 the thorough characterization of the transmitted viruses before seroconversion [70]. These  
224 studies have led to the understanding that in 60-90% of the transmission events, only one or a  
225 few HIV-1 variants are transmitted [71]. Taken into account that transmission fluids like  
226 semen or cervicovaginal fluid contain many HIV-1 variants, these so-called transmitted  
227 founder viruses (T/F virus) might harbor subtle differences that render them more successful  
228 in escaping the restrictions during transmission. Information about these T/F viruses gives  
229 vital clues about the decisive and critical events during transmission. Several studies have  
230 shown that T/F viruses are less prone to IFN restriction compared to chronic viruses [72,73].  
231 This suggests that somewhere in the course of transmission, IFN is produced. The relative  
232 resistance would give a crucial advantage that leads to transmission to the new host.

233 Further investigations have indicated that the T/F virus phenotype harbors an Env protein that  
234 has less N-linked glycosylation sites [72]. This finding is remarkable, as HIV-1 is known to  
235 shield its Env protein with glycans in order to escape the recognition of neutralizing  
236 antibodies. Lacking specific glycosylation sites might make the virus less susceptible to  
237 certain factors in the cervicovaginal fluids, as has been suggested before. Another explanation  
238 is that lesser glycosylation sites decreases the interaction probability with CLRs on local  
239 immune cells such as DCs and LCs. Another study found that the amount of Env seemed to  
240 be increased on T/F viruses, which increased the binding and transmission by DCs [72,74].  
241 Moreover, T/F viruses have been shown to be more infectious, and replicate better in T-cells,  
242 they are captured more efficiently by DCs and transmitted to T-cells [72]. These studies are  
243 important to understand the innate responses encountered by HIV-1 during transmission and  
244 further research will undoubtedly uncover more of these mechanisms.

245

## 246 **Conclusions and outlook**

247 DCs are crucial in the induction of both innate and adaptive responses to HIV-1 but  
248 paradoxically these cells are also responsible for viral transmission. The balance between  
249 antiviral immunity and viral transmission determines HIV-1 susceptibility and pathogenesis.

250 In recent years it has become clear that host restriction factors and sensing mechanisms  
251 control the function of DC subsets in HIV-1 infection and pathogenesis. The importance of  
252 type I IFN-mediated responses in blocking viral replication within the cell but also in  
253 promoting adaptive immunity to HIV-1 underscores the importance of innate sensing in  
254 mucosal DC subsets. The more so, since HIV-1 viruses that establish HIV-1 infection in the  
255 host, T/F viruses, are less sensitive to type I IFN.

256 Thus, our knowledge about intrinsic restriction and sensing mechanisms improved greatly in  
257 recent years, but many important details of the spatio-temporal triggering of these host  
258 antiviral factors and how they act in concert within primary human DC subsets using  
259 clinically-relevant HIV-1 strains remains poorly defined. Understanding these crosstalk  
260 mechanisms should ultimately provide novel therapeutic targets to selectively limit viral  
261 transmission while preserving innate immune recognition. In addition, there is accumulating  
262 evidence that components of the type I IFN response, such as TRIM5 $\alpha$  can trigger autophagy  
263 as well as components of autophagy machinery can limit cGAS-mediated type I IFN  
264 production [43,75,76]. Harnessing this intracellular degradative process may potentiate innate  
265 sensing as well as aid the design of novel small-molecule inhibitors that can act as antivirals.

266 Furthermore, uncovering viral immune evasion mechanisms employed by HIV-1 as well as  
267 defining novel viral sensors is paramount to design novel strategies to antagonize aberrant  
268 activation of PRRs or block interaction between viral PAMPs and host effector molecules.

269 Deciphering the molecular mechanisms by which genetic mutations in these host factors are  
270 associated with disease pathogenesis or inflammatory/autoimmune diseases may provide  
271 novel insights to boost immunogenicity of vaccines and antivirals as well as mitigate  
272 unwanted inflammation.

273 **Acknowledgements**

274 This work was supported by the Dutch Scientific Organization NWO (VENI 863.13.025),  
275 Aids Fonds (2012042) and European Research Council Advanced grant (670424).

276 **References**

- 277 1. Sandler NG, Bosinger SE, Estes JD, Zhu RT, Tharp GK, Boritz E, Levin D,  
278 Wijeyesinghe S, Makamdop KN, del Prete GQ, et al.: **Type I interferon responses in**  
279 **rhesus macaques prevent SIV infection and slow disease progression** . *Nature*  
280 2014, **511**:601–605.
- 281 2. Vaidya SA, Korner C, Sirignano MN, Amero M, Bazner S, Rychert J, Allen TM,  
282 Rosenberg ES, Bosch RJ, Altfeld M: **Tumor necrosis factor  $\alpha$  is associated with**  
283 **viral control and early disease progression in patients with HIV type 1 infection.**  
284 *The Journal of infectious diseases* 2014, **210**:1042–6.
- 285 3. Liovat AS, Rey-Cuillé MA, Lécuroux C, Jacquelin B, Girault I, Petitjean G, Zitoun Y,  
286 Venet A, Barré-Sinoussi F, Lebon P, et al.: **Acute Plasma Biomarkers of T Cell**  
287 **Activation Set-Point Levels and of Disease Progression in HIV-1 Infection.** *PLoS*  
288 *ONE* 2012, **7**:1–13.
- 289 4. Martin-Gayo E, Buzon MJ, Ouyang Z, Hickman T, Cronin J, Pimenova D, Walker  
290 BD, Lichterfeld M, Yu XG: **Potent Cell-Intrinsic Immune Responses in Dendritic**  
291 **Cells Facilitate HIV-1-Specific T Cell Immunity in HIV-1 Elite Controllers.** .  
292 *PLoS pathogens* 2015, **11**:e1004930.
- 293 5. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu Y, Pulendran B, Palucka  
294 K: **Immunobiology of Dendritic Cells.** *annual review of immunology* 2000, **18**:767–  
295 811.
- 296 6. Duluc D, Gannevat J, Anguiano E, Zurawski S, Carley M, Boreham M, Stecher J,  
297 Dullaers M, Banchereau J, Oh S: **Functional diversity of human vaginal APC**  
298 **subsets in directing T-cell responses.** *Mucosal immunology* 2013, **6**:626–38.
- 299 7. Ganor Y, Zhou Z, Tudor D, Schmitt a, Vacher-Lavenu M-C, Gibault L, Thiounn N,  
300 Tomasini J, Wolf J-P, Bomsel M: **Within 1 h, HIV-1 uses viral synapses to enter**  
301 **efficiently the inner, but not outer, foreskin mucosa and engages Langerhans-T**  
302 **cell conjugates.** . *Mucosal immunology* 2010, **3**:506–22.
- 303 8. Nudel I, Elnekave M, Furmanov K, Arizon M, Clausen BE, Wilensky A, Hovav A-H:  
304 **Dendritic cells in distinct oral mucosal tissues engage different mechanisms to**  
305 **prime CD8+ T cells.** *Journal of immunology (Baltimore, Md. : 1950)* 2011, **186**:891–  
306 900.
- 307 9. Preza GC, Tanner K, Elliott J, Yang OO, Anton PA, Ochoa M-T: **Antigen-presenting**  
308 **cell candidates for HIV-1 transmission in human distal colonic mucosa defined by**  
309 **CD207 dendritic cells and CD209 macrophages.** *AIDS research and human*

- 310 *retroviruses* 2014, **30**:241–9.
- 311 10. Takeuchi O, Akira S: **Pattern Recognition Receptors and Inflammation**. *Cell* 2010,  
312 **140**:805–820.
- 313 11. Iwasaki A, Medzhitov R: **Regulation of adaptative immunity by the innate**  
314 **immune system**. *Science* 2010, **327**:291–295.
- 315 12. Sousa CR e: **Dendritic cells in a mature age**. . *Nature Reviews: Immunology* 2006,  
316 **6**:476–483.
- 317 13. Durand M, Segura E: **The known unknowns of the human dendritic cell network**.  
318 *Frontiers in Immunology* 2015, **6**:2–8.
- 319 14. de Witte L, Nabatov A, Pion M, Fluitsma D, de Jong M a WP, de Gruijl T, Piguet V,  
320 van Kooyk Y, Geijtenbeek TBH: **Langerin is a natural barrier to HIV-1**  
321 **transmission by Langerhans cells**. . *Nature medicine* 2007, **13**:367–71.
- 322 15. Geijtenbeek TB, Kwon DS, Torensma R, van Vliet SJ, van Duijnhoven GC, Middel J,  
323 Cornelissen IL, Nottet HS, KewalRamani VN, Littman DR, et al.: **DC-SIGN, a**  
324 **dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T**  
325 **cells**. . *Cell* 2000, **100**:587–97.
- 326 16. Jameson B, Baribaud F, Pöhlmann S, Ghavimi D, Mortari F, Doms RW, Iwasaki A:  
327 **Expression of DC-SIGN by dendritic cells of intestinal and genital mucosae in**  
328 **humans and rhesus macaques**. *Journal of virology* 2002, **76**:1866–75.
- 329 17. Cameron P, Freudenthal P, Barker J, Gezelter S, Inaba K, Steinman R: **Dendritic cells**  
330 **exposed to human immunodeficiency virus type-1 transmit a vigorous cytopathic**  
331 **infection to CD4+ T cells** . *Science* 1992, **257**:383–387.
- 332 18. Manel N, Hogstad B, Wang Y, Levy DE, Unutmaz D, Littman DR: **A cryptic sensor**  
333 **for HIV-1 activates antiviral innate immunity in dendritic cells**. *Nature* 2010,  
334 **467**:214–7.
- 335 19. Granelli-Piperno A, Golebiowska A, Trumpheller C, Siegal FP, Steinman RM: **HIV-**  
336 **1-infected monocyte-derived dendritic cells do not undergo maturation but can**  
337 **elicit IL-10 production and T cell regulation**. . *Proceedings of the National Academy*  
338 *of Sciences of the United States of America* 2004, **101**:7669–74.
- 339 20. Smed-Sörensen A, Loré K, Vasudevan J, Louder MK, Andersson J, Mascola JR, Spetz  
340 A-L, Koup RA: **Differential susceptibility to human immunodeficiency virus type**  
341 **1 infection of myeloid and plasmacytoid dendritic cells**. . *Journal of virology* 2005,  
342 **79**:8861–9.
- 343 21. Gringhuis SI, den Dunnen J, Litjens M, van der Vlist M, Geijtenbeek TBH:

- 344 **Carbohydrate-specific signaling through the DC-SIGN signalosome tailors**  
345 **immunity to Mycobacterium tuberculosis, HIV-1 and Helicobacter pylori.** *Nature*  
346 *immunology* 2009, **10**:1081–8.
- 347 22. Hertoghs N, van der Aar a. MG, Setiawan LC, Kootstra N a., Gringhuis SI,  
348 Geijtenbeek TBH: **SAMHD1 Degradation Enhances Active Suppression of**  
349 **Dendritic Cell Maturation by HIV-1.** *The Journal of Immunology* 2015,  
350 doi:10.4049/jimmunol.1403016.
- 351 23. Gringhuis SI, van der Vlist M, van den Berg LM, den Dunnen J, Litjens M,  
352 Geijtenbeek TBH: **HIV-1 exploits innate signaling by TLR8 and DC-SIGN for**  
353 **productive infection of dendritic cells.** *Nature immunology* 2010, **11**:419–26.
- 354 24. Burleigh L, Lozach P-Y, Schiffer C, Staropoli I, Pezo V, Porrot F, Canque B,  
355 Virelizier J-L, Arenzana-Seisdedos F, Amara A: **Infection of Dendritic Cells (DCs),**  
356 **Not DC-SIGN-Mediated Internalization of Human Immunodeficiency Virus, Is**  
357 **Required for Long-Term Transfer of Virus to T Cells.** *Journal of Virology* 2006,  
358 **80**:2949–2957.
- 359 25. Turville SG, Santos JJ, Frank I, Cameron PU, Wilkinson J, Miranda-Saksena M, Dable  
360 J, Stössel H, Romani N, Piatak M, et al.: **Immunodeficiency virus uptake, turnover,**  
361 **and 2-phase transfer in human dendritic cells. .** *Blood* 2004, **103**:2170–9.
- 362 26. Kwon DS, Gregorio G, Bitton N, Hendrickson WA, Littman DR: **DC-SIGN-**  
363 **Mediated Internalization of HIV Is Required for Trans-Enhancement of T Cell**  
364 **Infection .** *Immunity* 2002, **16**:135–144.
- 365 27. Harman AN, Nasr N, Feetham A, Galoyan A, Alshehri AA, Rambukwelle D, Botting  
366 RA, Hiener BM, Diefenbach E, Diefenbach RJ, et al.: **HIV Blocks Interferon**  
367 **Induction in Human Dendritic Cells and Macrophages by Dysregulation of**  
368 **TBK1.** *Journal of virology* 2015, **89**:6575–84.
- 369 28. Harman AN, Lai J, Turville S, Samarajiwa S, Gray L, Marsden V, Mercier SK,  
370 Mercier S, Jones K, Nasr N, et al.: **HIV infection of dendritic cells subverts the IFN**  
371 **induction pathway via IRF-1 and inhibits type 1 IFN production. .** *Blood* 2011,  
372 **118**:298–308.
- 373 29. Sarrami-Forooshani R, Mesman AW, van Teijlingen NH, Sprokholt JK, van der Vlist  
374 M, Ribeiro CMS, Geijtenbeek TBH: **Human immature Langerhans cells restrict**  
375 **CXCR4-using HIV-1 transmission.** *Retrovirology* 2014, **11**:52.
- 376 30. van den Berg LM, Ribeiro CMS, Zijlstra-Willems EM, de Witte L, Fluitsma D,  
377 Tigchelaar W, Everts V, Geijtenbeek TBH: **Caveolin-1 mediated uptake via langerin**

- 378 **restricts HIV-1 infection in human Langerhans cells. *Retrovirology* 2014, **11**:3903.**
- 379 31. Ribeiro CMS, Sarrami-forooshani R, Geijtenbeek TBH: **HIV-1 border patrols :**  
380 **Langerhans cells control antiviral responses and viral transmission.** 2015,  
381 **10**:1231–1243.
- 382 32. Czubala MA, Finsterbusch K, Ivory MO, Mitchell JP, Ahmed Z, Shimauchi T, Karoo  
383 ROS, Coulman SA, Gateley C, Birchall JC, et al.: **TGFβ Induces a SAMHD1-**  
384 **Independent Post-Entry Restriction to HIV-1 Infection of Human Epithelial**  
385 **Langerhans Cells. *Journal of Investigative Dermatology* 2016, **136**:1981–1989.**
- 386 33. Yoh SM, Schneider M, Chanda SK, Yoh SM, Schneider M, Seifried J,  
387 Soonthornvacharin S, Akleh RE, Olivieri KC, Jesus PD De, et al.: **PQBP1 Is a**  
388 **Proximal Sensor of the cGAS-Dependent Innate Response to HIV-1 Article**  
389 **PQBP1 Is a Proximal Sensor of the cGAS-Dependent Innate Response to HIV-1.**  
390 2015, doi:10.1016/j.cell.2015.04.050.
- 391 34. Gao D, Wu J, Wu Y, Du F, Aroh C, Yan N, Sun L, Chen ZJ: **Cyclic GMP-AMP**  
392 **synthase is an innate immune sensor of HIV and other retroviruses. *Science (New*  
393 *York, N.Y.)* 2013, **341**:903–906.**
- 394 35. Sun L, Wu J, Du F, Chen X, Chen ZJ: **Cyclic GMP-AMP Synthase Is an. *Science*  
395 2013, **339**:786–791.**
- 396 36. Coleman CM, Wu L: **HIV interactions with monocytes and dendritic cells: viral**  
397 **latency and reservoirs. *Retrovirology* 2009, **6**:51.**
- 398 37. Doyle T, Goujon C, Malim MH: **HIV-1 and interferons: who’s interfering with**  
399 **whom? . *Nature Reviews Microbiology* 2015, doi:10.1038/nrmicro3449.**
- 400 38. Altfeld M, Gale MJ: **Innate immunity against HIV-1 infection. *Nature immunology*  
401 2015, **16**:554–562.**
- 402 39. Stremlau M, Owens CM, Perron MJ, Kiessling M, Autissier P, Sodroski J: **The**  
403 **cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World**  
404 **monkeys. *Nature* 2004, **427**:848–53.**
- 405 40. Stremlau M, Perron M, Lee M, Li Y, Song B, Javanbakht H, Diaz-Griffero F,  
406 Anderson DJ, Sundquist WI, Sodroski J: **Specific recognition and accelerated**  
407 **uncoating of retroviral capsids by the TRIM5alpha restriction factor. *Proceedings*  
408 *of the National Academy of Sciences of the United States of America* 2006, **103**:5514–  
409 9.**
- 410 41. Ganser-Pornillos BK, Chandrasekaran V, Pornillos O, Sodroski JG, Sundquist WI,  
411 Yeager M: **Hexagonal assembly of a restricting TRIM5alpha protein. *Proceedings***



- 412 of the National Academy of Sciences of the United States of America 2011, **108**:534–  
413 539.
- 414 42. Wu X, Anderson JL, Campbell EM, Joseph AM, Hope TJ: **Proteasome inhibitors**  
415 **uncouple rhesus TRIM5 $\alpha$  restriction of HIV-1 reverse transcription and**  
416 **infection.** *Proceedings of the National Academy of Sciences of the United States of*  
417 *America* 2006, **103**:7465–70.
- 418 43. Mandell MA, Jain A, Arko-Mensah J, Chauhan S, Kimura T, Dinkins C, Silvestri G,  
419 Münch J, Kirchhoff F, Simonsen A, et al.: **TRIM Proteins Regulate Autophagy and**  
420 **Can Target Autophagic Substrates by Direct Recognition.** *Developmental Cell*  
421 2014, **30**:394–409.
- 422 44. Pertel T, Hausmann S, Morger D, Züger S, Guerra J, Lascano J, Reinhard C, Santoni F  
423 a, Uchil PD, Chatel L, et al.: **TRIM5 is an innate immune sensor for the retrovirus**  
424 **capsid lattice.** *Nature* 2011, **472**:361–5.
- 425 45. Jimenez E, Ruiz A, Kløverpris HN, Rodriguez-Plata MT, Peña R, Blondeau C,  
426 Selwood DL, Izquierdo-Useros N, Moris A, Clotet B, et al.: **Non-human TRIM5**  
427 **variants enhance recognition of HIV-1–infected cells by CD8<sup>+</sup> T cells.** *Journal of*  
428 *Virology* 2016, **90**:JVI.00819-16.
- 429 46. Arhel NJ, Carthagen L, Souque P, Brussel A: **Brief report Lack of endogenous**  
430 **TRIM5  $\alpha$ -mediated restriction in rhesus macaque dendritic cells.** 2016,  
431 **112**:3772–3777.
- 432 47. Portilho DM, Fernandez J, Ringiard M, Machado AK, Boulay A, Mayer M, Müller-  
433 Trutwin M, Beignon AS, Kirchhoff F, Nisole S, et al.: **Endogenous TRIM5 $\alpha$**   
434 **Function Is Regulated by SUMOylation and Nuclear Sequestration for Efficient**  
435 **Innate Sensing in Dendritic Cells.** *Cell Reports* 2016, **14**:355–369.
- 436 48. Arriagada G, Muntean LN, Goff SP: **SUMO-interacting motifs of human TRIM5??**  
437 **are important for antiviral activity.** *PLoS Pathogens* 2011, **7**:23–27.
- 438 49. Brandariz-Nuñez A, Roa A, Valle-Casuso JC, Biris N, Ivanov D, Diaz-Griffero F:  
439 **Contribution of SUMO-interacting motifs and SUMOylation to the antiretroviral**  
440 **properties of TRIM5??** *Virology* 2013, **435**:463–471.
- 441 50. Lukic Z, Goff SP, Campbell EM, Arriagada G: **Role of SUMO-1 and SUMO**  
442 **interacting motifs in rhesus TRIM5 $\alpha$ -mediated restriction.** *Retrovirology* 2013,  
443 **10**:10.
- 444 51. Perez-Caballero D, Hatzioannou T, Yang A, Cowan S, Bieniasz PD: **Human**

- 445 **tripartite motif 5alpha domains responsible for retrovirus restriction activity and**  
446 **specificity.** *Journal of virology* 2005, **79**:8969–78.
- 447 52. Sawyer SL, Wu LI, Emerman M, Malik HS: **Positive selection of primate**  
448 **TRIM5alpha identifies a critical species-specific retroviral restriction domain.**  
449 *Proceedings of the National Academy of Sciences of the United States of America*  
450 2005, **102**:2832–7.
- 451 53. Grütter MG, Luban J: **TRIM5 structure, HIV-1 capsid recognition, and innate**  
452 **immune signaling.** *Current Opinion in Virology* 2012, **2**:142–150.
- 453 54. Song B, Javanbakht H, Perron M, Park H, Stremlau M, Sodroski J, Park DH:  
454 **Retrovirus Restriction by TRIM5  $\alpha$  Variants from Old World and New World**  
455 **Primates Retrovirus Restriction by TRIM5  $\alpha$  Variants from Old World and New**  
456 **World Primates.** 2005, **79**:3930–3937.
- 457 55. Sayah DM, Sokolskaja E, Berthoux L, Luban J: **Cyclophilin A retrotransposition**  
458 **into TRIM5 explains owl monkey resistance to HIV-1.** *Nature* 2004, **430**:569–573.
- 459 56. Van Manen D, Rits MAN, Beugeling C, Van Dort K, Schuitemaker H, Kootstra NA:  
460 **The effect of Trim5 polymorphisms on the clinical course of HIV-1 infection.**  
461 *PLoS Pathogens* 2008, **4**.
- 462 57. Battivelli E, Lecossier D, Matsuoka S, Migraine J, Clavel F, Hance AJ: **Strain-**  
463 **specific differences in the impact of human TRIM5alpha, different TRIM5alpha**  
464 **alleles, and the inhibition of capsid-cyclophilin A interactions on the infectivity of**  
465 **HIV-1.** *Journal of virology* 2010, **84**:11010–9.
- 466 58. Laguette N, Sobhian B, Casartelli N, Ringeard M, Chable-Bessia C, Ségéral E, Yatim  
467 A, Emiliani S, Schwartz O, Benkirane M: **SAMHD1 is the dendritic- and myeloid-**  
468 **cell-specific HIV-1 restriction factor counteracted by Vpx.** *Nature* 2011, **474**:654–  
469 7.
- 470 59. Goldstone DC, Ennis-Adeniran V, Hedden JJ, Groom HCT, Rice GI, Christodoulou E,  
471 Walker P a, Kelly G, Haire LF, Yap MW, et al.: **HIV-1 restriction factor SAMHD1**  
472 **is a deoxynucleoside triphosphate triphosphohydrolase.** *Nature* 2011, **480**:379–82.
- 473 60. Lahouassa H, Daddacha W, Hofmann H, Ayinde D, Logue EC, Dragin L, Bloch N,  
474 Maudet C, Bertrand M, Gramberg T, et al.: **SAMHD1 restricts the replication of**  
475 **human immunodeficiency virus type 1 by depleting the intracellular pool of**  
476 **deoxynucleoside triphosphates.** *Nature immunology* 2012, **13**:223–8.
- 477 61. Ryoo J, Choi J, Oh C, Kim S, Seo M, Kim S-Y, Seo D, Kim J, White TE, Brandariz-

- 478 Nuñez A, et al.: **The ribonuclease activity of SAMHD1 is required for HIV-1**  
479 **restriction** . *Nature Medicine* 2014, **20**.
- 480 62. Pertel T, Reinhard C, Luban J: **Vpx rescues HIV-1 transduction of dendritic cells**  
481 **from the antiviral state established by type 1 interferon**. *Retrovirology* 2011, **8**:49.
- 482 63. Mesman AW, Zijlstra-Willems EM, Kaptein TM, De Swart RL, Davis ME, Ludlow  
483 M, Duprex WP, Gack MU, Gringhuis SI, Geijtenbeek TBH: **Measles virus**  
484 **suppresses RIG-I-like receptor activation in dendritic cells via DC-SIGN-**  
485 **mediated inhibition of PP1 phosphatases** . *Cell Host and Microbe* 2014, **16**:31–42.
- 486 64. Yan N, Regalado-Magdos AD, Stiggelbout B, Lee-Kirsch MA, Lieberman J: **The**  
487 **cytosolic exonuclease TREX1 inhibits the innate immune response to human**  
488 **immunodeficiency virus type 1**. *Nature immunology* 2010, **11**:1005–13.
- 489 65. Berg RK, Melchjorsen J, Rintahaka J, Diget E, Søby S, Horan K a, Gorelick RJ,  
490 Matikainen S, Larsen CS, Ostergaard L, et al.: **Genomic HIV RNA induces innate**  
491 **immune responses through RIG-I-dependent sensing of secondary-structured**  
492 **RNA**. *PloS one* 2012, **7**:e29291.
- 493 66. Eckard SC, Rice GI, Fabre A, Badens C, Gray EE, Hartley JL, Crow YJ, Stetson DB:  
494 **The SKIV2L RNA exosome limits activation of the RIG-I-like receptors**. 2014, **15**.
- 495 67. Rasaiyaah J, Tan CP, Fletcher AJ, Price AJ, Blondeau C, Hilditch L, Jacques D a,  
496 Selwood DL, James LC, Noursadeghi M, et al.: **HIV-1 evades innate immune**  
497 **recognition through specific cofactor recruitment** . *Nature* 2013, **503**:402–405.
- 498 68. Jong MAWP De, Witte L De, Oudhoff MJ, Gringhuis SI, Gally P, Geijtenbeek TBH:  
499 **TNF-  $\alpha$  and TLR agonists increase susceptibility to HIV-1 transmission by human**  
500 **Langerhans cells ex vivo**. 2008, **118**.
- 501 69. Grivel J-C, Shattock RJ, Margolis LB: **Selective transmission of R5 HIV-1 variants:**  
502 **where is the gatekeeper?** . *Journal of translational medicine* 2011, **9 Suppl 1**:S6.
- 503 70. Salazar-Gonzalez JF, Bailes E, Pham KT, Salazar MG, Guffey MB, Keele BF,  
504 Derdeyn C a, Farmer P, Hunter E, Allen S, et al.: **Deciphering human**  
505 **immunodeficiency virus type 1 transmission and early envelope diversification by**  
506 **single-genome amplification and sequencing**. *Journal of virology* 2008, **82**:3952–  
507 3970.
- 508 71. Keele BF, Giorgi EE, Salazar-Gonzalez JF, Decker JM, Pham KT, Salazar MG, Sun C,  
509 Grayson T, Wang S, Li H, et al.: **Identification and characterization of transmitted**  
510 **and early founder virus envelopes in primary HIV-1 infection**. *Proceedings of the*  
511 *National Academy of Sciences of the United States of America* 2008, **105**:7552–7557.

- 512 72. Parrish NF, Gao F, Li H, Giorgi EE, Barbian HJ, Parrish EH, Zajic L, Iyer SS, Decker  
513 JM, Kumar A, et al.: **Phenotypic properties of transmitted founder HIV-1.**  
514 *Proceedings of the National Academy of Sciences of the United States of America*  
515 2013, **110**:6626–33.
- 516 73. Fenton-May AE, Dibben O, Emmerich T, Ding H, Pfafferoth K, Aasa-Chapman MM,  
517 Pellegrino P, Williams I, Cohen MS, Gao F, et al.: **Relative resistance of HIV-1**  
518 **founder viruses to control by interferon-alpha.** *Retrovirology* 2013, **10**:146.
- 519 74. Shen R, Kappes JC, Smythies LE, Richter HE, Novak L, Smith D: **Vaginal Myeloid**  
520 **Dendritic Cells Transmit Founder HIV-1.** 2014, **88**:7683–7688.
- 521 75. Konno H, Konno K, Barber GN: **XCyclic dinucleotides trigger ULK1 (ATG1)**  
522 **phosphorylation of STING to prevent sustained innate immune signaling.** *Cell*  
523 2013, **155**:688–698.
- 524 76. Liang Q, Seo GJ, Choi YJ, Kwak MJ, Ge J, Rodgers MA, Shi M, Leslie BJ, Hopfner  
525 KP, Ha T, et al.: **Crosstalk between the cGAS DNA sensor and beclin-1 autophagy**  
526 **protein shapes innate antimicrobial immune responses.** *Cell Host and Microbe*  
527 2014, **15**:228–238.

528

529 **Of special/outstanding interest:**

530 - Sandler, *Nature* 2014.

531 (\*\*) Crucial data on in vivo role of type I IFN production on SIV viraemia and disease  
532 progression

533 This paper shows that IFN-I helps to decrease the SIV reservoir size and accelerated  
534 CD4 T-cell depletion with progression to AIDS, while administration of IFN induced a  
535 worse prognosis.

536 - Martin-gayo, *Plos pathogens* 2014

537 (\*\*) Here the authors show that DCs from Elite controllers are better able to produce  
538 IFN-I and to activate CD8 T- cells. This effect was associated with decreased activity  
539 of SAMHD1 and LEDGF/p75. It underscores the *in vivo* relevance of DC function on HIV-1  
540 pathogenesis and disease progression.

541 - Portilho, *Cell reports* 2016

542 (\*) TRIM5a nuclear sequestration allows DC sensing of retroviral DNA by cGAS. The  
543 findings show that rhesus TRIM5a restriction is cell specific. Primate DCs lack  
544 TRIM5a restriction, in contrast to other target cells, like macrophages and T-cells

545 - Czubala, *Journal of Investigative Dermatology* 2016: SAMHD1-independent post-  
546 entry restriction in Langerhans cells

547 (\*) The authors show that restriction in LCs is not dependent on SAMHD1 nor MX2,  
548 but another factor post-fusion restriction factor

549 - Gao, *Science* 2013

550 (\*) The authors identify cGAS as a cytosolic sensor of HIV-1 cDNA

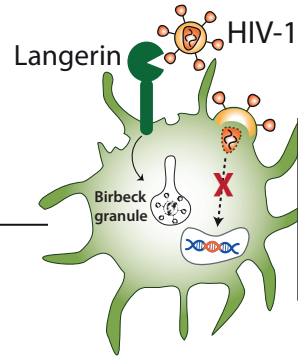
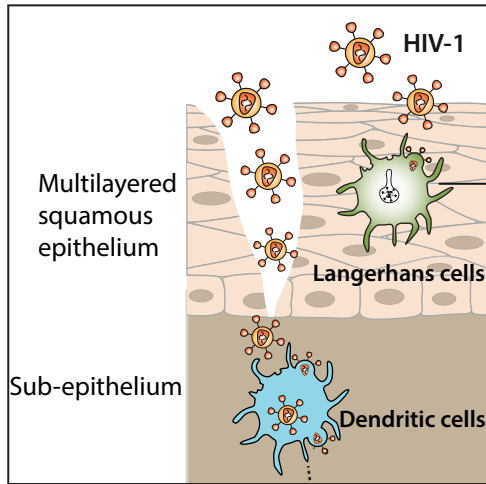
551 - Parrish, *Proceedings of the National Academy of Sciences of the United States of*  
552 *America* 2013

553 (\*\*) The authors use SGA, which is a very ingenious method to study the  
554 phenotypical properties of T/F viruses and find that these viruses are more resistant to  
555 IFN, have higher Env content, and are more infectious than chronis controls

556

557

## MUCOSAL ENTRY SITES

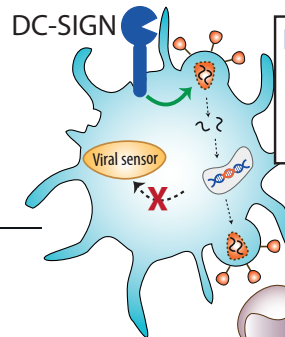
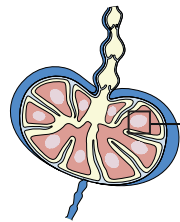


### Post-entry restriction mechanism in LCs:

- SAMHD1-independent
- MX2-independent

**No viral transmission**

## LYMPH NODES



### No type I IFN responses by myDCs:

- SAMHD1-dependent restriction
- TREX-1 activity
- Lack of cGAS innate sensing

### HIV-1 replication in myDCs :

- DC-SIGN and TLR8 signalling

**Viral transmission**

**No DC maturation**