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Thalia Garcia-Tellez, Nicolas Huot, Mickaël J.-Y. Ploquin, Philippe Rascle ...+2 more authors

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***Non-human primates in HIV research: Achievements, limits and alternatives***

**Thalía Garcia-Tellez<sup>a</sup>, Nicolas Huot<sup>a,b</sup>, Mickaël J. Ploquin<sup>a</sup>, Philippe Rascle<sup>a</sup>,  
Beatrice Jacquelin<sup>a</sup>, Michaela Müller-Trutwin<sup>a,b</sup>**

<sup>a</sup>Institut Pasteur, Unité HIV, Inflammation and Persistence, Paris, France; <sup>b</sup>Vaccine Research Institute, Créteil, France.

Thalia GARCIA-TELLEZ thalia.garcia-tellez@pasteur.fr, Nicolas HUOT nicolas.huot@pasteur.fr, Mickael PLOQUIN mickael.ploquin@pasteur.fr, Philippe RASCLE philippe.rascle@pasteur.fr, Béatrice JACQUELIN beatrice.jacquelin@pasteur.fr, Michaela MULLER-TRUTWIN michaela.muller-trutwin@pasteur.fr

Corresponding author: Michaela MULLER-TRUTWIN  
michaela.muller-trutwin@pasteur.fr

## ***Abstract***

An ideal model for HIV-1 research is still unavailable. However, infection of non-human primates (NHP), such as macaques, with Simian Immunodeficiency Virus (SIV) recapitulates most virological, immunological and clinical hallmarks of HIV infection in humans. It has become the most suitable model to study the mechanisms of transmission and physiopathology of HIV/AIDS. On the other hand, natural hosts of SIV, such as African green monkeys and sooty mangabeys that when infected do not progress to AIDS, represent an excellent model to elucidate the mechanisms involved in the capacity of controlling inflammation and disease progression. The use of NHP-SIV models has indeed enriched our knowledge in the fields of: i) viral transmission and viral reservoirs, ii) early immune responses, iii) host cell-virus interactions in tissues, iv) AIDS pathogenesis, v) virulence factors, vi) prevention and vii) drug development. The possibility to control many variables during experimental SIV infection, together with the resemblance between SIV and HIV infections, make the NHP model the most appropriate, so far, for HIV/AIDS research. Nonetheless, some limitations in using these models have to be considered. Alternative models for HIV/AIDS research, such as humanized mice and recombinant forms of HIV-SIV viruses (SHIV) for NHP infection, have been developed. The improvement of SHIV viruses that mimic even better the natural history of HIV infection and of humanized mice that develop a greater variety of human immune cell lineages, is ongoing. None of these models is perfect, but they allow contributing to the progress in managing or preventing HIV infection.

***Keywords:*** HIV, SIV, AIDS, non-human primates, animal models

## Highlights

<sup>35</sup><sub>17</sub> NHP allow studying viral transmission, immunopathology, immune response and prevention.

<sup>35</sup><sub>17</sub> Natural SIV hosts help to reveal mechanisms of HIV disease control.

<sup>35</sup><sub>17</sub> NHP models of spontaneous or ART-induced control provide insights for HIV cure.

<sup>35</sup><sub>17</sub> NHP models have allowed major advances in HIV/AIDS field but they are not perfect.

<sup>35</sup><sub>17</sub> Alternative models (humanized mice, SHIV) are useful for specific research questions.

## INTRODUCTION

HIV/AIDS is still a major public health issue. According to the World Health Organization, HIV infection figures, even today, among the ten major leading causes of death and is the second cause of mortality in adolescents. Since the first report in 1981 and the identification of HIV as a causative agent in 1983<sup>1</sup>, AIDS has claimed more than 35 million of lives and only in 2015, 2.1 million of people became newly infected with HIV. HIV infection is characterized by a slow and progressive loss of CD4<sup>+</sup>T cells that, in absence of treatment, generally leads to an immunosuppressive condition. Nowadays, it is admitted that chronic immune activation is the driving force of such immunodeficiency<sup>2</sup>. Under successful combined antiretroviral therapy (cART), the virus is controlled up to undetectable level in blood, but a residual chronic inflammation persists and is associated with the morbidity and mortality observed in the antiretroviral-treated patients.

Despite of the great advances obtained in HIV/AIDS knowledge, there are still key problems to solve, in particular the lack of a vaccine and a cure and the absence of treatments for resolution of HIV-induced inflammation. Animal models for HIV have already contributed to answer major questions, but they also have several limitations. The “perfect animal model” for HIV-1 research is indeed still unavailable. However, infection of non-human primates (NHP), such as macaques, with Simian Immunodeficiency Virus (SIV) leads to a disease that is similar to AIDS induced by HIV in humans. So far, this is the most suitable model to study the mechanisms of transmission and pathophysiology of the disease. Indeed, SIV infection in macaques fulfills numerous conditions generally requested to constitute a reliable animal model for a human disease:

1. The virus causing disease in the model should cause the same disease in humans;
2. The course of the disease in the animals should resemble that in humans;
3. The range of cells, tissues and organs involved should be similar in humans and in the animal;
4. Immune responses to infection in the animal model should be similar to those in humans.

These conditions are not fulfilled by other animal models, such as FIV in cats or HIV-1 in humanized mice (see below). Here, we review characteristics of the SIV infection in NHP that have favored its use as a model for HIV/AIDS research and summarize some of the major past and recent advances in the field obtained thanks to the NHP models (Table 1). We will briefly evoke advances in other models, such as humanized mice, in research toward a HIV vaccine and cure. Finally, we will explain the limits of NHP models and discuss how these models could nonetheless help in the global effort to achieve the development of efficient preventive and cure approaches.

## 1. SIV MODELS AND THEIR CONTRIBUTIONS TO RESEARCH ON HIV PREVENTION AND TREATMENT

Human AIDS is caused by two types of HIV (HIV-1 and HIV-2). These viruses are subdivided into groups (M, N, O, and P for HIV-1; A to I for HIV-2), subtypes, circulating recombinant forms (CRF) and unique recombinant forms (URF), HIV-1 group M subtype CRF being the most prevalent in the world<sup>3,4</sup>.

Since the first cases of HIV infection, there has been interest in identifying the origin of the epidemic. The first insight came to light when a close relationship between HIV-2 and a virus that infects macaques was found<sup>5</sup>. This virus was called SIV<sub>mac</sub> in analogy to HIV and according to the species from which it was isolated. Thereafter, another phylogenetic association was discovered between HIV-2 and SIV<sub>smm</sub>, a virus that infects sooty mangabeys in West Africa<sup>6</sup>. Subsequent studies confirmed that SIV<sub>mac</sub> and HIV-2 derived both from SIV<sub>smm</sub><sup>6-9</sup>.

The origin of HIV-1 was traced on non-human primates, as well. The human virus is closely related to SIV<sub>cpz</sub>, which infects West-Central Africa chimpanzees (*Pan troglodytes troglodytes*)<sup>7,8,10-12</sup> and from which HIV-1 M and N derived<sup>11-16</sup>. On the other hand, the analysis of fecal samples from Cameroon gorillas revealed the existence of SIV<sub>gor</sub><sup>17,18</sup>. The latter virus is related to HIV-1 O and P. Phylogenetic analyses indicate that chimpanzees constitute most likely the original reservoir and source of SIV<sub>gor</sub> as well as of HIV-1 O and P<sup>18-20</sup> (Figure 1).

More than 40 NHP species have been found to carry SIV in the wild. Noteworthy, natural carriers of SIV are all African species. In contrast, Asian monkeys, such as macaques, are

only infected in captivity.

The first report of AIDS in a NHP was provided by Letvin and colleagues in 1983<sup>21</sup>, soon after the discovery of HIV. This syndrome was detected in captive macaques (*Macaca cyclopis* and *Macaca mulatta*) that died of lymphomas or opportunistic infections like *Pneumocystis carinii*. The revision of autopsy records and laboratory studies revealed that these animals suffered of anemia, neutropenia and monocytosis before death. A lymphocyte ratio (CD4/CD8) reversion and a loss of T cell numbers and functionality were observed as well before death. The causes of death included necrotizing gingivitis, *Pneumocystis carinii* and cytomegalovirus infections, as well as three atypical cases of lymphoma.

Macaques infected by SIVmac became the most important animal model for HIV/AIDS research. The disease progression profile during SIV infections in macaques depends both on the macaque species and the SIVmac strain used (Figure 2). The most frequently used animals are Indian and Chinese rhesus macaques as well as cynomolgus macaques infected by the SIVmac239 molecular clone or the SIVmac251 viral isolate. The most rapid disease progression is generally observed in Indian rhesus macaques infected with SIVmac239.

This macaque model revealed the massive CD4<sup>+</sup>T cell depletion in the gut in the very early phase of infection<sup>22-24</sup>. While it was already known that HIV replicates in the gut<sup>25</sup>, the macaque model helped to underscore the rapidity of the events in this tissue (within the first 24h upon infection) and to what extent the degree of T lymphocyte loss in the gut is associated with disease progression. It was subsequently shown that resting memory CD4<sup>+</sup> T cells were the most frequently infected cells within the gastrointestinal (GI) tract<sup>26,27</sup>. These cells can live for decades and are now considered as a major reservoir for HIV-1<sup>28,29</sup>. Experimental SIV infections can be performed through the intravenous route. Several additional experimental protocols have been developed for infection through the rectal, vaginal or oral route in order to mimic the predominant routes of transmission encountered in humans, i.e. sexual or mother-to-child transmission by breast feeding<sup>20,22-24</sup>. To better resemble even more what is happening during infection and dissemination of the virus throughout the body in humans, protocols for repetitive low-dose challenges have been set up as well. These models contribute to evaluate vaccine candidates and already lead to the demonstration of two constructions that can confer strong control, i.e. SIVΔnef and rhesus cytomegalovirus (CMV)-based vectors. However, the degree of protection correlates



inversely with the level of attenuation, the least-attenuated strain giving the greatest protection<sup>33,34</sup>. Vaccine candidates based on CMV-vectors generate very strong and persistent T effector memory responses in half of the animals leading to a controlled infection and elimination of viral reservoirs<sup>35</sup>. While it is at the moment unclear if such constructions can be used as a vaccine, the studies of these vaccine candidates have

already and will continue to provide important clues about the correlates of protection against HIV<sup>36,37</sup>.

The macaque/SIVmac models also allow to examine the very first immunological events after viral exposure in relation to the transmission route or to study the selection mechanisms of transmitted/founder virus resulting from the genetic bottleneck that occurs during transmission (Table 1)<sup>38-42</sup>. It was shown for instance in the macaque model, that while in most cases the transmission is based on the selection and persistence of only one viral variant from the donor, the number of transmitted founder variants increases with the viral dose in the challenge<sup>31,43-45</sup>.

In the search for a vaccine against HIV-1, there is a need for an animal model that can be infected with the human virus. Such a model would help, for instance, in the study of neutralizing antibodies (Nabs) against HIV-1. Macaques are susceptible to HIV-2 but not to HIV-1 infection. Chimpanzees constitute the original reservoir of HIV-1 and therefore are naturally susceptible to HIV-1 viruses. However, HIV-1 had adapted to the new human host, most likely by circumventing restriction factors, among other reasons. Therefore, the results obtained from HIV-1 infection in these primates have been non conclusive. Some groups have reported the development of AIDS in this model,<sup>46-49</sup> characterized by marked depletion of CD4<sup>+</sup>T cells, sustained viremia, severe CD4:CD8 inversion and increased T cell apoptosis. Others have observed animals that do not only slowly progress to AIDS, maintaining their normal CD4<sup>+</sup>T cell counts and displaying undetectable viremia<sup>50</sup>. The scientific limitations of the model, together with the new guidelines for the use of chimpanzees in biomedical research, led to the interruption of its use for HIV<sup>51</sup>. Infection of macaques with HIV-1 has also revealed to be challenging. Indeed, HIV-1 faces in macaques the existence of cellular proteins that restrict the replication of the human virus, such as TRIM5<sup>52</sup>, APOBEC3G and Tetherin<sup>53</sup>. This makes it difficult to infect macaques or their CD4<sup>+</sup>T cells by HIV-1 *in vivo* and *in vitro*, but allowed to contribute to

the discovery and extensive characterization of restriction factors (Table 1). Several TRIM5 $\alpha$  alleles have been identified and characterized in monkeys. It has been clearly shown that the viral replication differs depending on the TRIM5 $\alpha$  allele present in the simian host<sup>54,55</sup>. The only macaque susceptible to be infected by HIV-1 is the pig-tailed macaque (*Macaca nemestrina*). This occurs as a result of a 2-nucleotide deletion in the 5'-end of TRIM5 $\alpha$  transcript, which impairs the action of this RF<sup>16</sup>. However, the viral replication is not efficient and there is no disease progression.

A recombinant virus has been engineered, which consists of a HIV-1 backbone where target sites of restriction factors were replaced by the corresponding SIVmac sequences<sup>56</sup>. While this virus induces persistent viremia, disease progression is only observed after *in vivo* depletion of CD8+T cells in acute infection. This modified model allows the study of some virus-host interactions, but needs further development for its application in HIV research.

Another attempt to circumvent the lack of a macaque model for HIV-1 consists in the construction of other types of recombinant viruses of HIV and SIV, called SHIV<sup>57</sup>. These have been used since many years to overcome the lack of an animal model by constructing for instance SIVmac viruses coding for HIV-1 Env instead of SIVmac Env. Such macaque/SHIV models were essential for providing the proof of concept that antibodies alone can protect against infection by taking advantage of the possibility to passively transfer the antibodies and challenge the animals experimentally<sup>58</sup> (Table 1). However, these types of approaches are challenged by the large diversity of the envelope glycoprotein, their glycan shields and by the high plasma titers of NAbs needed for protection. Lately, the improvement of broadly neutralizing monoclonal antibodies (bNAbs) allowed to enhance their neutralization potency and to protect, for instance, SHIV-challenged macaques with much lower NAb concentrations<sup>59</sup>. This new generation of very broad and potent Abs might have a potential not only as pre-exposure blocking agents but also in view of a cure or remission of HIV. The treatment with those Abs resulted indeed in control of viremia and reduced proviral DNA in blood and tissues<sup>60,61</sup>.

Very early on, SIVs that code for HIV-1 Pol have also been engineered. Indeed, SIVmac viruses are not susceptible to some drugs used against HIV-1, such as non-nucleoside

reverse transcriptase inhibitors (NNRTIs), fusion inhibitors and some integrase inhibitors. The engineering of SHIVs expressing the HIV-1 Pol protein makes them susceptible to such antiretrovirals. They contributed to the development of therapeutic approaches. As an example, NHP infection models have demonstrated the effectiveness of subcutaneous, gel, and oral formulations of tenofovir (PMPA) in preventing transmission of SIV or SHIV

viruses, even when applied several hours after viral challenge<sup>62</sup>. Such *in vivo* activity of tenofovir made it a promising agent for prevention of HIV-1 infection.

Most SHIV viruses, however, do not reproduce all characteristics of HIV-1 infection in humans. The first generation of SHIV was composed of X4 viruses and therefore displayed a distinct cellular tropism than primary HIV in early infection. CD8+ T cell depletion in monkeys is still often needed for disease progression to AIDS. Nevertheless, SHIV models have allowed overcoming specific hurdles and cannot be missed so far for pre-clinical trials of vaccine and drug candidates<sup>63-67</sup>.

As we have recapitulated, SIV infection in NHP constitutes a good model, in many aspects, for HIV research. It is, however, not perfect. One cannot ignore that SIV and HIV are close but different viruses, which can lead to differences in certain aspects of their interactions with the host or susceptibility to drugs and vaccine candidates.

## 2. MODELS FOR SPONTANEOUS SIV CONTROL

The majority of the individuals infected by HIV progress to AIDS within 7 to 10 years in the absence of cART. There exist, however, a few individuals (<0.2%) known as HIV- controllers who spontaneously and efficiently control viral replication. The deep characterization of these individuals and the factors that are involved in the control of the infection have been the focus of many researches<sup>68,69</sup>. Multiple causes are suspected, and are not mutually exclusive. In particular the genetic background of the individuals enriched in MHC alleles such as B27 and/or B57, strong CD8+ T cell responses, reduced susceptibility of CD4+ T cells to HIV infection and early control of viral replication are likely involved<sup>70,71</sup>. All distinct profiles of disease progression in humans are recapitulated by macaques after SIV infection, including the occurrence of a spontaneously controlled infection in a minority of macaques that can also be related to a specific MHC background<sup>51,97</sup>. The disease progression rate depends both on the virus and host species

(Figure 2), as well as on individual host features, as in humans. Studies in the macaque

models allow deciphering, one by one, the role of each viral gene *in vivo* by infecting macaques with genetically engineered SIV mac clones containing defective or lacked accessory genes. This is how it was discovered that Nef is essential for high viral replication *in vivo*, while *in vitro*, Nef was dispensable<sup>72</sup>. Mutations in *Nef* indeed are associated with attenuated HIV-1 infection in humans.

The role of MHC alleles (Mamu alleles in rhesus macaque) has been extensively studied in the spontaneous control in macaques. Some *Mamu* alleles (e.g. *Mamu-A\*01*<sup>73</sup>) are associated with a better containment of viral replication while others are linked to a faster disease progression<sup>74</sup>. Furthermore, the combination of *Mamu* alleles and KIR receptors in NK cells increases the complexity of the response<sup>75,76</sup>, as showed for example in an epistatic analysis of KIR3DL05, KIR3DS05, and KIR3DL10 in association with *Mamu-B\*012* that contribute to elevate the viral load in rhesus macaques<sup>76</sup>.

The NHP models allow investigators to address not only the very early events that follow SIV exposure, but also to study these events in tissues, such as lymphoid tissues, genital tract, lung, liver, intestine, and central nervous system (CNS)<sup>77</sup>. Latent reservoirs of HIV are located throughout the body and persist during infection even in presence of highly efficient cART. NHP models allow to study the establishment of these reservoirs in tissues, which occurs in the first hours and days following infection<sup>78-80</sup>. Advances in our understanding of the role of the different immune cell populations as viral target cells, have been provided by experiments in which these populations are depleted in NHP models. Depletion of CD4<sup>+</sup>T-cells in macaques prior to SIV infection was associated with higher viral load, massive activation and infection of macrophages and microglia that become the predominant infected cells<sup>81</sup>. The SIV mac-infected macaque model was used as a proof-of-concept to demonstrate that CD8<sup>+</sup> cells participate in the control of infection, using *in vivo* CD8<sup>+</sup>T cell depletion (Table 1)<sup>82-84</sup>. Additionally, this model allowed to demonstrate the presence of a CTL response as soon as 7 days p.i., and helped to understand how quickly HIV/SIV evades this cellular response through the acquisition of mutations very early on in acute infection<sup>85</sup>. The macaque model also provided the concept that CD8<sup>+</sup>T cell responses arrive “too little” and “too late” into vaginal mucosa to control viral dissemination and that the “window of opportunity” to prevent infection is very short<sup>86,87</sup>. Furthermore, depletion of NK cells resulted in modest changes in plasma viral load but in a

significant increase in the gut<sup>88,89</sup>. However, no tool exists so far to specifically deplete NK cells and CD8+T cells. Noteworthy, cell depletion induce homeostatic proliferations of other cells, this side effect in addition to others need to be taken into consideration in the interpretation of the results.

### 3. MODELS FOR DISEASE CONTROL

About 40 distinct African NHP are natural hosts of SIV. Only in a few species though, studies could be conducted to evaluate the natural history of SIV infection and its outcome in these animals. Studies based on non-invasive techniques have shown that SIVcpz infection in wild chimpanzees reduces their lifespan, when compared to non-infected animals in the same habitat<sup>16,90</sup>. One case of AIDS-related symptoms was also reported in a naturally infected Central African chimpanzee, which presented lymphopenia, weight loss and opportunistic infections 7 years after SIV positive screening. Efforts should be made to better characterize the pathogenicity of SIV in natural hosts and to find out whether SIV infection also plays a role in a population decline<sup>91</sup>. Other studies in semi-free mandrills infected by SIV<sub>mand</sub> in their natural habitat revealed, in contrast, a strong protection against AIDS. Similarly, other African NHP, such as African Green Monkeys (AGM) and Sooty mangabeys (SM) revealed to be resistant to AIDS<sup>92</sup>. The latter serve today as a model to study the control of the disease, in particular SM and AGM, and are called the “natural hosts” models. Cross-species transmissions demonstrated that the same SIV strain can cause opposite outcomes of infection, depending on the host species (Figure 3). On the other hand, not all SIV strains induce AIDS in macaques, some SIV viruses being easily controlled in the animals, while others not. This demonstrates that the outcome of the infection depends on a combination of both viral and host determinants.

Natural hosts of SIV have been used to better understand the mechanisms responsible for disease progression in HIV infection<sup>92,93</sup>. The most striking difference between non-pathogenic SIV and pathogenic HIV-1/SIV infections is the lack of chronic immune activation. Paradoxically, natural hosts of SIV exhibit high titers of virus in plasma, but they do not display chronic activation of the adaptive and innate immune system<sup>94,95</sup>. This feature resembles the ‘viremic non-progressors’, very rare human individuals who display elevated viremia but maintain CD4 T+ cell counts and avoid disease progression for

years<sup>96</sup>. Extensive studies are ongoing in order to elucidate the mechanisms involved in the capacity for controlling inflammation and disease progression. Some non-mutually exclusive hypotheses are listed below<sup>97</sup>:

<sup>35</sup><sub>17</sub> Intact mucosa barrier, thereby, lack of microbial translocation and lack of microbial products that would drive the continuous stimulation of the immune system<sup>98</sup>. Experimentally mimicking microbial translocation in these non-pathogenic models provided evidence of the link between this phenomenon and immune activation. LPS administration in AGMs led indeed to elevated T cell activation levels<sup>99</sup>. However, it is unlikely that this is the only event involved in the deleterious chronic inflammation as it has been shown that infection of macaques with a mutated virus still leads to AIDS without acute loss of CD4+ T cells and microbial translocation<sup>100</sup>.

<sup>35</sup><sub>17</sub> Ancient infection that led to an adaptation of the host's immune response responsible for differences in the intensity or nature of SIV sensing. The capacity to produce IFN- $\lambda$  is normal in natural hosts, but other sensing pathways have only poorly been explored in natural hosts so far<sup>101,102</sup>.

<sup>35</sup><sub>17</sub> The ability of the Nef protein to block the activation of infected T cells by downregulation of CD3<sup>103</sup>.

<sup>35</sup><sub>17</sub> Natural hosts show low levels of CCR5 surface expression on CD4 + T cells and apparent protection of central memory T cells from SIV infection<sup>104–106</sup>

<sup>35</sup><sub>17</sub> Controlled viral replication in secondary lymphoid organs<sup>107</sup>. One hallmark of SIV infection in natural hosts is the low viral burden in lymph nodes in the chronic phase of infection in contrast to other tissues<sup>108–112</sup>. This constitutes one of the major differences in lymph nodes of AGMs and SMs. Furthermore, lymph nodes in these natural hosts are characterized by: (i) lack of lymphadenopathy and thus no extensive sequestration of lymphocytes in AGMLNs, (ii) no or less follicular dendritic cell deposition of virus in AGM and SM compared to SIVmac infections<sup>110,112,113</sup>; (iii) more rapid control of interferon-stimulated genes (ISGs) in LNs as compared to blood and gut<sup>101,109–111</sup>. The control of viral replication and immune activation in lymph nodes prevents fibrosis and maintains normal immune

function<sup>108,114,115</sup> in this organ which is essential for the induction and shaping of adaptive immune responses. Maintenance of normal immune functions might lead to a better control of other infections in the host (i.e. CMV, virome) that otherwise could also contribute to immune activation.

<sup>35</sup><sub>17</sub> Depletion of CD4+T cells through apoptosis leading to homeostatic proliferation of T cells<sup>116,117</sup>

#### 4. SMALL ANIMAL MODELS FOR HIV RESEARCH

Besides NHPs, other animal models have been used for the study of HIV-1. In the past, feline immunodeficiency virus (FIV) infection in cats served as a model of naturally occurring immunodeficiency. During FIV infection, CD4+T cells are depleted and a chronic inflammatory state is established, such as it happens during HIV/SIV infection<sup>118</sup>. The FIV model has also been useful in the past to test some antiretroviral drugs<sup>119</sup>. Nowadays, however, this model is generally not used anymore for HIV research since

some important features of the infection are clearly different. For example, FIV is able to infect CD8+T cells and B cells in addition to CD4+T cells and macrophages, due to its affinity for CD134 as a receptor. Thus, FIV establishes different viral reservoirs in comparison with the human or primate infection by HIV/SIV.

Other attempts for studying HIV-1 infection in small animals such as rats, mice or rabbits were performed without success. Indeed, rodent cells are refractory to HIV infection. This could not be circumvented by the expression of the human viral receptor on the cell surface. When the murine cells were engineered for allowing HIV to enter, the virus encountered additional problems to effectively replicate, most likely due to restriction factors, among others.

The development of humanized mice arose the possibility to infect them with HIV-1 and answer some specific research questions. Examples of humanized mice used in HIV research comprise, *inter alia*, SCID-hu, SCID-hu-PBL, NOD-SCID, Hu-HSC and BLT mice<sup>67,68,120-122</sup>. Humanized mice have been used to study particular aspects of HIV-1 infection, such as T cell exhaustion<sup>123</sup>, mucosal immunity<sup>120,124,125</sup>, viral latency, antiretroviral drug efficacies and infection of macrophages<sup>124,126,127</sup>, among others (Table



2). Humanized mice have already contributed to the knowledge of specific aspects of HIV infection. However, their development requires complex surgical engineering. Moreover, they need to be generated *denovo* for each experiment, being tailored according to the immunological requirements of the research, which increases the cost of their establishment and maintenance. In addition, there exist anatomical differences, for example, at the level of lymphoid organs that are not fully developed and a lack of several human immune cell lineages, in particular related to innate immune responses. Of note, the field is evolving fast and much effort is put on the improvement of humanized mouse models<sup>121</sup>.

## 5. LIMITATIONS, PERSPECTIVES AND CONCLUSIONS

Despite the numerous advantages that NHP represent, it is important not to forget that choosing the right model for each research question is an essential point. Macaque models of transmission were established very early on as models for HIV<sup>128</sup>. Animal models offer the possibility to control the viral strain, viral dose and infection route. However, while it is well admitted that rectal SIV infection mimics what is happening in humans, vaginal infections are more difficult to modelize as menstrual cycle variations impact the thickness of the epithelium and the efficacy of infection<sup>32,129</sup>. Progesterone is used to control the cycle but to what extent this impacts the relevance of the studies is still under debate.

Also, humans are infected through biological fluids that do not only contain free virus, but also infected cells and other components, such as inflammatory cytokines. Studies are ongoing to evaluate if there are differences depending on the composition of the inoculum<sup>130,131</sup>.

Natural transmission of SIV in African NHPs is predominantly horizontal and thought to occur through sexual contacts or bite wounds. In contrast to HIV infections, vertical transmission of SIV is extremely rare. The expression of the co-receptor CCR5 on CD4<sup>+</sup>T cells in AGMs is low in infants and dramatically increases in adults<sup>132</sup>. Susceptibility to infection through the vaginal and rectal route was linked to the availability of memory CCR5<sup>+</sup>CD4<sup>+</sup>T cells in the targeted mucosa and it has been suggested that the low rate of vertical SIV infection is associated with the few target cell availability in newborns and infants<sup>133,134</sup>. Thus, while HIV and SIV infections are distinct in the frequency of mother to

child transmission, NHP models can be used to better understand the underlying mechanism of this difference<sup>133,135,136</sup>.

Once infection takes place at mucosal sites, the virus crosses the epithelial barrier, establishes a first pool of infected cells (foci) and disseminates thereafter in draining lymph nodes (LNs)<sup>30</sup>. It is still under debate which cells are the first targets of the virus. It has been suggested that CD4+CCR5+T cells are the primary targets of infection in mucosa<sup>24,26,27,137,138</sup>. Dendritic cells (DCs) might also play a role in the process of viral dissemination. The use of macaque models permitted to analyze their role in virus dissemination during the first hours and days *in vivo*<sup>139</sup>. Nonetheless, the events leading to the establishment of infection are still not fully elucidated.

Repeated low-dose viral challenges might provide a benefit for the evaluation of vaccine candidates or the understanding of the establishment of viral reservoirs. The low number of animals for ethical and economic reasons renders interpretation of the results however sometimes difficult. Taken this into account, technical improvements are being made. For instance, novel techniques, such as *in vivo* imaging, are highly promising<sup>77</sup>. It is important to mention that not only the number of specimens allowed for each research is often limited, but the tools are limited as well. Thus, there are still markers for which no monoclonal antibody exists in monkeys. This is the case for example for most of the KIRs. NHP are the closest animal model for HIV/AIDS research, but an ideal model for HIV-1 is still not available. SIV and HIV are close but distinct viruses, which caused differences in certain aspects of their interactions with the host, vaccines and drugs. To overcome these potential discrepancies between SIV and HIV, recombinant viruses, including SHIVs, have been generated. SHIVs have been and still are particularly useful in the study of humoral responses, vaccine candidates and antiretroviral drugs<sup>67</sup>. In the future, it would be useful however to dispose of SHIV viruses that mimic even better the natural history of HIV infection. The development of new generations of SHIV strains is already ongoing. In conclusion, non-human primates infected by SIV represent a model with numerous advantages for the study of HIV infection. Its close resemblance to HIV infection in humans probably makes it the best or at least the most deeply characterized animal model for a human disease. NHP-SIV models have allowed the study of: i) viral transmission, ii)

early immune responses, iii) host cell-virus interactions in tissues, iv) prevention and v) drug development (Table 3).

Despite of all the caveats noted and the potential difficulty in translating the findings from primates to humans, these models can be and have been highly instructive in establishing certain basic principles that would have been difficult or impossible to determine by experimentation in humans for safety reasons.

Of note, the suitability of each model depends on the study's specific question, the available tools and appropriate interpretation of the results. Nonetheless, if used correctly, it constitutes an essential model, in many aspects, for HIV research until a vaccine and therapy for HIV cure or HIV remission are discovered.

Table 1. Examples of major contributions of NHP models to HIV/AIDS research

<ul style="list-style-type: none"><li>☐ Discovery of initial founder populations of infected cells (foci)<sup>30</sup></li><li>☐ CD8+T cell response: «too little, too late» to clear infection<sup>86</sup></li><li>☐ Short window of opportunity to prevent infection<sup>38</sup></li><li>☐ CD8+T cells : impact on viral set-point<sup>74,140</sup></li><li>☐ Proof of concept that Nab can protect against infection<sup>141</sup></li><li>☐ Nef viral protein: necessary for high viral load in vivo<sup>72</sup></li><li>☐ Resting memory T cells: main target of the virus in lymphoid tissues<sup>24,27</sup></li><li>☐ Rapid and dramatic depletion of CD4+T cells in gut<sup>22,27</sup></li><li>☐ Trafficking of Treg, PDC, NK cells to the gut<sup>142-144</sup></li><li>☐ Loss of Tcm associated with disease progression<sup>24,145</sup></li><li>☐ Events in acute infection determine disease progression<sup>70</sup></li><li>☐ TRIM5 alleles restrict viral replication in vivo<sup>86</sup></li><li>☐ Analyses of the virome and microbiome in tissues<sup>31-134</sup></li><li>☐ In vivo imaging of SIV<sup>77</sup></li></ul>
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<b>Model</b>	<b>Characteristics</b>	<b>Examples of utility</b>	<b>Drawbacks</b>
<b><i>Alternative viruses</i></b>			
SHIV	Chimeric viruses that express HIV proteins in a SIV backbone to replicate in NHP.	Antiretroviral development Vaccination strategies Study of viral restriction	Variability in the infectivity Lack of AIDS induction Unusual pathophysiology
<b><i>Alternative hosts</i></b>			
SCID-hu <sup>150</sup>	Human hematopoietic progenitor stem cells that mature mainly into T cells.	Study of CD4+ T cell loss Test of antiretroviral drugs <sup>126</sup>	Absence of innate immunity. Not suitable to study viral transmission.
Hu-HSC	Irradiated non-obese diabetic (NOD) mice injected with human hematopoietic stem cells. Produces human T and B cells.	Neuropathogenesis Viral latency <sup>151</sup>	Absence of innate immune response Not suitable to study primary infection
BLT <sup>152</sup> (Bone-liver-thymus)	Human T and B lymphocytes, monocytes, macrophages, NK and dendritic cells. Develops mucosal immunity, including GALT.	Antiretroviral treatment tests <sup>124</sup> Studies of viral transmission and replication in mucosa <sup>124,125,153</sup>	Defect in class-switched antibody production. Predominance of pre-mature B cells <sup>154</sup>

Table 3. NHP use towards a cure for HIV: advantages and applications

Aim	Advantage of NHP use	Examples of strategies studied
<b>Pharmacological viral suppression and diminution of viral reservoirs</b> <sup>78,155,156</sup>	Control of viral strain Control of viral dose and nature of inoculum Control of route of administration and timing	Diffusion of antiretroviral drugs in tissues Very early treatment initiation Treatment with IFN- <input type="checkbox"/> Treatment with bNabs
<b>Restoration and enhancing of immune response</b> <sup>85,86</sup>	Control of duration, type and combination of antiretrovirals Extensive characterization of viral reservoirs in tissues	Treatment with Interleukins (IL-7, IL-15, IL-21) Treatment with TLR7 agonists Treatment with anti PD-1
<b>Purge latent HIV-reservoir</b> <sup>159-163</sup>	Analyses of immune responses in tissues including immediately after infection Intervention in the early stage of primary infection Administration of potentially risky substances	Administration of inhibitors of chromatin-remodeling molecules (SAHA-inhibitors) Gene editing Nanoparticles

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## CONFLICT OF INTERESTS

The authors declare not to have any conflict of interests.

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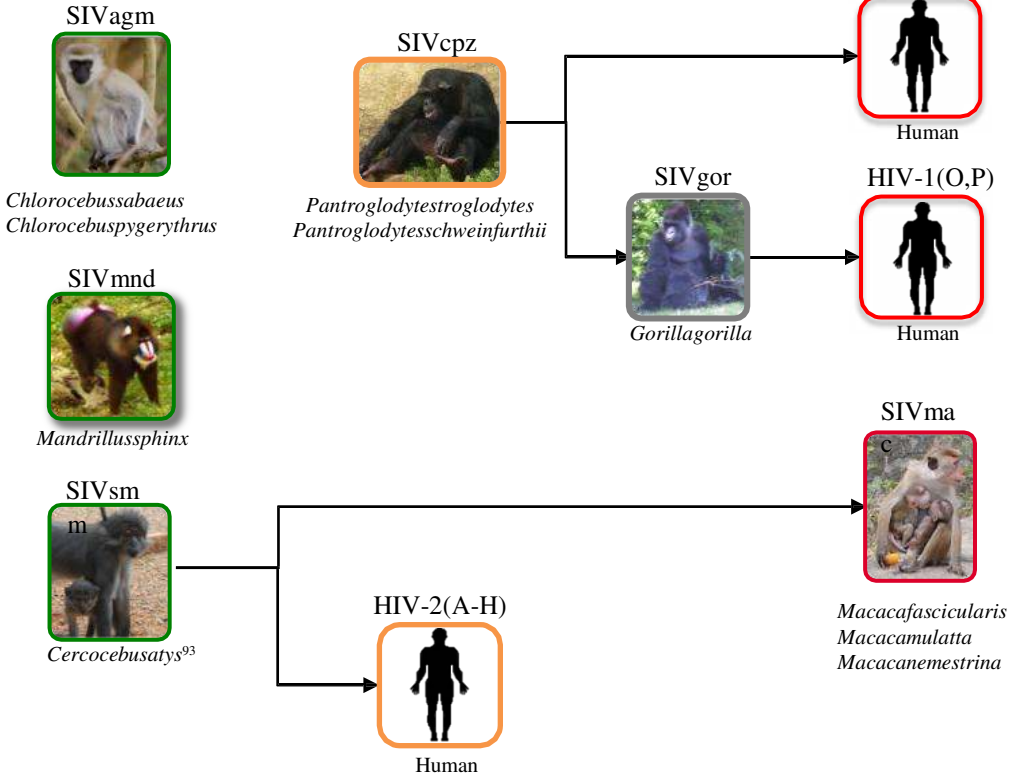
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**Figure 1**



*Non-pathogenic infection*

*Slow progression*

?

*Pathogenic infection*

Figure 2

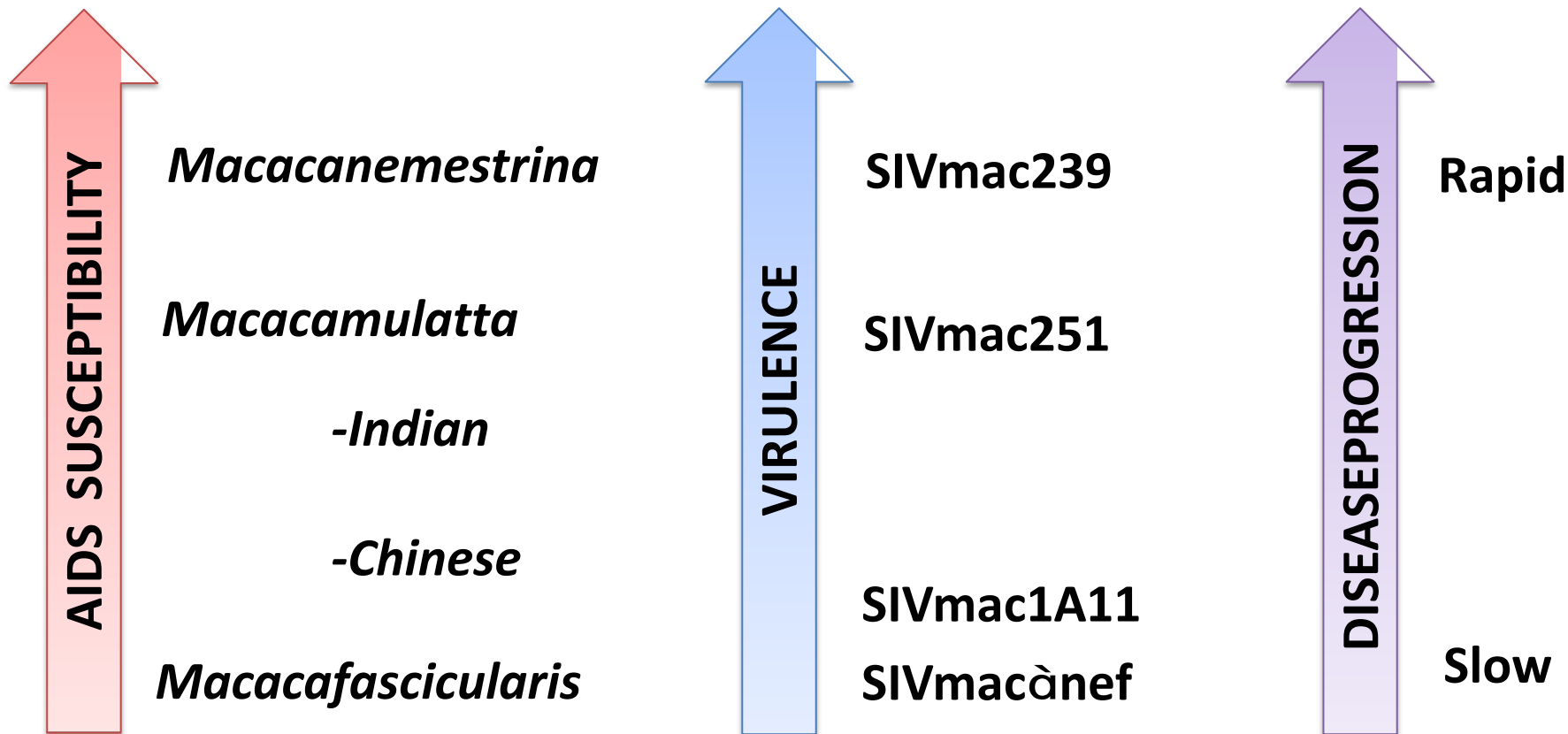


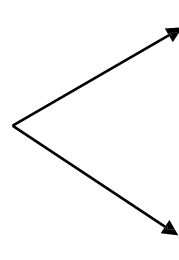
Figure 3



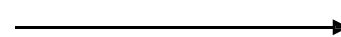
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SIVsmm9



Mangabey



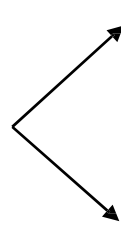
asymptomatic

Rhesus Macaque



**AIDS**

SIVagm.ver90

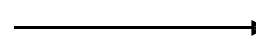


Rhesus Macaque



asymptomatic

Pigtailed Macaque



**AIDS**

SIVagm.ver155



Pigtailed Macaque



asymptomatic

### Captions

**Figure 1. Non-human primate models for the study of HIV infection.** Non-human primates can be divided into pathogenic (macaques) and non-pathogenic (sooty mangabeys, mandrills and African Green Monkeys) models for HIV research. The figure depicts the relationship between the HIV and SIV viruses and the type of infection caused by them.

**Figure 2. Host and viral determinants of disease progression rate.** The progression of the disease depends on the intrinsic susceptibility of each species to develop AIDS and on the virulence of the SIV strain used.

**Figure 3. Cross-species transmissions of SIV and fates of infection.** The presence or absence of progression depends on both, viral and host factors; i.e. the infection with a given SIV strain will not cause disease in some primates, whereas in others will lead to the development of AIDS. Host and viral determinants interact with each other and a combination of both determines the outcome of infection.