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Predictive Value of Primate Models for AIDS

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Abstract

A number of obstacles remain in the search for an animal model for HIV infection and pathogenesis that can serve to predict efficacy in humans. HIV-1 fails to replicate and cause disease except in humans or chimpanzees, thereby limiting our ability to evaluate compounds or vaccines prior to human testing. Despite this limitation, nonhuman primate lentivirus models have been established that recapitulate the modes of infection, disease course, and antiviral immunity that is seen in HIV infection of humans. These models have been utilized to understand key aspects of disease and to evaluate concepts in therapies and vaccine development. By necessity, animal models can only be validated after successful trials in humans and the determination of correlates of protection. Because the only vaccine product tested in phase III trials in humans failed to achieve the desired protective threshold, we are as yet unable to validate any of the currently used nonhuman primate models for vaccine research. In the absence of a validated model, many experts in the field have concluded that prophylactic vaccines and therapeutic concepts should bypass primate models, and rely solely upon the systematic testing of each individual and combined vaccine element in human phase I or I/II trials to determine their relative merits. Indeed, a large effort is underway to expand efforts to test all products as part of an international effort termed "The HIV Vaccine Enterprise", with major contributions from the Bill and Melinda Gates Foundation. This Herculean task could potentially be reduced if it were possible to utilize even partially validated nonhuman primate models as part of the screening efforts. The purpose of this article is to review the data from nonhuman primate models that have contributed to our understanding of lentivirus infection and pathogenesis, and to critically evaluate how well these models have predicted outcomes in humans. Key features of the models developed to date are described and their contributions to HIV pathogenesis, therapeutics, and vaccines, are compared. This analysis shows that many of the models at hand have yielded data on drug action and immune responses to vaccines that are congruent with clinical data. This finding suggests that primate models are valuable as adjunctive testing systems to prioritize future therapeutic and vaccine strategies. Nonhuman primate testing of vaccine approaches in particular has provided valuable information and can significantly enhance and accelerate the evaluation of novel concepts necessary to achieve acceptable levels of efficacy. Because major gaps remain in the quest for fully effective vaccines and therapies, it seems prudent to continue aggressive research programs in the nonhuman primate models. **(AIDS Reviews 2004;6:187-98)**

Key words

Nonhuman primate models. Vaccines. Therapies. Pathogenesis.

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Introduction

Nonhuman primate models for AIDS research have been a major focus of vaccine and pathogenesis work since the discovery of simian AIDS, following accidental cross-species transmission of SIV in the primate centers in the early 1980s[1,2]. Since that time, a great deal of progress has been made in understanding primate lentiviruses in their natural hosts and in their new hosts, with the goal of developing nonhuman models for HIV replication and pathogenesis[3]. Lack of a readily available host, and failure to progress to disease before 10 years, has limited the use of HIV-1 in nonhuman primates[4]. Divergence in protein sequences, and differences in antigenicity between HIV-1 and HIV-2/SIV, required that many therapies and vaccines be tailored specifically for the two lineages. Serial in vivo passage of some human HIV-2 isolates in baboons and in macaques was shown to "heat up" the virus and result in depletion of CD4+ T-cells, a hallmark of AIDS in humans[5-7]. Subsequently, chimeric SHIV viruses bearing HIV envelope genes in a backbone of the SIV genome have been developed[8]; these have been similarly passaged in vivo to achieve high levels of replication and reproducible CD4+ T-cell decline and pathogenesis[9-11]. The ability to recapitulate Koch's postulate with viral mutants has allowed the unequivocal identification of genes that are key for pathogenesis, routes of infection, and targets for drugs and therapies. Using these chimeric SHIVs, several groups have shown that human HIV Env-directed monoclonal antibodies, capable of blocking infection in rodent models[12], were also effective in primates[13-15].

Several excellent reviews of progress in HIV pathogenesis, therapies, and vaccine development, have been written in recent years that point to the use of nonhuman primate models to evaluate concepts and types of compounds[16,17] and vaccines[18-20]. By necessity, animal models can only be validated after successful trials in humans, and correlates of protective immunity may then be identified. The recently completed phase III trials, testing a recombinant gp120 subunit in humans, failed to achieve the desired protective threshold[21]. The HIV Vaccine Enterprise, with major funding from the Bill and Melinda Gates Foundation, has the goal of mounting a concerted effort to develop and test, in parallel, multiple vaccine candidates in humans[22]. The HIV vaccine field faces years, perhaps decades, of clinical evaluation of vaccine candidates. If it were possible to utilize even partially validated nonhuman primate models as part of the screening efforts, then this timeline might be significantly reduced. The purpose of this article is to review the data from nonhuman primate models that have contributed to our understanding of lentivirus infection, pathogenesis, and antiviral immunity, and to critically evaluate how well these models have predicted outcomes for therapies and vaccines in humans.

Current models: pathogenesis and immunology

Animal models have been utilized as tools for understanding elements of infection and pathogenesis for many infectious diseases. Despite concerted efforts, there is as yet no reproducible HIV-1 infection and pathogenesis model other than the chimpanzee[4,23]. The discovery that primate lentivirus infection leads to AIDS-like disease in macaques has allowed the development of models for key aspects of HIV-1 infection in humans. Specific combinations of lentiviruses in different hosts have led to a number of observations that have confirmed or informed HIV-1 infection of humans. Using these models, certain types of studies can be performed that would be risky or unethical to pursue in human clinical studies. A summary of the major nonhuman primate lentivirus infection models is shown in table 1, noting the nonhuman primate common name, the viruses tested, and the concepts elucidated by these models.

From our 21st century perspective, we can see that the models that result in pathogenesis represent infection in non-natural hosts, where the virus is by definition poorly adapted. One of the first models to be utilized was the infection of chimpanzees *(Pan troglodytes)* with HIV-1, using lab-adapted viruses that were the only ones available at the time: HIV-IIIB/LAI and HIV-SF2. This model was useful in recapitulating the infection process, route of infection, and antiviral immunity established. It was only after more than 10 years of study that disease was observed[4]. Given the knowledge that HIV arose from chimpanzees[24], it is less surprising that the human-adapted HIV-1 strains were not very pathogenic when reintroduced into the chimpanzee. For comparison, we need look only at the African simian lentiviruses in their native hosts. SIVsm infection of sooty mangabeys[25], much as SIVagm infection in African green monkeys[26], shows high replication without pathogenesis, evidence of a virus that is well adapted to the host. HIV-1 originally looked promising in the pigtailed macaque[27], but viral replication was not sustained and pathogenesis did not ensue.

Table 1. Pathogenesis and immunity in nonhuman primate lentivirus models

Natural host	Virus	Concepts elucidated (reference)
Sooty mangabey	SIVsm	– Significant viral replication in natural host[91,92] – Lack of pathogenesis due to adaptation or lack of immune activation[25]
African green monkey	SIVagm	– Significant viral replication[93,94] – Lack of pathogenesis due to adaptation[26]
Experimental host	**Virus**	**Concepts elucidated (reference)**
Chimpanzee	HIV-1	– Time to disease similar to humans[4,95,96] – Superinfection observed by multiple HIV-1 clones[97] – Infection by mucosal and intravenous routes[98] – Immunity: T-cell and B-cell immunity[23,99-101]
Pig-tailed macaque	HIV-1	– No sustained replication and no pathogenesis[102,103]
Baboon	HIV-2	– Relatively low-level replication with no sustained disease[5,28,104]
Macaque species	SIVmac, SIVmne, SIVsm	– Progression to disease typically accompanied by loss of CD4+ T-cells[105] – Replication dependent upon virus isolate or clone[3] – Time to disease predicted by plasma virus load[32,33] – Roles of individual genes in infection, pathogenesis in vivo[106,107] – Breakthrough SIV or SHIV after sustained control[108,109] – Mucosal transmission and fate of infecting virus[110-112] – 100-fold more virus required for mucosal vs. intravenous infection[113,114] – Tissue tropism of certain viruses and clones[115] – Coreceptor studies[116-118] – Rapid disease progression in newborns[119] – Viral diversification from clonal infection[120,121] – Escape from CTL[122,123] – Escape from NAb[123-125] – Removal of CD8 cells results in viral rebound[35]; B-cells also important[37]
Macaque species	HIV-2, SHIV (X4)	– Rapid, irreversible CD4+ T-cell decline after multiple passages in vivo[7,126,127]
Macaque species	SHIV (R5)	– Variable set-points similar to SIV[11] – No rapid CD4+ T-cell decline – Vaginal infection

The next step toward finding a host for human viruses was to test HIV-2 in baboons and macaques, which was done with varying degrees of success. Disease was seen in the baboon model with HIV-2-UC 2[5,28], and an animal-passaged HIV-2-EHO replicated to very high levels and caused reproducible loss of CD4+ T-cell in pigtailed macaques[6]. The mechanism of rapid CD4+ T-cell loss is not well understood.

Most of the progress in studying pathogenesis and immunity has arisen from the study of African SIV in the Asian macaques: rhesus *(Macaca mulatta)*, pigtailed *(M. nemestrina)*, and crab-eating macaques *(M. fascicularis)*. There are two major phylogenetic groups, the SIVmac and SIVmne viruses, and the SIVsm viruses, which are closest to HIV-2 in sequence homology[29]. In these models, disease is accompanied by loss of CD4+ T-cells and death is usually, though not always, dependent upon acquisition of an opportunistic infection. SIV infection of macaques proved that pathogenicity was dependent upon the virus, whether clonal or non-cloned viral isolate, and upon the host[30]. The role of individual genes in pathogenesis could be directly tested, leading to a better understanding of regulatory genes such as *nef*[31]. A major step forward in validating nonhuman primate models was the discovery that plasma viral load predicts time to disease[32,33], similar to the finding that plasma viral loads are the key variable for disease progression in HIV-infected patients[34]. This correlate has allowed the evaluation of therapies and vaccines that are unable to provide "sterilizing immunity", but do affect the set-point of viral load. The relative importance of CD8+ T-cells in controlling early acute infection was directly demonstrated by depletion in vivo[35,36], and subsequently the role of neutralizing antibodies was also explored by B-cell depletion[37]. Neutralizing antibodies were shown to directly reduce the in vivo infectivity of HIV-1 in macaques, using IgG from an HIV-infected

chimpanzee (HIVIG)[38]. The development of chimeric SHIV clones bearing HIV *env* genes in the SIV backbone has allowed the testing of vaccines and therapies that are directed at the Env protein. One of the pathogenic SHIV models (SHIV-89.6P) also shows the rapid CD4+ T-cell depletion seen with macaque-passaged HIV-2-287[39]. These studies, and other similar studies with therapies and vaccines described below, underscore the power of the nonhuman primate models in understanding key immune responses in vivo.

Successes with antivirals and immune-based therapies

Antiretroviral drugs have been tested to a limited degree in nonhuman primates, and many of these studies followed FDA approval of compounds for human use. Conservation of reverse transcriptase (RT)[40] meant that RT inhibitors could be tested using SIV. Monotherapy with zidovudine (azidothymidine, or AZT) was only poorly effective in controlling acute SIV infection, and this outcome was interpreted as a weakness of the primate models[41]. Viewed in hindsight, and in comparison with more effective drugs such as protease inhibitors or with cocktails in acute infection, clinical experience with AZT has been similarly disappointing. However, there are three key discoveries in therapeutics that stemmed from successes in nonhuman primate models. It was the successful testing of (R)-9-(2-phosphonylmethoxypropyl) adenine (PMPA) by Tsai, et al.[42] that led to the development of this drug for humans, in contrast to most other antiretrovirals, which were developed on the basis of in vitro testing prior to phase I trials in humans.

The second advance was immediate postexposure prophylaxis (PEP) with stavudine (D4T) in the HIV-2-287 model. Prior to this point, there was epidemiological evidence that PEP in humans using AZT could prevent infection[43]. The macaque study showed that short-course prophylaxis at very high doses, followed by cessation of therapy, was effective in controlling viral load and preventing CD4+ T-cell decline in five out of six treated animals for more than a year after withdrawal of treatment[6]. Control of viremia and prevention of CD4 declines correlated with seroconversion, soluble CD8-produced factors, and Class I-associated control. These results demonstrate that early antiviral intervention, even of a limited duration, may constitute an important strategy against lentiviral-induced disease if antiviral immunity is present. A number of additional studies have explored the limits of very early and interrupted treatment in the SIV model[44,45] – studies that have been more difficult to perform in humans[46]. In both the human and the macaque studies, early control of viremia is important, and in cases where infection is established, host immunity is necessary for viral containment in the absence of drug[47-49].

A third advance has been in defining the potency and role of neutralizing antibodies in preventing and limiting infection. Animal models have allowed the testing of polyclonal and monoclonal preparations, both as preexposure and postexposure therapies (Table 2), as summarized in a recent review[17]. Originally these experiments were performed with human polyclonal HIVIG[50] or V3-region-specific monoclonal antibodies[51] in HIV-1-infected chimpanzees or macaques, to demonstrate sterilizing immunity. With the advent of SHIV viruses that not only replicate, but also cause disease in macaques, it has been possible to study the role of human monoclonal antibodies and polyclonal preparations as PEP and therapy. These studies demonstrated that complex neutralizing antibodies can limit the infectivity of HIV in vivo[38]. PEP therapy with polyclonal SIVIG at a high dose can ameliorate SIV infection and delay disease[52]. Parameters such as timing[53,54], potency of antibody combinations[55] and routes of challenge[14,15], and dose[56] can be explored without risking human lives. These advances have led to the testing of HIVIG[57,58] and planned testing of monoclonal antibodies as therapeutics for mother-to-child transmission in humans[59].

Vaccine protection and immunity

Given some of the useful information derived from nonhuman primate models in the therapeutic area, it is at least theoretically possible that one or more of these models may inform vaccine design. Two types of readouts are used in nonhuman primate work: vaccine-elicited immune responses and protection following viral challenge. As noted in table 1, the quality and magnitude of antiviral immune responses to HIV, SHIV and SIV infection in the non-adapted host have many commonalities. In the absence of proven correlates, an indication of the congruence of data between humans and nonhuman primates is the direct comparison of products in the two systems, and the use of validated assays to compare the immune responses. For a system to be useful as a screen, this minimal criterion must be met. Considerable efforts have been applied to the development of standardized immunological assays that can be used for both human and macaque

Table 2. Examples of therapeutic approaches tested in nonhuman primate models

Type of study	Host	Virus	Outcome or concept (reference)
D4T treatment	Pigtailed macaque	HIV-2-287	– Immediate prophylaxis controls infection[6]
Antiretrovirals	Pigtailed macaque	SIVmne	– Postexposure chemoprophylaxis with PMPA prevents infection[42,128,129]; AZT is less effective[41] – Effects on chronic infection are poor[130,131]
Antiretrovirals	Rhesus macaque	SIV	– Transient treatment during acute infection improves outcome[45]
PMPA*, tenofovir in newborns	Rhesus macaque	SIVmac 251 SHIV-SF33	– Infection in newborns is blocked by drug treatment[132-135]
CCR5 inhibitor	Rhesus macaque	SIVmac; SHIV-89.6P; SHIV-SF162P4	– CCR5 inhibitor reduces viremia in high-replication models that use CCR5 and reduces viremia in SF162P4 infection[136]
Preexposure passive IgG	Chimpanzee	HIV-1	– HIVIG and MAbs directed to V3 can protect against HIV-IIIB (lab-adapted) challenge[50,51]
Preexposure passive IgG	Rhesus macaque	SIV, SHIV-DH12	– IgG with neutralizing activity can block infection at high doses[137,138]
Postexposure passive IgG	Rhesus macaque	SIVsmE660, SHIV-KU2 and SHIV-DH12	– Very high levels of NAb are needed to slow infection and affect disease[52,53,139,140]
Preexposure passive mAb	Rhesus macaque	SHIV89.6P	– Combinations of mAbs effective in blocking oral or vaginal infection[14,114,141-143]
Postexposure passive mAb	Rhesus macaque infants	SHIV	– Cocktails of monoclonals can block infection if given within hours of exposure[54]

*9-[2-(phosphonomethoxy)propyl]adenine.

samples. In both systems, cellular immunity is determined by antigen (peptide)-specific cytokine secretion by ELISPOT and neutralizing antibodies against panels of HIV-1 patient isolates using standard cell line-based assays. Although these assays are not yet to the stage of good laboratory practice (GLP) validation, they are close to this threshold.

Some of the key advances learned from vaccine studies in nonhuman primate models are summarized in table 3. These include:

– the relative efficacy of different types of vaccines (subunits, live recombinant viral vectors, prime-boost, and live-attenuated);

– the merits of including individual and multiple components in the vaccine (e.g. Env only, multiple antigens, regulatory genes or proteins);

– the inclusion of cytokines as adjuvants; and

– the effects of different routes of challenge.

Will these lessons translate into appropriate choices for HIV vaccines in humans? A review of the qualitative

Table 3. Key advances in vaccine development from primate models

Concept	References
– Subunit Env gp120 vaccines provide sterilizing protection only with low-replication models	61-63
– Subunit Env gp160 and gp140 vaccines do not provide sterilizing immunity against SIV	144
– Prime-boost vaccines provide sterilizing protection with low- and moderate- but not high-replication challenges	72,73,108,145
– DNA vaccines can serve as prime or boost with vaccinia virus	90
– Parenteral vaccines protect from mucosal challenge	146
– Protection with live-attenuated vaccines is dependent upon viral replication	147,148
– Cytokine (interleukin-2) as adjuvant improves DNA and recombinant vaccinia virus vaccine immunity and efficacy	146,149
– Protection from disease is improved by inclusion of both Gag and Env antigens	144,150
– Attenuated viruses that were safe in adult, juvenile macaques cause disease in newborns	151
– Adoptive transfer of SIV-naive autologous CD4+ T-cells to macaques chronically infected with SIV is sufficient to induce long-term nonprogressor status	152

Table 4. Comparison of immune responses in vaccinated humans and nonhuman primates

Vaccines in testing	Protection in nonhuman primates	Nonhuman primate immunity (reference)	Human responses in phase I trials (reference)
Env gp120 subunit (CHO cells)	Sterilizing in chimpanzees vs. HIV-1 Limited or none vs. SIV in macaques	Low level Abs and NAbs (lab-adapted)[61,64,80]	Low level Abs and NAbs (lab-adapted)[153,154] No effect on CTL; low-level proliferation[155,156]
Env gp160 subunit (baculovirus)	No protection from SIVmac251 infection	Low-level Abs and NAbs (lab-adapted)[63]	Transient increased T-helper responses in infected patients[157,158]
Recombinant vaccinia virus expressing Env gp160	No protection in chimpanzees	Strong CTL responses[159]	Responses similar to primates but limited by prior vaccinia exposure[70]
Recombinant NYVAC *gag-pol-env* with DNA	Control of SIVmac251 infection	CD4 and CD8 responses[160]	NT
Recombinant MVA, Gag-Pol plus Env; multi-epitopes and Tat, Rev, and Nef	Attenuated viremia; SHIV-89.6P in macaques; poor protection against SIVmac239	CTL at day of challenge; post infectioncellular and humoral immunity[161,162]	NT
Canarypox *gag-pol-env* plus Env gp120 subunit	Protection from SIVmac251 disease	CD4+ and CD8+ T-cell responses[80]	Canarypox only; very weak ELISPOT responses and NAbs[153,163]
Multi-epitope CTL vaccines (peptide and lipopeptide)	None	Weak responses to Gag and Nef in majority of animals[164,165]	Weak responses in 9/12 by CTL; in 5/6 by ELISPOT[166]
Replication-incompetent adenovirus expressing Gag	Attenuated infection with SHIV challenge	Strong cell-mediated responses[87]	Significant CTL responses by ELISPOT[167]
Replication-competent adenovirus expressing Gag and Env	Protection from SIVmac251 infection and disease in macaques	Antibody and cell-mediated responses correlated with better outcome[168]	NT
Enhanced DNA vaccines; DNA/PLG microparticles	NT	Strong CMI by CTL and ELISPOT to Gag, Env[165]	Trial underway in 2004
Oligomeric Env gp140 subunits and deletion subunits	Reduction in viremia with SHIV challenge	NAbs against primary and lab-adapted HIV[169] and some heterologous primary HIV (deletion mutants)[170,171]	Trial underway in 2004

NAbs: neutralizing antibodies; VEE: Venezuelan equine encephalitis virus; MVA: modified vaccinia Ankara; NT: not tested.

and quantitative immune responses elicited by different and similar vaccines yielded a surprising degree of congruence for some assays and for many of the approaches tested to date, as summarized in table 4. The list of vaccines that have been tested in both systems is increasing, and the examples shown here are illustrative rather than comprehensive.

The earliest vaccine approaches were focused on the recombinant Env subunits gp120 and gp160. In primates, these had shown some ability to elicit neutralizing antibodies against laboratory isolates, and limited activity against primary HIV-1. Env preparations with conformational determinants preserved was more effective in generating neutralizing antibodies in baboons than denatured non-glycosylated Env, and the magnitude of responses was adjuvant-dependent, with alum being the least effective[60]. Relative to HIV-1 infection, however, the magnitude of neutralizing antibodies was at least 10-fold lower. Although there was evidence of complete protection from HIV-1 challenge in chimpanzees[61,62], these subunits did not provide sterilizing protection in macaques using the SIV-homologous gp130[63,64], but could block or limit infection by a lower-replicating SHIV[65]. The first vaccine product to be tested in humans in an FDA-approved trial was the baculovirus-produced gp160 protein. When gp120 products were tested in humans, they also elicited neutralizing antibodies restricted to laboratory isolates, at levels at least 10-fold lower than in infected humans[66]. And when tested in phase III clinical trials, gp120 failed to achieve the 30% efficacy of sterilizing protection that the trial was powered to observe[21]. Recent efforts have been directed at testing oligomeric Env proteins that can present oligomeric and conformational determinants[67].

The first FDA-approved recombinant viral vector vaccine trial tested HIVAC-1e, recombinant vaccinia virus expressing gp160 from HIV-IIIB/LAI. This system was viewed as attractive from a number of standpoints, including the expression of native Env gp160 in vivo, which allowed induction of cytotoxic T lymphocytes (CTL) as well as antibodies, and the virus infection was

self-limiting due to anti-vaccinia clearance. The relatively weak immunity raised by HIVAC-1e in chimpanzees[68,69], and ultimately in humans[70,71], led to the development of a strategy that now is termed "prime-boost." Originally envisioned as a method to boost humoral immunity using an orthogonal antigen delivery method, macaques primed with recombinant vaccinia virus expressing HIV Env gp160 were boosted with purified Env gp160 glycoprotein, which increased antibody responses. When challenged with SIVmne, these macaques fully resisted infection[72]. Unfortunately, more stringent SIV-challenge models failed to show sterilizing immunity[63,73]. Results in humans were similarly weak, showing some cellular responses and neutralizing antibodies against laboratory isolates[74-76].

Safety issues with vaccinia virus in humans, as well as evidence that macaques[77] and persons[70] with preexisting vaccinia immunity were poor responders, led to explorations of more attenuated poxvirus vectors[78,79], including modified vaccinia Ankara (MVA) and Avipox or canarypox vectors[80,81]. When used alone, these vectors were effective in eliciting CTL[82] and, in conjunction with protein boosting, were effective in limiting post-challenge pathogenesis[83,84]. In humans, immunity was detectable but weak[85]. Other strategies aimed at presenting specific CTL epitopes alone, or in combination as multi-epitope vaccines, have elicited weak responses, both in nonhuman primates and in humans.

Alternative recombinant adenovirus vectors, either one-round or replication competent, are also showing significant promise in macaques and in humans in generating both humoral and fairly strong cellular immunity[86,87]. Experience to date with these two types of adenovirus is shown as an example in table 4[88]. Where comparative data are available, they show similar levels of immunity elicited. DNA vaccines have the potential of generating broad responses against multiple antigens with relative ease. The first generation of these have been tested fairly extensively in macaque SHIV-challenge models, reviewed in[89], and these experiments show the value of combining two or more vaccine types[90]. The relatively weak immunity elicited by DNA vaccines in macaques and in humans suggests that better adjuvants and delivery systems are needed, and some of these are showing promise in nonhuman primates. DNA complexed inside, or on the surface of PLG microspheres, reduces the amount of DNA needed per immunization. This strategy has entered human phase I testing in conjunction with a modified oligomeric Env gp140 subunit that has shown promise in nonhuman primates in eliciting primary HIV-1 neutralizing antibodies. If these newer recombinant viral vectors, DNA delivery systems, and oligomeric protein strategies elicit improved immunity in humans, this will be additional supportive data for the predictive value of nonhuman primate testing in vaccine development.

Remaining issues

We are faced with several critical challenges in the control and prevention of HIV infection and disease. In infected humans, the virus causes extreme suffering and 100% mortality. Effective nontoxic drugs are still desperately needed for those who become infected and to more effectively prevent mother-to-child transmission. If vaccines are to protect against any of the multiple genetic variants that continue to diversify and recombine worldwide, persistent, broad cellular and humoral immunity are both needed. None of the vaccine candidates currently in testing comes close to eliciting the level of responses seen in infected individuals such as long-term nonprogressors.

The data summarized here suggest that, where beneficial effects of drugs, immune-based antiviral therapies, and vaccines, are seen in the nonhuman primate models, these may be indicative of potential success in humans. Clearly there are limitations to the use of nonhuman primate models, particularly in enzymatic drug targets that differ between SIV and HIV-1, such as with protease. Are models that cause rapid, irreversible CD4+ T-cell decline representative of HIV, with its steady slow decline over years? It is also not yet clear whether SHIVs are representative of HIV-1 in their pathogenic course. No single animal model is likely to serve as a perfect model for HIV infection of humans. Each of the models has advantages, but none can replace the knowledge gained from human clinical work. As a field, most investigators agree that we are still years away from having nontoxic drugs that will effectively control infection, or a vaccine candidate that will provide even modest protection from disease. Currently, testing in nonhuman primates is not considered to be on the critical path for drug or vaccine testing. However, there are compelling arguments for a parallel pathway of discovery and testing in nonhuman primates. Testing of orphan drugs such as PMPA proceeded in humans only after successful testing in nonhuman primates – an example of the use of positive data in the model systems to ignite enthusiasm for clinical testing. As antiretrovirals become more widely available and become the standard of care, it may be difficult to design low-cost trials to test new products;

primate testing can complement or augment these findings by the ethical testing of new components, such as monoclonals, for efficacy in the absence of the current standard-of-care.

Should nonhuman primates be on the critical path for vaccine testing? The published experimental data for vaccines show that the quality and magnitude of immune responses elicited in macaques is in many cases similar to that seen in humans, and thus may be at least relatively predictive of responses in humans. It would be risky to extrapolate vaccine success based solely on results of challenge studies in nonhuman primates. However, given the surprising congruence of the immunogenicity data, it can be argued that the vaccine successes we have seen in the nonhuman primate models may portend the ultimate success for human vaccines that can blunt infection, if not prevent it. Vaccines with strong safety profiles that are successful in protection from disease or infection in more than one nonhuman virus-host model should be considered first for testing in humans, as they may ultimately lead to successful HIV vaccines. Advances in science are derived both from individual breakthroughs as well as the combined wisdom of multiple concordant studies that define limits and show reproducibility. It will take new ideas as well as the continued collaborative efforts of the entire field to control this difficult and challenging pathogen. The nonhuman primate models for AIDS remain a critical tool in this endeavor.

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