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Review

Current advances in HIV vaccine preclinical studies using Macaque models

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ABSTRACT

The macaque simian or simian/human immunodeficiency virus (SIV/SHIV) challenge model has been widely used to inform and guide human vaccine trials. Substantial advances have been made recently in the application of repeated-low-dose challenge (RLD) approach to assess SIV/SHIV vaccine efficacies (VE). Some candidate HIV vaccines have shown protective effects in preclinical studies using the macaque SIV/SHIV model but the model's true predictive value for screening potential HIV vaccine candidates needs to be evaluated further. Here, we review key parameters used in the RLD approach and discuss their relevance for evaluating VE to improve preclinical studies of candidate HIV vaccines.

Contents

1. Introduction

Antiretroviral therapy has dramatically reduced morbidity and mortality of HIV-infected individuals, and the rates of HIV transmission [1], but a safe and effective vaccine is still needed to end

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the pandemic [2,3]. To date, six human HIV vaccine trials have been conducted [4] and only the RV144 Thai trial showed moderate (31%) vaccine efficacy [5]. The key hurdles for developing effective HIV vaccines are: (a) HIV preferentially targets CD4+ T cells; (b) the immunological correlates of protection are unclear; and (c) HIV is extremely diverse and can persist in latent viral reservoirs [2,3,6]. Trials of candidate vaccines therefore need to demonstrate persistent and longer-term efficacy. As human trials are too expensive, labor-intensive, complicated, and attended by high risks [7,8], preclinical trials use nonhuman primates (NHP) and the SIV/SHIV model to evaluate new candidate HIV-vaccines. Largely, the most promising candidates from these preclinical trials are then advanced into human clinical trials [9].

HIV preclinical trials have been conducted in macaque models as there are no ideal *in vitro* systems or computer programs to recapitulate all the salient features of HIV infection in humans [8–10]. Asian macaques' infection by SIV closely resembles that of HIV in humans with respect to transmission, pathogenesis, and latency. Moreover, as with HIV in humans, SIV infection of macaques causes high viral loads, and progressively kills CD4+ T cells [7,10]. Asian macaques are therefore the most commonly used models in preclinical studies. In this review, we will examine the important aspects of using this model to evaluate the efficacy of candidate HIV vaccines in preclinical trials. We will review recent advances in HIV preclinical studies, and focus on viral challenges, route and dose of administration, and the evaluation of vaccine efficacy.

2. Species of macaques

Over 40 African NHP species, often referred to as "natural SIV hosts", are endemically infected by host species-specific SIV strains [11,12]. Examples of these hosts (SIV strains) include chimpanzees (SIVcpz, origin of HIV-1), sooty mangabeys (SIVsm, origin of HIV-2), African green monkeys (SIVagm), and L'Hoest monkeys (SIVlhoest) [11–14]. Among them, SIVsm infection of sooty mangabeys (Cercocebus atys) and SIVagm infection of African green monkeys (Chlorocebus aethiops) have been best studied [10,15,16]. Natural SIV infections generally do not result in AIDS and lack of the typical pathological features of human HIV infections – chronic immune activation, depletion of CD4+ T cells and destruction of mucosal and lymphoid architecture and function, despite sustained viral replication [10,15]. Key correlates of non-pathogenicity are the resolution of immune activation during the acute-to-chronic transition phase [17] and preferential sparing of CD4+ central memory T cells and T memory stem cells [18–20]. Several mechanisms have been hypothesized to explain these phenomena, along with some preliminary insights into associated immunological, virological and genetic factors [15,17,21]. Elucidating the mechanisms underlying the disease avoidance in SIV-infected natural hosts will likely provide useful clues for the development of successful AIDS vaccines [15,17,22]. Such vaccines are anticipated to induce protective immune responses based on limiting excessive immune activation and inflammation that are responsible for increasing the viral target cells [22].

In contrast, SIV infection of Asian macaques (non-natural hosts) leads to a disease that resembles HIV-1 infection of humans. Three such macaque species have been popularly used in HIV vaccine studies, including rhesus macaques (RM -*Macaca mulatta*), cynomolgus macaques (MCM - *Macaca fascicularis*), and pig-tailed macaques (PTM - *Macaca nemestrina*) with Indian RMs being the most commonly used NHP species in HIV vaccine research [23]. The most frequently used and stringent SIV challenge strains - SIVmac251 (viral swarm) and its derived viral clone - SIVmac239, were generated as a result of SIV infection and adaptation in RMs [24,25]. Infections with these viruses in Indian RMs resulted in a high peak viral load ($\log_{10}$ viral RNA copies/ml plasma) of 7.5 and set point viral load of 5.7, values higher than those observed in HIV-1-infected humans (peak 6.7 and set point 4.4) [10,26]. Moreover, disease progression to AIDS in RMs is more rapid than in humans [10]. The major limitation for the use of RMs is their reduced availability following the exportation ban by India in 1987. The current major sources of these animals are breeding colonies in the USA and Europe [27,28].

A popular alternative is MCM which is more frequently used simian species in HIV vaccine studies in Europe than North America [29]. Currently, the largest source is the island of Mauritius [30] and this population is descended from a small number of founder animals that were possibly imported from India by migrant sailors. MCMs are characterized by high genetic homogeneity, with only seven identified major MHC haplotypes [27,30]. This may provide several unique advantages: (1) in studying restricted immune responses against candidate vaccines [31–33]; (2) in facilitating the development of standard reagents and tools [27]; (3) in easily allocating animals for balanced MHC distributions among animal groups [31,32,34], which helps reduce MHC bias that confounds vaccine effect and is much less readily feasible with other, more outbred NHP species [29]; and (4) in reducing the animal numbers needed to achieve statistical power due to reduced variability between animals [27]. However, the simple MHC genetics does not represent the enormous human MHC diversity and polymorphism. Thus, the MCM model may not be powerful in recapitulating all immune responses generated in different human populations against a vaccine. In terms of its potential advantages and disadvantage, the MCM model is particularly useful for evaluating the effect of defined specific immune responses of interest on infection outcome, but may be less so in characterizing extensively what immune responses can be induced by a vaccine in humans.

In comparison to Indian RMs, SIVmac251 (or SIVmac239) infection in MCMs leads to lower peak and set-point viral loads, and slower disease progression [30,35]. SIVmac251 or SIVmac239 infection of MCMs is therefore considered to more closely recapitulate HIV-1 infection in humans [30]. This infection model has proven to be stringent for testing prophylactic vaccines [31,36–42]. Recently, it has also been used to test immunity induced by modified replication-incompetent lymphocytic chriomeningitis virus (rLCMV) vaccine vector expressing SIV Env and Gag [43]. So far, none of the candidate vaccines tested using this model has demonstrated significant efficacy against acquisition of infection.

Pig-tailed macaques (PTM) are relatively less frequently used for HIV vaccine research. Following SIV infection, PTMs develop higher peak and set point viral loads, and progress more rapidly to AIDS compared to RMs [10,44]. Although PTMs can be productively infected with HIV-2 leading to an AIDS-like disease, they are still not widely used in vaccine studies [45,46]. HIV-1 can also develop a low-level transient infection in PTMs, possibly due to their variant version of TRIM5 viral restriction factor that does not effectively restrict HIV-1 replication [29]. These findings suggested a potential to develop minimally chimeric HIV-1 strains that can productively replicate in PTMs to closely mimic HIV-1 infection in humans. Recently, intravaginal challenge studies in PTMs have been used to investigate the effect of contraceptives, and certain microbicides on susceptibility to infection through the genital tract, which is the most common route of HIV/SIV infection in females [29].

A comparison among RMs, PTMs, and CMs has been described in details and their pros and cons have been well summarized in table [47].

3. Viruses used for challenge

Selecting the appropriate virus with which to challenge vaccinated macaques is the primary consideration in vaccine studies of this type. Choosing a highly virulent virus that is capable of

robust replication will usually cause an excessive pathology and may overwhelm the host's immune responses following vaccination, and lead to underestimate of vaccine efficacy. On the other hand, an avirulent virus with weak replication and pathogenicity might easily be controlled by a vaccine-induced immune response, thus leading to an overestimate of efficacy. As approximately 80% of HIV transmissions are caused by a single virulent virion [48], a virus stock with either high or low variance may compromise the accuracy of modeling natural HIV infection. It is usually better to apply heterologous challenges even if a great level of protection had been demonstrated by homologous challenges since similar immunogens might not induce significant protection against heterologous challenges [49]. Moreover, some viral strains are very sensitive to neutralizing antibodies, and thus not appropriate to use when evaluating mucosal transmissions [50]. So far, many challenge viruses have been developed, providing an adequate array of options for use in preclinical vaccine studies with NHP models. These viruses have been well reviewed and summarized in tables [23,47].

3.1. SIV

SIV is a lentivirus which originated from its presumed natural host, the West African sooty mangabey. The ability of SIV to infect macaques and cause an AIDS-like disease has made it a popular choice for research in developing an HIV vaccine. Both HIV and SIV use CD4 as the cell receptor and CCR5/CXCR4 as co-receptor for infecting target cells. The SIV strains used in preclinical research can be categorized into several major groups: SIVmac, SIVsmm, SIVagm, and SIVmne. These SIVs are related to HIV morphologically and antigenically, and each virus has both biological and cloned isolates.

SIVmac251 and SIVmac239 are the most widely used viruses in initial NHP vaccine studies. SIVmac251 originated from a sooty mangabey (CFU287-1979) from the California National Primate Research Center. It was initially isolated from a rhesus macaque Mm251-79 with a viral swarm named SIVmac251_1991. Many different SIVmac251_1991 stocks have since been generated through *in vitro* passage, or through isolation of a new swarm from animals infected with the 1991 quasi-species. These are all heterogeneous swarms of viruses that can transmit multiple variants across mucosal tissues [51]. SIVmac251 is probably the most stringent virus to date among those which more closely represent naturally transmitted isolates of HIV-1 in terms of resistance to neutralizing antibodies, co-receptor CCR5 usage, preferential replication in memory CD4+ T cells, and progression to AIDS [52]. SIVmac239 is a molecular clone derived from SIVmac251 with similar pathogenic properties to SIVmac251 but the clonality of SIVmac239 may reduce the variability of the challenge outcome [27].

SIVsmE660 is an uncloned pathogenic virus isolated later than SIVmac251 [10]. It also contains multiple heterogeneous variants similar to SIVmac251 [53]. In comparison to SIVmac251, SIVsmE660 is more sensitive to neutralization, favoring its use in studies of neutralizing antibodies [54]. Based on its passage history, SIVsmE543-3 is a pathogenic and neutralizing-resistant molecular clone related to SIVsmE660. Both SIVsmE660 and SIVsmE543-3 have been used in some recent heterologous immunization and challenge studies that evaluated heterologous protection in macaques vaccinated with immunogens derived from the different SIVmac251 and SIVmac239 lineage viruses, respectively [29].

SIVmne was initially isolated from a pig-tailed macaque MnT76321 with a lymphoma at the University of Washington Regional Primate Research Center in Seattle. The origin of SIVmne can be traced back to SIVsmm/SIVmac lineage isolated from sooty mangabey CFU287-1979. A number of cloned SIVmne derivatives have since been generated. SIVsmneCL8 is a chimeric virus constructed by introducing variant envelope genes into the SIVmne parental clone [10].

3.2. SHIV

Simian-human immunodeficiency viruses (SHIV) were initially engineered to create viruses which could infect NHPs yet bear HIV-like characteristics and pathogenesis. Typically, SHIV has the *env*, *tat*, *rev*, and *vpu* of HIV while the remaining genes are from SIV. HIV Env from Clade A, B, C and E have been engineered into SHIV.

SHIV89.6p was extensively used in early chimeric virus model studies. Incorporating HIV Env sequences enables the virus to express HIV envelope glycoproteins on its surface while retaining the expression of SIV glycoproteins which enable it to infect macaques, which native HIV cannot do. It also facilitates the evaluation of HIV env-based neutralizing antibodies (NAbs) in the NHP vaccine model [14]. A major disadvantage of SHIV89.6P is that it uses CXCR4 as its co-receptor but not CCR5 which is preferred by founder HIV-1 viruses. It also differs from a typical course of HIV or SIV infection in pathogenic profile, in that it profoundly depletes naïve T cells during the acute phase and induces rapid disease progression [15]. For these reasons, the use of SHIV89.6P as a challenge virus for evaluating T cell-based vaccines has diminished.

The SHIVSF162 lineage of viruses was developed later and is well characterized in NHP studies. SHIVSF162P3 was the first pathogenic R5-tropic chimera produced which is capable of replicating in memory CD4+ T cells. However, SHIVSF162P3 failed to generate persistent viral replication [55]. To overcome this limitation, a related clone - SHIVSF162P3N was produced, and it has shown greater pathogenicity, more sustained viral load, and better adaption to rhesus macaques than the original chimera [56].

SHIVAD8 is a pathogenic R5-tropic SHIV carrying the *env* gene from the HIV-1Ada, which is a prototypical macrophage tropic strain with a possibility for eliciting NAbs against HIV-1 gp120 [57]. Initial tests conducted using this chimera demonstrated sustained viremia, depletion of CD4+ T cells, induction of AIDS and cross-clade induction of plasma NAb responses [51]. It has recently been used as passive immunotherapy to study long lasting immunity during SHIV infection [58].

SHIV-1157ipd3N4 is a pathogenic R5-trophic SHIV, encoding HIV clade C *env* isolated from a Zambian infant T/F virus which is considered to be more useful in evaluating prophylactics and treatment intervention [59]. Moreover, it is mucosally transmissible with enhanced replication in both RMs of Indian and Chinese origin.

SHIV-375 is a recently developed pathogenic SHIV with envelope residue 375 substitutions, which line the Phe43 CD4-binding cavity [43]. SHIV-375 encodes T/F Envs corresponding to HIV-1 CH505, CH848, and BG505, which are all shown to elicit NAbs in human hosts. These viruses were able to enhance CD4 binding and replication in rhesus macaques [43,60] and thus are suitable for constructing SHIVs with Env of interest in eliciting NAbs or binding to B-cell receptors [61].

Despite all these new desirable features of current SHIV lineages, an obvious drawback of these chimeras is the increased susceptibility to vaccine-induced immune control.

3.3. stHIV

To achieve the same goals, some researchers have started to engineer chimeric viruses with the opposite approach taken in engineering SHIV. StHIV-1 (SCA, SVIF0) is a HIV-based/SIV chimera with 88% sequence homology to HIV-1, in which the capsid and *vif* regions of HIV-1 are replaced with those of SIVmac239. The

capacity to evade TRIM5α and APOBEC3G enables it to infect both human and macaque cell lines. stHIV has proven to be a useful tool evaluating drug resistance mutations in an NHP model [62].

Both SIVs and SHIVs have their own characteristics as well as have been used in preclinical studies using NHP macaque models. A comparison between SIVs and SHIVs has been summarized in Table 1.

4. Route, dose, and challenging times of virus infection

A variety of challenge routes such as intravenous (IV), penile, oral, nasal, intrarectal (IR), and intravaginal (Ivag) have been used in macaque models [29,63]. As HIV infection is often acquired by heterosexual transmission through mucosal exposures, the majority of the preclinical studies conducted in macaques focused on mucosal challenges. Historically, IR challenge was predominantly used in preclinical studies due to the ease of infection and the ability to challenge male macaques. Ivag challenge has not been used very often because female macaques are in short supply. In addition, the menstrual cycle, structure of vaginal mucosa, and microbial composition all influence susceptibility to SIV or SHIV infection [64]. The menstrual cycle has been shown to alter the thickness of vaginal epithelial layers in the female genital track (FGT) and influence the outcomes of Ivag challenges. Both RMs and MCMs had an increased susceptibility to SIVmac251 or SHIVSF162P3 infections during luteal phase [65,66]. The increased susceptibility of SIV acquisition was linked to enhanced virus-target cell interactions in FGT by the elevated endogenous progestin during the luteal phase [67]. Microbial and FGT changes owing to menstrual cycle and variations lead to changes in pH and inflammation environment. These are key factors related to HIV acquisition in humans [68]. Despite these limitations of Ivag challenge, preclinical trials using female macaques via Ivag approaches are the best, and thus encouraged, in simulating the male-to-female HIV transmission route, through which most HIV transmission occurs.

For practical reasons, a single high-dose SIV challenge (HD) was used in the early HIV vaccine preclinical studies. However, HD is unnatural and its application fails to mimic the actual amount of HIV viruses in heterosexual HIV transmission and thus not adequate in evaluating prophylactic vaccines. In general, the HIV transmission rate per coital act is estimated to be very low in humans [69,70]. The average HIV viral loads in semen are 11,000 copies/ml [71]. Even low dose challenges (120–250 TCID50) with SIVmac251 used in macaque model contain over 1 million copies/ml of viruses [72,73]. These doses of SIV are considerably higher than the amount of viruses in human heterosexual transmission. A single HD often infects all studied macaques in one challenge which likely masks the effect of vaccine. Recently, repeated-low-dose challenges (RLD) have been employed in most current preclinical studies in order to more closely mimic natural sexual transmission of HIV in humans (Table 2) [50,66,74–102]. RLD challenge requires each macaque be challenged with a lower viral dose at multiple time points until most of unvaccinated macaques are infected. It was shown that the protective effects of a vaccine could otherwise be masked by HD challenges that overwhelmed vaccine-induced immune responses [82]. These findings demonstrate that the RLD approach is more useful for assessing the potential efficacy of candidate vaccines. Moreover, RLD challenge better recapitulated features of human mucosal HIV infection [53,103]. The RLD approach can also be used for studying the bottleneck of mucosal HIV-1 transmission. More importantly, RLD challenge is a cost-efficient approach in preclinical trials since this design requires a smaller numbers of macaques. Based on modeling, it was estimated that 5 macaques per group can reach the statistical power greater than 95% if the vaccines are 90% effective [104]. In a separate study, 25 macaques per group achieved sufficient statistical power to detect 50% per-exposure reduction which is similar to what was observed in phase IIB or III clinical trials [103].

There are considerably variations in the dosages of uncloned SIV or SHIV used in RLD challenges of different studies. For instance, a range of 100–1000 $TCID_{50}$ of SIVmac251 has been used through IR or Ivag routes to infect rhesus macaques (Table 2) [74,75,77–79,81–83,86,87,101,102]. Variation among SIVmac251 challenge dosages reflects the various compositions of viral stocks from different laboratories depending on their passage history and *in vitro* production methods. Detailed studies of widely used SIV or SHIV challenge stocks are very valuable, but rare. One study has comprehensively characterized nine SIV stocks comprising infection-derived SIVmac251 and transfected-293T–cell-derived SIVmac239 in terms of virus content, infectious titer, and induction of cytokine/chemokine contents [72]. The stocks examined from different laboratories induced variable infectivity *in vitro,* potentially influencing *in vivo* infectivity, mucosal transmissibility and early infection [72]. Even in a specific lab, the viral stocks such as

Table 1
Comparison of SIV and SHIV commonly used in NHP macaque models.

	SIV	SHIV	Reference
Genomic content	SIV	SIV + *env/tat/rev/vpu/vpr/nef/integrase/reverse transcriptase* of HIV-1	[10]
NHP species used	RM, MCM, PTM	RM, MCM, PTM	[27]
Route of inoculation	Mucosal (IR, Ivag, oral, penile), IV	Mucosal (IR, Ivag, oral, penile), IV	[47,172,173]
Target	Predominantly memory CD4+ T-cells	Memory (R5-tropic) or naïve CD4 + T-cells (X4-tropic)	[52,174,175]
Tropism	Mostly CCR5	Both CCR5 and CXCR4	[7,175,176]
Neutralization profile	Most resistant to NAbs; Few sensitive to NAbs (SIV_{smE660})	Sensitive to NAbs	[9,54,57]
Host susceptibility	Possibly restricted by TRIM5 (SIV_{smE660})	Not restricted by TRIM5	[136,177]
Pathogenesis/disease course	Gradual and moderate loss of CD4 + T cells ; slower disease progression	Rapid loss of CD4+ T cells; rapid disease progression ($SHIV_{89.6P}$)	[15,175,176,178]
ART	Susceptible to the most ARTs; resistant to NNRTIs	Susceptible to the ARTs, including NNRTIs	[179,180]
PrEP	Mostly NRTI-based	NRTI, NNRTI, integrase, CCR5 antagonist-based	[47,181-183]
Application	HIV pathogenesis HIV vaccine efficacy PrEP studies	Transmission and early T-cell responses HIV-1 Env-based vaccine strategies NNRTI-containing ART strategies PrEP studies	[47,184]

NHP: non-human primate; RM: rhesus macaque; MCM: cynomolgus macaque; PTM: pig-tail macaque; IR: intra-rectal; Ivag: intravaginal; IV: intravenous; NAbs: neutralizing antibodies; TRIM5: tripartite motif-containing protein 5; NNRTIs: non-nucleoside reverse transcriptase inhibitors; NRTIs: nucleoside reverse transcriptase inhibitors; PrEP: pre-exposure prophylaxis; ART: antiretroviral therapy;

Table 2
Summary of repeated low-dose SIV/SHIV challenges applied in NHP macaque models.

Author	Species	Origin	Gender	Vectors or Passive	Challenge Virus	Challenge dose ($TCID_{50}$)	Challenge route	No. of challenges	Challenge frequency (wk)	Reference
Bomsel M, et al.	Rhesus	Chinese	F	Virosome	$SHIV_{SF162P3}$	20–30	Ivag	13	1	[89]
Singh S, et al.	Rhesus	Indian	F/M	DNA/gp120	SIVsmE660	100	IR	6	1	[88]
Manrique M, et al	Rhesus	Indian	F	MVA/DNA	SIVmac251	100	Ivag	32	1	[86]
Strbo N, et al.	Rhesus	Indian	F/M	$gp96^{SIV}$Ig SIVgp120	SIVmac251	120	IR	7	1	[87]
Tuero I, et al.	Rhesus	Indian	F/M	Ad5hr/gp120/ gp140	SIVmac251	120	IR	9	1	[92]
Gupta S, et al.	Rhesus	Indian	N/A	ALVAC-SIV/gp120	SIVmac251	120	IR	5	1	[102]
Vaccari M, et al.	Rhesus	Indian	F/M	ALVAC	SIVmac251	120	IR	10	1	[75]
Xiao P, et al.	Rhesus	Indian	F/M	Ad5/SIVgp120	SIVmac251	130	IR	10	1	[93]
Martins MA, et al.	Rhesus	Indian	F/M	DNA/Ad5 DNA/VSV DNA/RRV	SIVmac239	200	IR	19	2	[100]
Reynolds MR, et al.	Rhesus	Indian	N/A	DNA (SIVΔnef)	SIVsmE660	225	IR	10	1	[99]
Morris MR, et al.	Rhesus	Indian	F	None	SIVmac239	250	Ivag	6	1	[66]
Byrareddy SN, et al.	Rhesus	Indian	F	A4β7-mAb	SIVmac251	250	Ivag	10	1	[80]
Lagenaur LA, et al.	Rhesus	Chinese	F	Live recombinant Lactobacillus	$SHIV_{SF162P3}$	300	Ivag	6	1	[85]
Kurupati R, et al.	Rhesus	Indian	F/M	AdHu5/DNA (SIVΔnef)	SIVmac251	300	IR	10	1	[101]
Bradley T, et al.	Rhesus	Indian	F/M	ALVAC/gp120	$SHIV_{1157\ (QNE)Y173H}$	400	IR	8	1	[77]
Vaccari M, et al.	Rhesus	Indian	F/M	DNA/ALVAC	SIVmac251	470	IR	2	1	[82]
Barouch DH, et al.	Rhesus	Indian	F/M	Ad26/Ad35 Ad26/gp140	SIVmac251	500	IR	6	1	[79]
Barouch DH, et al.	Rhesus	Indian	F/M	Ad26/Ad26/gp140 Ad26/Ad26 Ad26/MVA/gp140 Ad26/MVA Ad26/gp140	$SHIV_{SF162P3}$	500	IR	6	1	[50]
Barouch DH, et al.	Rhesus	Indian	F/M	DNA/MVA MVA/MVA Ad26/MVA MVA/Ad26	SIVmac251	930	IR	6	1	[74]
Dubie RA, et al.	Rhesus	Indian	F	DNA (SIV/CMVΔvif)	SIVmac251	1000	Ivag	6	1	[83]
Qureshi H, et al.	Rhesus	Indian/ Chinese	M	Ad5-SIV	SIVmac251	1000–10,000	Penile	20	1	[95]
Jensen K, et al.	Rhesus	N/A	F/M	Live attenuated Mc/MVA	SIVmac251	5000	Oral	9	1	[84]
Kwa S, et al.	Rhesus	Indian	M	DNA/MVA	SIVsmE660	5000	IR	12	1	[90]
Lai L, et al.	Rhesus	Indian	M	DNA/MVA	SIVsmE660	5000	IR	12	1	[96]
Sholukh AM, et al.	Rhesus	N/A	F	SHIVIG	$SHIV_{2873Nip}$	5000	IR	5	1	[97]
Lakhashe SK, et al.	Rhesus	Indian	N/A	Lmdd-Bdop (SIVgag) Ad5hr (SIVgag) Ad5hr	$SHIV_{1157ipELp}$	8000	IR	5	1	[98]
Chang HW, et al.	Rhesus	Indian	F/M	None	$SHIV_{327cRM}$	30,000	IR	6	1	[91]
Hansen SG, et al.	Rhesus	Indian	F	RhCMV/SIV	SIVmac239	N/A	Ivag	10	1	[81]

IO: Indian origin; F: female; M: male; IR: intra-rectal; Ivag: intra-vaginal; N/A: not available; $TCID_{50}$:50% cell culture infectious dose; Mc: mycobacterium tuberculosis;

SIVmac 251 may vary depending on primary cells or cell lines that were used to generate the stocks. In fact, each stock has its own characteristic, co-receptor usage, host range, infectivity, and route by which the virus is utilized for infection. For example, SIVmac251-8/27/2008 is generated by infecting human PBMCs [105] while other commonly used SIVmac251 viral stocks are all generated by infecting RM. SIVmac251-7/9/2010 displays higher specific infectivity in comparison to SIVmac251-06/2004 based on mean primary cell titer [52]. As a result, it is difficult to compare the results among studies using different viral stocks of the same viruses. The worst case is that the specific transmitted variant(s) in one study is phenotypically distinct from other studies when the range of phenotypic breadth within a given viral stock is unknown. In this regard, it is a good practice to conduct a pilot study to titer SIV stocks in the unvaccinated macaques. Such a study can determine a dose that can reliably infect a certain number of unvaccinated macaques (<50%) per challenge before the actual preclinical studies. To facilitate the evaluation of candidate HIV vaccines using the macaque/SIV/SHIV model and to compare results from different studies, the NIH Vaccine Research Program, Preclinical Research and Development Branch offers standard SIVmac251 and SHIVSF162P3 stocks to research laboratories all over the world. The SIVmac251 stock is the same viral stock that was evaluated with several other SIVmac251 viral stocks [72]. Although the detailed information of the SHIVSF162P3 stock is lacking, a SHIVSF162P3 stock produced in one batch with the same cell lines for different studies is valuable for comparing efficacies of different preclinical studies.

The frequency of SIV/SHIV challenges in the RLD approach is another important factor which affects the evaluation of efficacy of vaccine candidates. Macaques are often challenged weekly with SIV/SHIV through mucosal routes [74,75,77–79,81,83,87,102,106]. This challenge schedule attempts to replicate natural HIV transmission in humans. An infectivity rate of 20–40% per challenge in

unvaccinated macaques could be achieved with this schedule [27]. Weekly challenge schedule has been successful in detecting partial protective efficacy of SIV/SHIV vaccines and identifying protective correlates according to the challenge numbers of SIV or SHIV acquisition in a number of vaccine studies [74,75,77–79]. Although the infectivity rate derived from RLD challenges is much higher than the one observed in HIV transmission, RLD challenges are more useful in detecting a risk difference of acquiring SIV between vector control and candidate vaccines within a reasonable time frame [27]. In fact, SIV infections could occur on day 5–14 after a single low dose mucosal challenge [76]. More studies have since started to extend viral infection monitoring time after each challenge. RLD challenges every two weeks (biweekly) have been used and shown to be able to measure vaccine efficacy more accurately [76,107].

We recently concluded a study in which animals were vaginally challenged. Our unpublished findings showed that MCM macaque seroconversion can be detected on day 6, 10 and 14 following each SIVmac251 challenge. Of the 19 female MCM macaques infected, only 26% were infected on day 6, 53% of them were infected on day 10, and 21% of them were infected on day 14. Thus, using weekly challenges may overestimate protection in comparison to every two weeks challenge and monitoring the viral load more frequently after each challenge. The biweekly challenges could provide more accurate evaluation of the candidate vaccines. The drawback of the biweekly approach is the increased duration of studies and the cost of animal care and viral load monitoring. However, the more accurate evaluation of vaccine efficacy should outweigh its disadvantages.

Despite the advantages of the RLD approach, there is always limitation in this approach. IR or Ivag challenges may induce trauma while menses may influence RLD following Ivag challenges. However, experienced staffs and detailed monitoring menses cycles could help overcome these challenges.

5. Host factors associated with resistance to viral challenge

There are numerous restriction factors in NHPs that are capable of hampering the establishment of retroviral infection in a species-specific manner, thus limiting the use of certain monkey species in studying HIV pathogenesis. Much like HIV infections in human, the clinical course of SIV infection in NHPs varies in part due to host factors such as MHC I/II and other restriction factors, including TRIM5α, KIR's, and FcR.

5.1. MHC

The extreme polymorphism of the major histocompatibility complex (MHC) enables NHPs to recognize and initiate immune responses to a variety of pathogens including SIV, a subject which has been well reviewed [108]. Certain MHC haplotypes in RMs are associated with spontaneously controlling SIV replication and SIV disease progression [109]. For example, *Mamu-A1*002* was enriched in elite controller. *Mamu-A1*001* and *Mamu-B*047:01* were associated with longer survival and lower set-point viral load, respectively. Whereas *Mamu-A1*004* was associated with higher set-point viral load, Mamu-B*008:01 and Mamu-B*017:01:01 were associated with the control of SIV replication during the chronic phase of infection although they were not found in elite controllers [100].

The MHC genetics of MCMs is much simpler and 6 common haplotypes account for two-thirds of the MHC haplotypes among them [110]. The low diversity of MHC makes MCM an ideal model for studying host-viral interactions and cellular immune responses. One study has shown that M3 haplotype was associated with a reduction of viremia at 28 days post infection, whereas haplotype M6 is associated with elevated viremia [111]. In our pilot vaccine study, 12 MHC-genotyped MCMs were infected with SIVmac251 and two MCMs with M3M4 genotype maintained the lowest peak viral loads and healthy CD4+ T-cell counts compared to the rest of MCMs with other MHC haplotypes. Furthermore, a macaque with recombination in the MHC class I region (M3/M5) and same MHC class II (M3/M4) could not control SIV viral load. Our study demonstrated that both M3 and M4 class I regions are required to control SIV infection [31]. Our other study also showed that host MHC haplotypes may influence natural antibody responses to SIV gag peptides [32].

Recently, the MHC of PTMs was sequenced by Pacific Biosciences' sequencing technology and *Mane-A1*084* was found to be associated with delayed disease progression [112]. Lately, MHC-E was shown to be associated with a tolerogenic immune response that was associated with protection from SIV infection in Chinese Rhesus macaques [113]. The vaccinated Chinese macaques developed non-classic MHC-Ib/E- restricted CD8+ T cells responses which sterilely protected the macaques for 5 years. Interestingly, MHC-E was found functionally conserved among humans, RMs, and MCMs [114].

5.2. Killer-cell immunoglobulin-like receptors (KIRs)

The polymorphisms of KIR genes were highly associated with resistance to the immunodeficiency virus and their roles were well reviewed in the NHP models [109]. The interactions between KIRs on NK cells and their MHC class I ligands on target cells could regulate NK cells, one of the first line of defense against viral pathogens. Regulation of NK cells by KIRs depended on RM KIR3D molecules bound to Mamu-A and Mamu-B of MHC class I proteins [115]. KIR3D genes consist of both inhibitory (KIR3DL02, KIR3DL10) and activating KIR genes (KIR3DSW08, KIR3DS02, KIR3DS05). The presence of different genes and the epistasis between KIR and MHC class I alleles resulted in the varied SIV infection outcomes [109,116]. It was recently shown that enrichment of KIR3DL01+ NK cells increased expression of CD16+ population in response to SIVmac239 infection in KIR3DL01+ and KIR3DL05+ macaques [117]. Moreover, the different binding avidity of SIV peptide epitopes to KIR-MHC I complex was also involved in regulating NK cell response and evaded the NK cell defense [115].

5.3. Fc receptors

Research on Fc-receptor polymorphisms has intensified following the identification of the role played by these receptors in protection in the Thai RV144 HIV vaccine trial [118]. In fact, Fc-and Fcγ receptor (Fcγ R) mediated antibody functions could regulate protective immunity and control of viremia in both humans and NHPs [119,120]. One early study characterized RM CD32 (FcγRII) and CD64 (FcγRI) homologues and indicated that they were structurally similar but genetically even more polymorphic comparing to their human counterparts [121,122]. Although the strong relationship between FcγR polymorphisms and disease progression was not identified in a cohort of HIV-1 seroconverts [123], FcgammaR was found to activate p21 (Cip1/WAF1) and mediate restriction of SIV replications [124]. A recent study demonstrated that lack of Fc receptor (FcR) signaling chain (Δg) is a mechanism used by primate NK cells to acquire adaptive features and this virus-dependent alternative signaling could be a new target for vaccine development [125].

5.4. Host restriction factors

There are a number of host restriction factors as components of the host innate immune system that can limit the infection and disease severity.

Host restriction factors such as TRIM5α make NHP cells resistant to infection with lentivirus [126]. TRIM5α belongs to the enormous tripartite motif (TRIM) family of cellular proteins involved in diverse cellular processes such as cell proliferation, differentiation, apoptosis, oncogenesis, development and innate immunity. Only a handful of the TRIM genes exhibit anti-retroviral activity, including the most widely studied *TRIM5* [127–129]. TRIM5 proteins block lentiviral infection soon after entering the target cells by recognizing and binding to viral capsid, and destabilizing the viral core [130]. The presence of certain genetic polymorphisms has been shown to reduce TRIM5α activity depending on the SIV capsid sequences [131,132]. SIVmac239 appear to be more refractory to TRIM5α inhibitory effects whereas SIVsmE543 and SIVsmE040 are more sensitive to the same. Other strains like SIVmac251 and SIVsmE660 are in the intermediate range. There are conflicting reports on the effects of TRIM5α on SIVmac251 infection. One study found that a homozygous restrictive $TRIM5^{TFP/TFP}$ (alleles 1–5) genotype was associated with lower viral loads, while heterozygous $TRIM5^{TFP/Q}$ (alleles 6–11) was associated with intermediate restriction and viral loads, whereas homozygous $TRIM5^{Q}$ (alleles 6–11) genotypes were associated with permissive or higher viral loads in RM [133]. In another study, the restrictive TRIM5α alleles did not affect SIVmac251 replication in RM regardless of vaccination, infection dose or MHC I alleles [134]. TRIM5α genotypes affected the peak viral loads over the clinical course of SIVsmE543-3. Up to 3-fold lower viral loads were observed in RMs with $TRIM5^{TFP/TFP}$ and $TRIM5^{TFP/CypA}$ genotypes in comparison to other animals [132]. Similarly, TRIM5α restricted IR and penile transmission of uncloned SIVmacE660 despite repeated exposures but had no effect on SIVmac239 [135,136]. In spite of the restrictive effects of TRIM5α, a number of SIV vaccine candidates showed efficacy in preclinical studies using SIVmacE660 as challenge virus despite the use of macaques with restrictive genotypes in these studies [137,138].

Apolipoprotein B mRNA editing enzyme catalytic polypeptide 3 G (APOBEC3G) host restriction activity was first identified for its ability to limit infection of human cells by Vif deficient HIV [139]. The APOBEC3 proteins are encapsulated into budding retroviruses through association with viral RNA [140]. When such retrovirions infect a target cell, the restriction activity of APOBEC3G is mediated by cytidine deaminase activity on the minus strand mRNA of HIV leading conversion of cytidine (C) to uridine (U), resulting in guanine (G) to Adenine (A) hypermutations during proviral DNA synthesis [139]. The A3G edited provirus contains defective proteins which results in non-functional or uninfectious virions. Both HIV and SIV genomes contain the *vif* gene expressing the Vif protein, which counteracts A3G by inducing its proteosomal degradation through ElonginB/C-Cullin-5 E3 ubiquitin ligase after Vif recruits the core-binding factor beta binding to transcription regulator RUNX [141–143]. SIVmac Vif recruits CBPβ to aid in degradation of rhesus macaque A3G. Other members of the APOBEC family present in human and macaque cells include A3A, A3B, A3C, A3D, A3F, A3G and A3H [144–146]. All the members of the APOBEC family are cytidine deaminases and possess H-x-E-x24−28-P-C-x-x-C deaminase domains [147]. Some members contain single cytidine deaminase domains (A3A, A3C, A3H) while others have duplicate domains, including A3B, A3D, A3F and A3G [144,146,148]. Only single domain containing human A3C incorporates HIV *vif* and HIVΔ*vif* that is capable of inducing G-A mutations, but not as much as A3G [149]. In RM, A3B, A3F, A3G and A3H can restrict HIV-1 and are resistant to HIVΔ*vif*. However, differential restriction has been observed between human and macaque A3A, A3C and A3H [150].

Bone marrow stromal antigen 2 (BST) or tetherin is an IFN inducible type II transmembrane protein anchored to the plasma membrane through N-terminus, and containing a lipid glycophosphatidylinositol (GPI) in its c-terminus. Tertiary folding of the protein, mediated by cysteine residues linked through disulfide bonds, leads to formation of a tetherin dimer capable of tethering nascent virions preventing their release from infected cells [151]. A number of HIV and SIV proteins possess anti-tetherin activity. For instance, HIV-vpu can co-precipitate tetherin, thus reducing its surface expression by inhibiting its secretory pathway [152,153]. SIV lacks vpu, instead utilizes Nef which induces the assembly of AP2-clathrin adapter complex beneath the cell membrane, leading to tetherin internalization [154]. A number of SIVs contain Nef mediated tetherin antagonistic activity, with the switch from Nef to Vpu antagonist activity in SIV and HIV, respectively, through an evolutionary deletion of 5 residues in the cytoplasmic tail of the tetherin protein [155].

Sterile Alpha Motif Domain and Histidine Aspartate Domain containing protein 1 (SAMHD1) is a cellular enzyme with triphosphohydrolase capable of converting dNTPs into deoxynucleoside and inorganic triphosphate (iPPP) and thus depletes the dNTPs available for HIV replication [156]. SAMHD1 can hydrolyse all four dNTPs in myeloid cells, thereby preventing proviral DNA formation and viral replication in these cells [157,158]. SAMHD1 exhibits RNAse activity by targeting viral RNA prior to reverse transcription, a highly disputed view that is yet to be clarified [159–161]. Viral protein Vpx, present in HIV-2 and some SIV strains (SIVsm and SIVmac) overcomes SAMHD1 restriction by recruiting the Cullin-4 E3 ubiquitin ligase complex, which targets SAMHD1 for proteosomal degradation. SIVcpz, which lacks Vpx and thus is unable to overcome SAMHD1 mediated restriction, is vulnerable to its activity [157]. The hydrolysing activity of SAMHD1 has linked it to cell-cycle progression, evidenced by Cyclin-dependent kinase 6 (CDK6) coupled with cyclin D3 mediated phosphorylation control of SAMHD1 [162,163].

SERINC5 is another host restriction factor which was related with high infectivity and its restriction by incorporating into assembling viroins could be counteracted by HIV and SIV Nef proteins depending on monkey species [164].

In summary, host factors listed above are important factors to be considered when selecting NHPs for use in preclinical screening experiments for evaluating HIV vaccine candidates.

6. Vaccine efficacy

The preclinical trials using macaque/SIV/SHIV models are conducted to evaluate vaccine efficacy (VE) - rates of infection, between vaccine and placebo groups. To achieve this goal, a randomized and placebo-controlled design is usually required to detect different rates of infection between vaccine and placebo groups [165]. However, very few preclinical studies have addressed how VEs are evaluated.

To assess VE, the endpoint(s) must be clearly defined prospectively, that is before the preclinical studies are conducted. Endpoint is thus called "efficacy endpoint". Similar to HIV infection in humans, it would take years for SIV-infected macaques to develop simian AIDS. Thus, evaluating the effect of vaccine in protection from disease progression to AIDS in a macaque model requires longer study time and increases the cost [10]. As SIV acquisition can be readily measured by ultra-sensitive RT-PCR assays for viral RNA, it has been widely used as an endpoint to predict VE in macaque models in order to reduce the time and cost of vaccine preclinical studies. In practice, vaccine efficacy is generally assessed with endpoint(s) of the numbers of challenges needed for SIV/SHIV infection in RLD macaque models [30,74,75,78,79]. The selection of endpoint(s) is mainly based on relevance of the effect of the tested vaccine on the endpoint and reliability of the endpoint measurement [166]. An ideal primary endpoint of vaccine preclinical

trials is the time point when all the tested macaques are infected [74–76,78,87,94,167,168]. However, the uncertainty of acquisition of SIV/SHIV infection in a vaccinated group makes it hard to estimate the number of challenges required to infect all monkeys. The uncertainty may lead to much longer times to complete the study and thus increased costs. By contrast, rates of acquisition of infection can be defined in an unvaccinated group by conducting pilot studies. In practice, primary endpoint has been preferably defined as the time when the majority of unvaccinated macaques are infected [50,77,79,80,90,169].

Survival analyses are the "gold standard" for assessing VE in macaque models. In these analyses, the risks of SIV/SHIV infection from different groups (vaccinated and unvaccinated) are statistically compared with the log rank test through Cox's proportional hazard models based on the assumption that the probability of infection (hazard ratio) is consistent over time. Alternatively, the model-base likelihood ratio test (LTR) can be used and has been proven to be the most powerful method but it needs larger sample sizes [170]. In this model, maximal likelihood methods are employed for estimating the probability of infection in susceptible and unvaccinated macaques, the probability of vaccinated macaques that are protected, and a constant (the percentage of vaccinated macaques were infected). VE can thus be defined as the relative risk reduction in the per contact transmission probability by comparing vaccinated macaques to unvaccinated macaques [171].

The assessment of vaccine efficacy is affected greatly by the design of challenge experiments. Besides endpoints, study parameters such as total sample size, the infection rate of unvaccinated macaques, the proportion of susceptible macaques, and statistical methods have been shown to affect the statistical power of detecting VE [170,171]. Among these parameters, the proportion of susceptible macaques cannot be controlled in vaccine trials even if macaques are carefully selected to avoid the influence of restricting factors such as the class I alleles associated with viral control and resistant TRIM5a alleles. It has been reported that around 10–20% of macaques are not susceptible to SIV/SHIV infection [76,80]. In our current vaccine study, 2 out of 8 (25%) unvaccinated macaques were suspected to be refractory to SIVmac251 infection and the mechanism for this remains unknown. Challenge experiments should thus be designed based on the above factors that potentially influence the preclinical evaluation of vaccine efficacy. A good practice is to estimate a reasonable statistical power (up to 80%) after defining the effective sample size and number of challenges (endpoint) based on the calculated infection rate of unvaccinated macaques in the pilot study, assuming 80–100% macaques are susceptible to SIV infection [80].

7. Conclusion

In recent years, considerable advances have been made in developing macaque SIV/SHIV models for preclinical evaluation of candidate HIV vaccines. These advances have provided us with a better understanding of HIV biology and helped evaluate vaccine candidates. The macaque model is expansive and many factors need to be considered in order to optimize the study design. RLD has become a standard approach in HIV vaccine preclinical studies and is successful in identifying potential vaccine candidates. Variations of SIV/SHIV viral stocks, doses, routes, and duration/frequencies of SIV/SHIV challenges of RLD approaches will affect the sensitivity and accuracy of VE evaluation. Thus, optimization and standardization of RLD approaches will be crucial in future preclinical vaccine studies.

In addition, the sample size of the study should be carefully determined to achieve a statistical power of 80% or higher. A statistical power calculation to predict VE is strongly recommended before conducting preclinical studies. As more preclinical studies using macaque models are conducted, the macaque models can be further optimized for efficacy testing of HIV-1 vaccine candidates and used to guide clinical trials.

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Declaration of interest

There is no competing financial interest.

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