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Review

Evaluation of antiretrovirals in animal models of HIV infection

Koen K.A. Van Rompay*

California National Primate Research Center, University of California, Davis, CA 95616, USA

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ABSTRACT

Animal models of HIV infection have played an important role in the development of antiretroviral drugs. Although each animal model has its limitations and never completely mimics HIV infection of humans, a carefully designed study allows experimental approaches that are not feasible in humans, but that can help to better understand disease pathogenesis and to provide proof-of-concept of novel intervention strategies. While rodent and feline models are useful for initial screening, further testing is best done in non-human primate models, such as simian immunodeficiency virus (SIV) infection of macaques, because they share more similarities with HIV infection of humans. In the early years of the HIV pandemic, non-human primate models played a relatively minor role in the antiretroviral drug development process. Since then, a better understanding of the disease and the development of better drugs and assays to monitor antiviral efficacy have increased the usefulness of the animal models. In particular, non-human primate models have provided proof-of-concept for (i) the benefits of chemoprophylaxis and early treatment, (ii) the preclinical efficacy of novel drugs such as tenofovir, (iii) the virulence and clinical significance of drug-resistant viral mutants, and (iv) the role of antiviral immune responses during drug therapy. Ongoing comparison of results obtained in animal models with those observed in human studies will further validate and improve these animal models so they can continue to help advance our scientific knowledge and to guide clinical trials.

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Contents

1. Introduction

During the past decade, the growing arsenal of antiretroviral drugs that target various steps in the viral replication cycle has led to major improvement in the clinical management of HIV-infected people (Sabin et al., 2005). Despite the considerable success of this

* Tel.: +1 530 752 5281; fax: +1 530 754 4411.
E-mail address: kkvanrompay@ucdavis.edu.

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so-called "highly active antiretroviral therapy" (HAART), there is no reason for complacency, as long-term administration of many drugs is associated with problems of cost, toxicity, compliance, or drug resistance. The ideal drug regimen would be one that induces strong and persistent suppression of virus replication, gives prolonged immunological and clinical benefits without toxicity, can be administered at infrequent dosage intervals, is affordable and easy to store, and can thus benefit the greatest number of HIV-infected people, including those in developing countries. Accordingly, novel compounds are continuously being developed (De Clercq, 2004, 2007). In addition, the quest continues to find strategies to boost immunological control to reduce the need for antiretroviral drugs, or even more ambitiously, to purge out viral reservoirs with the ultimate aim of curing HIV infection so that antiretroviral drug treatment can be withdrawn permanently.

The pipeline that new drug candidates need to cross between the first demonstration of *in vitro* antiviral effects and approval for clinical use is tedious, time-consuming and very expensive. Most compounds that look promising *in vitro* are not developed further due to lack of resources, or they show unfavorable pharmacokinetics, toxicity or insufficient antiviral efficacy *in vivo* (Demeter et al., 1998). The correlation between the *in vitro* inhibitory concentrations of antiviral compounds and their relative *in vivo* efficacy in HIV-infected persons is rather weak. Although regulatory agencies request safety/toxicity data from animal models, they do not require efficacy data from animal models before allowing a novel antiretroviral drug to enter clinical trials. Accordingly an opportunity to discard ineffective drugs early in the development process (and thus save much time and resources) is lost whenever an available appropriate animal model of efficacy is bypassed. In other words, antiretroviral drug development can be accelerated by efficient and predictive animal models capable of screening and selecting the best compounds at each decision point (Fig. 1).

The desired outcome of drug treatment – sustained suppression of virus replication and improvement in the overall health – is determined by many complex interactions between the virus, the host and the antiviral drugs, most of which cannot be mimicked appropriately by *in vitro* studies or mathematical models but which can be studied in animal models (Fig. 2). Besides being a test system to screen novel drugs or drug regimens, animal models can also be used to test hypotheses that are logistically or ethically difficult to explore in humans. By manipulating the input variables (e.g., the age of the animals; the virulence and drug susceptibility of the virus inoculum; the composition, timing and duration of the drug regimen), investigators can design studies to unravel and address specific questions on the many virus–host–drug interactions (Haigwood et al., 2004). As discussed further in this review, examples of this are studies focused on evaluating chemoprophylaxis, the *in vivo* virulence and clinical implications of drug-resistant viral mutants, and the role of antiviral immune responses on antiviral drug efficacy. Animal models will most likely also play a crucial role in the development of anti-latency therapies that have the ultimate aim of purging out the viral reservoirs and curing infection (Richman et al., 2009).

2. Overview of the different animal models for HIV disease and control

The ideal animal model would be one that involves HIV infection of a relevant small animal and that completely models HIV transmission, pathogenesis, and the effects of antiviral strategies. However, because such animal model does not exist yet, it is important to acknowledge that each of the currently available animal models has its limitations. Accordingly, ongoing comparison of results obtained in animal models with those observed in human studies is needed for validation of the various models and for further improvement.

Several lentiviruses are associated with slowly progressive degenerative diseases of certain farm animals, including maedivisa virus (sheep), caprine arthritis encephalitis virus (goats) and equine infectious anemia (horses). However, a major difference with HIV infection of humans is that these lentiviruses infect only the macrophages/monocytes and not CD4+ T helper cells and, therefore, do not cause immunosuppression in their hosts; this limits their relevance as a model for HIV immunopathogenesis (reviewed in Gardner (2006)). Accordingly, the animal models that have been more useful to test anti-HIV drugs are rodents, cats and non-human primates.

2.1. Rodent models

Advantages of rodent models are that they are relative inexpensive, they can be housed in large numbers in a relatively small facility and reproduce quickly. Although murine AIDS models with distantly related oncoviruses (e.g., murine leukemia virus) have been used in some early drug studies and have demonstrated efficacy of zidovudine and acyclic nucleoside phosphonates (Balzarini et al., 1997b; Ruprecht et al., 1986), an obstacle has been that native

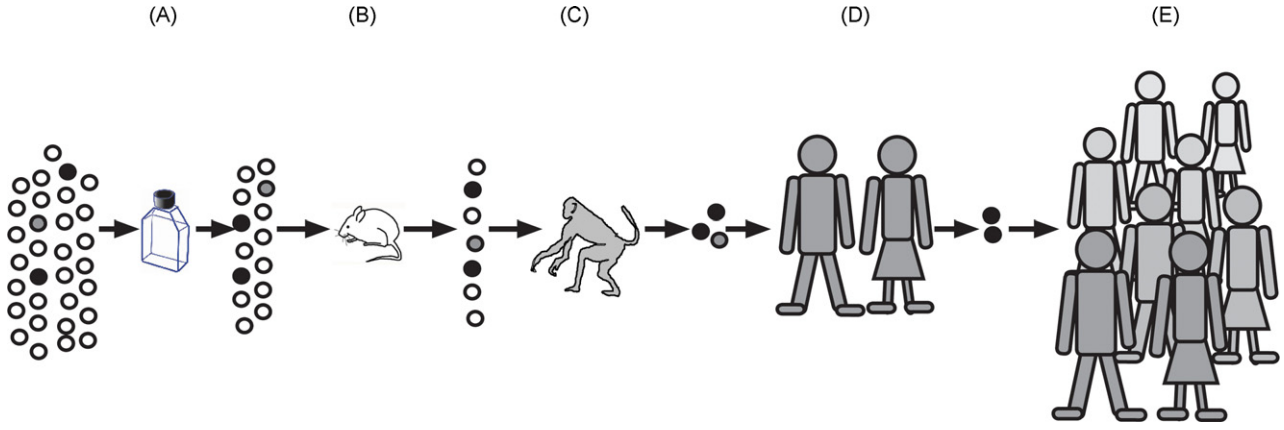

Fig. 1. Role of animal models in antiviral drug development. Antiviral drug testing involves multiple levels of screening of efficacy and toxicity. High-throughput systems with relatively low cost, such as *in vitro* testing (A) should be used as an initial screening method, before proceeding to animal testing. Although rodent and feline models (B) are useful for initial *in vivo* screening, non-human primate models (C) resemble more closely HIV infection of humans and are therefore recommended for a final pre-clinical evaluation step. Because human trials are very expensive and time-consuming, such screening process can prevent that precious time and resources are wasted on testing non-effective or toxic drugs (open circles) so that effective drugs (black circles) can be guided more rapidly towards human clinical trials (D) for subsequent clinical approval and widespread use (E).

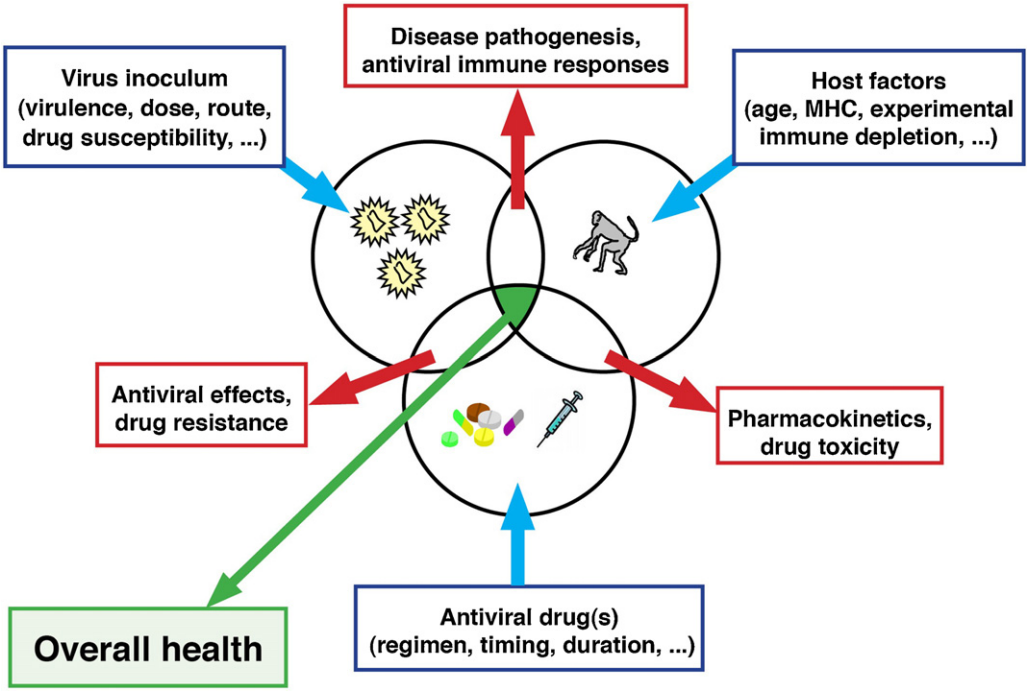

Fig. 2. Variables and interactions involved in determining the outcome of antiviral drug treatment: The ultimate goal of drug treatment is to improve the overall health of the host and indefinitely delay disease progression. This outcome is determined by many complex interactions between the virus, the host and the antiviral drugs, most of which cannot be mimicked appropriately by *in vitro* studies. Animal models are very valuable because they allow us to control and manipulate many input variables through experimental approaches that are not feasible or ethical in humans (such as experimental inoculation of animals with drug-resistant mutants, or *in vivo* depletion of certain immune cells, or drug monotherapy) but that are often the most direct way to unravel specific questions of antiviral drug treatment.

mice and rats cannot be infected with HIV. Accordingly, attempts have been made to render rodents more permissive to HIV infection. Rats that were engineered to express human CD4, CCR5 and cycline T1 support some HIV expression, but additional obstacles remain to improve virus replication and dissemination (Goffinet et al., 2007; Michel et al., 2009). Other transgenic rodent models in which viral genes have been incorporated have been used to model select pathogenic manifestations of chronic HIV-1 diseases (reviewed in Anderson et al. (2006)).

Another group of murine models that have been used for antiretroviral drug studies are the SCID/hu mouse models, in which severe combined immunodeficient (SCID) mice receive human transplants of thymus, fetal liver, or PBMC (Borkow, 2005; Stoddart and Reyes, 2006). Although the immune cells in the implanted immunocompetent human tissues allow for reconstitution of the immune system of the SCID mice, most of these models have a limited repertoire of human cell types and limited distribution of these cells outside of the implant. In these SCID/hu models, early pre- and post-exposure prophylaxis with drugs such as zidovudine (AZT), saquinavir or ritonavir suppressed viremia but did not prevent infection (McCune et al., 1990; Pettoello-Mantovani et al., 1997, 1998; Shih et al., 1991); these results were likely due to the weak-to-moderate potency of these drugs when used as single agents against a sometimes high-dose viral inoculum. In contrast, one month of combination treatment (zidovudine, lamivudine and ritonavir) started early after virus inoculation was able to prevent HIV infection (Pettoello-Mantovani et al., 1998).

A recently developed model, the humanized bone marrow/liver/thymus or "BLT" mouse, results in a more complete systemic reconstitution of all major human hematopoietic lineages, including T, B, monocyte/macrophage, dendritic and natural killer cells (Denton et al., 2008). This model, in which the female reproductive tract is also populated by HIV-susceptible human CD4+ T cells, has been used to demonstrate the prophylactic efficacy of systemic administration of an emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) regimen against vaginal HIV infection, similarly to what was previously reported in non-human primate models (see further). While these murine models may be useful as an initial *in vivo* screening method for antiviral strategies (Fig. 1), their disadvantages include that they remain technically challenging and time-consuming, and that they do not recapitulate the full spectrum of immunopathological events that occur during HIV infection; in addition, their physiology (including reproductive tract, drug pharmacokinetics) remains quite different from that of humans.

2.2. Feline models

Domestic cats infected with feline immunodeficiency virus (FIV) develop an AIDS-like terminal syndrome after a long incubation time of ~7–9 years (reviewed in Sparger (2006)). Benefits of the FIV model include its relatively low expense, and that cats also experience a CD4+ T lymphocyte depletion, the hallmark of HIV/AIDS. The exploration of this model to test antiretroviral drugs (reviewed in Bendinelli et al. (1995), Elder et al. (1998), Hartmann and Stengel (2006)) was encouraged by the many similarities between FIV and HIV-1 RT in sequence, function and *in vitro* sensitivity to nucleoside RT inhibitors (NRTI) inhibitors such as zidovudine, lamivudine (3TC), didanosine (ddI), and the nucleotide RT inhibitor adefovir (PMEA) (Cronn et al., 1992; Hartmann et al., 1992, 1998; North et al., 1989, 1990; Vahlenkamp et al., 1995). In contrast, most non-nucleoside RT inhibitors (NNRTI) and protease inhibitors are not active against FIV (Auwerx et al., 2004). The number of compounds that has been studied *in vivo* is more limited. While zidovudine alone did not prevent infection but reduced initial viremia, a zidovudine and lamivudine regimen had more prophylactic efficacy but was also not effective (and sometimes toxic) in cats with chronic FIV infection (Arai et al., 2002; Hayes et al., 1993, 1995;

Smyth et al., 1994). Acyclic nucleoside phosphonate analogs, such as (*S*)-9-(3-fluoro-2-phosphonylmethoxypropyl)adenine (FPMPA), 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and 9-[(2*R*,5*R*-2,5-dihydro-5-phosphonomethoxy)-2-furanyl]adenine (D4API) were more effective in preventing FIV infection or treating chronically infected cats (Egberink et al., 1990; Hartmann et al., 1992, 1997, 1998; Hayes et al., 1993, 1995). Although the high-dose regimens of some of these compounds led to toxicity, these studies were important because the high antiviral efficacy seen with the acyclic nucleoside analogs in the FIV model set the stage to explore this class of compounds subsequently in non-human primates (see further).

The FIV model has also been used to study emergence of nucleoside analog-resistant mutants *in vitro* (Gobert et al., 1994; Medlin et al., 1996; Zhu et al., 1996). FIV was the first lentivirus for which a zidovudine-resistant mutant was described to emerge during *in vitro* passage (Remington et al., 1991).

Despite the usefulness of the FIV model as an early screening method (Fig. 1), several factors have made it less popular than the non-human primate models, including the observations that FIV does not use the CD4 receptor, and infects not only CD4+ T lymphocytes but also CD8+ T lymphocytes and B lymphocytes (Dean et al., 1996). In addition, the long incubation period is a disadvantage to screen the efficacy of drugs in experimentally infected cats.

2.3. Non-human primate models

While the rodent and feline models are appropriate for initial screening, further testing is done best in non-human primate models that resemble more closely HIV infection of humans and therefore allow a more reliable extrapolation of results of antiviral strategies. Non-human primates are phylogenetically the closest to humans, and have similar immunology and physiology (including drug metabolism, placentation, fetal and infant development). A common theme among the different non-human primate models is that disease is most consistently seen during infection of non-natural hosts.

Although chimpanzees can be infected with HIV-1, this animal model is not practical due to the low availability, high price, ethical issues and the observation that disease develops rarely (Nath et al., 2000; Novembre et al., 1997, 2001). HIV-1 infection could be induced in young pigtailed macaques, but virus replication was not sustained and no disease was observed (Frumkin et al., 1993). HIV-2 infection models have been developed with hamadryas baboons (*Papio hamadryas*) and several macaque species; depending on the HIV-2 isolates, the outcome varied from an AIDS-like disease with CD4+ T cell decline to no disease (Livartowski et al., 1992; Locher et al., 2001; Putkonen et al., 1989).

Many non-human primate species in Africa are naturally infected with simian immunodeficiency virus (SIV) strains, such as African green monkeys (SIVagm) and sooty mangabeys (SIVsm). These viruses are closely related to HIV-2. Despite persistent high-level virus replication, these natural hosts do rarely develop disease, possibly because infection is associated with little immune activation (Pandrea et al., 2009; Silvestri et al., 2003, 2005). In contrast, as a coincidental result of co-housing different primate species (Gardner, 2003), it was discovered in the mid 1980s that SIV infection of non-natural hosts such as macaques results in a disease which resembles human AIDS in many aspects. Although limitations of the SIV-macaque models remain their high cost, relative availability, and the subtle differences between HIV and SIV (i.e., SIV resembles more HIV-2 than HIV-1), the many similarities in virus, host and disease pathogenesis have made them currently the premier animal model in HIV research. For this reason, they are the focus of the remainder of this review.

3. Main characteristics of the SIV-macaque models

The most commonly used species are rhesus macaques (*Macaca mulatta*), cynomolgus macaques (*Macaca fascicularis*), and pigtailed macaques (*Macaca nemestrina*). The SIV isolates generally belong to a few groups, in particular SIVmac, SIVsm and SIVmne. To mimic the common routes of HIV transmission in humans, models have been developed for different routes of virus inoculation (i.e., intravenous, intravaginal, intrarectal, or oral) (Baba et al., 1994; Miller et al., 1989; Pauza et al., 1993).

Infection of macaques with virulent SIV isolates results, after an asymptomatic period, in a disease which resembles human AIDS in many aspects, including cell tropism, generalized immune activation, CD4+ T cell depletion (especially from mucosal sites), opportunistic infections, weight loss and wasting (Daniel et al., 1985; Veazey et al., 1998). The same clinical and laboratory markers (including viral RNA levels in plasma and CD4+ T lymphocyte counts) can be used to monitor and predict disease progression (Haigwood et al., 2004; Lifson et al., 1997; Watson et al., 1997b).

It is important to remember that SIV infection of macaques is not necessarily fatal, because based on the selection of the host and the SIV isolate or clone, a broad spectrum of clinical outcomes is observed. This spectrum spans from persistently high viremia and rapid disease progression induced by highly virulent isolates, over intermediate viremia and slower disease progression with less virulent isolates, to transient or low-level viremia and no disease, even in newborn macaques, with avirulent isolates such as SIVmac1A11 (Marthas et al., 1995). This spectrum of infection outcomes makes this model also suitable to assess how genetic changes in the virus (e.g., drug resistance mutations) affect viral virulence.

When juvenile or adult macaques are infected with virulent SIV isolates such as uncloned SIVmac251, most animals have persistently high viremia and develop clinical disease within 6–24 months. Similarly to observations in HIV-infected babies, newborn macaques inoculated with such virulent SIV isolates develop disease faster (i.e., within 2–3 months) (Bohm et al., 1993; Marthas et al., 1995). This accelerated disease course relative to humans can be used as an advantage for antiviral drug studies, because the impact of antiviral strategies on disease progression can be evaluated in a shorter time. Although highly virulent models may reduce our ability to detect the efficacy of compounds with moderate or weak activity, the demonstration of antiviral effects in such model suggests potency that merits consideration as a lead candidate for further clinical development.

4. Historical development of the SIV-macaque model for antiviral drug studies

During the first decade of the HIV pandemic, the role of non-human primate models in pre-clinical development of anti-HIV drugs was rather limited, as many of the macaque studies were performed after clinical approval of the compounds for human use. Most of the initial drug studies were not very successful in demonstrating efficacy in SIV-infected animals, which at that time was sometimes interpreted as a sign of weakness of the primate models (see review Van Rompay (2005)). Viewed in hindsight, however, several factors are responsible for these observations. Most drugs that were available at that time had complicated dosage regimens (i.e., a short half-life, necessitating frequent administration), or had problems of toxicity, which limited long-term administration. In addition, as discussed further, an antiretroviral drug is only able to showcase its full *in vivo* antiviral potency if assisted by antiviral immune responses. Untreated macaques that are infected with virulent isolates such as SIVmac251 have higher viremia, lower cell-mediated antiviral immune responses and a more rapid disease course than HIV-infected humans (McChesney et al., 1998). As the

drugs available at that time were not very potent in suppressing viremia in HIV-infected humans, it is now no surprise that they fared more poorly in macaques infected with virulent SIV isolates. In addition, the measurement of p27 antigen or infectious virus in plasma or PBMC was not sensitive enough to detect any minor changes in viral replication, particularly during the asymptomatic stage of SIV infection, and highly sensitive assays to accurately quantitate viral RNA levels in plasma were not available. Thus, the primary measures of drug efficacy consisted of infection status (infected or uninfected) in prophylaxis studies, and the rate of disease progression and CD4+ T cell counts for infected animals. Because disease progression is variable especially in juvenile and adult macaques, the relatively small animal numbers made it difficult to determine whether a small difference in clinical outcome was due to host factors or to the effect of the drug regimen (Van Rompay et al., 1995).

Fortunately, many of these problems have been solved since the mid-1990s. Quantitative and sensitive assays to monitor virus replication in SIV-infected macaques have been developed and allow monitoring the effects of antiviral drugs during the asymptomatic stage of infection (Leutenegger et al., 2001; Lifson et al., 1997). The availability of more potent and less toxic drugs (such as tenofovir (PMPA)) allowed studies that demonstrated the proof-of-concept of drug efficacy in this animal model and the feasibility of long-term drug studies (Van Rompay et al., 2008). The development of a pediatric SIV model has also been very useful, as the more uniformly rapid disease course (~3–4 months) observed in untreated infant macaques infected with virulent SIV isolates permits also evaluation of the impact of the drugs on disease-free survival in a relatively short time and with fewer animals than if juvenile animals would be used (Van Rompay et al., 1995, 1996, 2004c). Infant macaques are also easier to handle for drug administration, and require less drug, which is useful especially for novel compounds that are initially very expensive to produce in test quantities.

Preclinical testing of antiretroviral drugs in macaques is most relevant for compounds for which the susceptibility of SIV naturally resembles, or can be engineered to resemble that of HIV-1. Because the polymerase region of these SIV isolates has about 60% and 85% amino acid homology to HIV-1 and HIV-2, respectively, SIV is susceptible to many of the same NRTI (e.g., zidovudine), nucleotide RT inhibitors (tenofovir, adefovir), integrase and protease inhibitors (Black et al., 1993; Desrosiers, 1990; Giuffre et al., 2003; Hazuda et al., 2004; Sager et al., 1990; Witvrouw et al., 2004). Because most SIV isolates use the CCR5 chemokine coreceptor, they are also susceptible to some CCR5-targeting entry inhibitors (Veazey et al., 2003). However, other compounds including nonnucleoside RT inhibitors (NNRTI) such as nevirapine and efavirenz, are active only against HIV-1 and not against HIV-2 or SIV (De Clercq, 1992). Accordingly, the construction of infectious SIV/HIV-1 chimeric viruses, in which the reverse transcriptase (RT) gene of SIV was replaced by its counterpart of HIV-1 (so called RT-SHIV's) has been useful to evaluate NNRTI in primate models (Ambrose et al., 2004; Balzarini et al., 1997a; Hofman et al., 2004; Mori et al., 2000; Uberla et al., 1995; Zuber et al., 2001). Similarly, env-SHIV's that contain the envelope region of HIV-1 have been constructed and are susceptible to fusion inhibitors such as enfuvirtide (Witvrouw et al., 2004). Many env-SHIV's are attenuated but some pathogenic isolates have been derived through serial passage. Most pathogenic env-SHIVs such as SHIV-89.6P, while useful to address specific questions, have the limitation that their disease pathogenesis (including CXCR4 coreceptor usage and very rapid CD4+ cell depletion) differs from the typical course seen with HIV and SIV infection and may therefore not be the best model to predict drug or vaccine efficacy in humans (Feinberg and Moore, 2002; Lifson and Martin, 2002; Nishimura et al., 2004; Watkins et al., 2008). The few currently available CCR5-using env-SHIV's (such as SHIV-SF162P, SHIV-SF162P3 and the clade C env-SHIV-1157i) have the limitation that after the initial peak of viremia, a significant portion of untreated animals is able to suppress viremia to low or undetectable levels and do not develop disease (Harouse et al., 1999; Humbert et al., 2008; Subbarao et al., 2006). In an ongoing attempt to use a virus that resembles HIV-1 as much as possible, investigators constructed recently simian-tropic (st)HIV-1 strains that differ from HIV-1 only in the nef gene; these viruses caused persistent viremia in pigtailed macaques for several months after which viremia was controlled by the immune system (Hatziioannou et al., 2009). Accordingly, while these different env-SHIV's and stHIV-1 isolates are useful to test prophylactic or early post-infection interventions, this large variability in chronic viremia set-point and disease outcome makes them currently less practical to test the efficacy of antiviral strategies during established infection, especially when animal numbers are limited. Further development of these SHIV and stHIV-1 models may lead to a more persistent viremia.

5. Contributions of the non-human primate models to antiretroviral drug development

The validity of an animal model increases if comparison with data from human studies reveals its predictability of both negative and positive results (Haigwood, 2004). While the absence of an effective HIV vaccine has made it more difficult to validate the different SIV vaccine models (with their sometimes conflicting outcomes), the antiretroviral drug research field has been more fortunate because of the success stories in the treatment of HIV. The RT inhibitor tenofovir is a prime example of a compound that has anchored the relevance of this animal model in the pipeline of drug development: prior to its clinical development in humans, the initial reports on tenofovir demonstrated an unprecedented efficacy in different macaque models, either to prevent infection as well as to treat established SIV infection (Tsai et al., 1995a; Van Rompay et al., 1996). These animal model data turned out to be predictive of the high antiviral efficacy in HIV-infected humans. The following discussion will highlight how studies in macaque models have contributed to our knowledge on the many aspects of antiretroviral drug administration.

5.1. Pharmacokinetics and toxicity

Because of their similar physiology and metabolism, non-human primates have been useful to study the toxicity and pharmacokinetics (including oral bioavailability, tissue distribution and intracellular drug levels) of antiviral drugs; some studies investigated the effects of pregnancy and drug transfer across the placenta and into breast milk (Ha et al., 1994; Kinman et al., 2006; Lopez-Anaya et al., 1991; Odineces et al., 1996; Pereira et al., 1995; Ravasco et al., 1992; Tuntland et al., 1996; Van Rompay et al., 2005). While most studies used short-term drug administration, studies with tenofovir have also assessed the safety of prolonged daily treatment (>1–14 years), starting at birth and continuing throughout adulthood, including pregnancy (Van Rompay et al., 2004a, 2008). These studies found that prolonged daily treatment of macaques with a high dose of tenofovir resulted in a Fanconi-like syndrome (proximal renal tubular disorder). In contrast, prolonged low-dose regimens of tenofovir in which plasma and intracellular drug concentrations were similar or slightly higher than those observed in tenofovir-treated humans, were safe and were not associated with any detectable teratogenic effects during pregnancy (Van Rompay et al., 2004a, 2008). All these data are consistent with the favorable safety profile of tenofovir observed in adults and in the Antiretroviral Pregnancy Registry (Antiretroviral Pregnancy Registry Steering Committee, 2007; Cassetti et al., 2007; Nelson et al., 2007).

Tenofovir is currently classified as a pregnancy category B drug (no evidence of risk to humans).

Severe birth defects were observed in an estimated one quarter of infant cynomolgus macaques born to mothers taking efavirenz early in gestation at a dose that gave similar exposure as the dosage regimen in humans (Cadman, 1998); this observation led to a category C pregnancy warning (risk cannot be ruled out) from the Food and Drug Administration (FDA), but was subsequently changed to category D (positive evidence of fetal risk) as a result of five retrospective reports to the FDA of neural tube defects in infants born to women who had taken efavirenz during the first 3 months of pregnancy (Bristol-Myers Squibb, 2008).

5.2. Prophylaxis: Prevention of infection

Many studies in non-human primates investigated whether drug administration starting near the time of virus inoculation could prevent infection. The development of increasingly sensitive techniques to detect virus or antiviral immune responses has sometimes resulted in transient detection of low-level signs of infection, usually within the first weeks after virus inoculation (Grob et al., 1997; Van Rompay et al., 2001). Accordingly, for the purposes of this review, prophylaxis is defined as "protection against persistent infection", with persistent infection being defined as "persistent viremia or persistently detectable virus-specific immune responses".

The macaque model has been used to evaluate topical application of antiviral compounds as microbicides to prevent mucosal infection; topical high-dose administration of a number of compounds protected adult macaques against intravaginal or intrarectal SIV or SHIV infection at varying rates of efficacy (Boadi et al., 2005; Lederman et al., 2004; Li et al., 2009; Manson et al., 2000; Miller et al., 1996; Tsai et al., 2003, 2004; Veazey et al., 2005a; Weber et al., 2001; Wyand et al., 1999). Despite this relative success in the animal models, except for one promising compound (PRO 2000), all other microbicides that have been tested so far in clinical trials have failed poorly. A likely reason for this discrepancy is that most macaque studies used a single, atraumatic administration of microbicide; in contrast, the repeated administration of microbicide in clinical trials may have led to irritation and inflammation of the vaginal mucosa, which, in combination with potential mechanical trauma during sexual intercourse, likely increased the susceptibility to infection upon exposure to HIV. The development of better methodologies to study the effect of chronic microbicide exposure on vaginal mucosa (Schlievert et al., 2008)), and the exploration of more virus-specific inhibitors that are less likely to affect mucosal physiology can improve the usefulness of the non-human primate model for the preclinical testing of microbicides in the coming years (Cranage et al., 2008; Grant et al., 2008).

Many prophylaxis studies evaluated regimens that provided systemic drug levels. Early studies were not very effective in preventing infection, but a likely reason for this was the combination of a high-dose virus inoculum, the direct intravenous route of virus inoculation, and the relative weak potency of drugs at that time (Black, 1997; Fazely et al., 1991; Lundgren et al., 1991; McClure et al., 1990; Wyand, 1992). The proof-of-concept that antiretroviral drugs could prevent infection was demonstrated with zidovudine, which protected infant macaques following a low-dose intravenous inoculation (Van Rompay et al., 1992). Subsequently, a growing series of studies which used lower virus doses, sometimes combined with a mucosal route of virus inoculation, have demonstrated that administration of some antiretroviral drugs (including adefovir (PMEA), tenofovir (PMPA), emtricitabine (FTC), and the CCR5 inhibitor CMPD167) starting prior to, or at the time of virus inoculation was able to prevent infection at varying success rates (Böttiger et al., 1992a,c; Grob et al., 1997; Subbarao et al., 2006; Tsai et al., 1994; Van Rompay et al., 1998a,b, 2001, 2006a; Veazey et al., 2005b). Although few direct comparisons have been done, the available data suggest that (i) the intravenous route of virus infection is the most difficult one to protect against, similarly to what is observed in SIV vaccine studies, and (ii) the demonstrated efficacy of a chemoprophylactic regimen with systemic drug levels against one mucosal route of virus inoculation can generally be extrapolated to other mucosal routes.

Only very few compounds (tenofovir, BEA-005 and GW420867, and CMPD167) have been shown to reduce infection rates when treatment was started after virus inoculation. Of these three compounds, tenofovir was effective as post-exposure prophylaxis against all tested routes of virus inoculation (intravenous, oral, intravaginal, intrarectal), and is currently the only one approved for therapeutic use in humans (Otten et al., 2000; Tsai et al., 1995b; Van Rompay et al., 1998a); BEA-005 and GW420867 are no longer in clinical development. In these post-exposure prophylaxis (PEP) studies, a combination of the timing and duration of drug administration was found to determine the success rate, because a delay in the start, a shorter duration, or interruption of the treatment regimen all reduced the prophylactic efficacy (Böttiger et al., 1997; Emau et al., 2006; Mori et al., 2000; Otten et al., 2000; Tsai et al., 1998, 1995a; Van Rompay et al., 1998b).

While many of the compounds that showed prophylactic efficacy in the macaque model are no longer in clinical development, the promising data with tenofovir have sparked further studies aimed at testing its efficacy against drug-resistant mutants or simplifying the prophylactic regimen. Two studies have demonstrated that tenofovir administration was still (partially) effective in protecting macaques following inoculation of viral mutants with a lysine-to-arginine substitution in RT (K65R) associated with reduced susceptibility to tenofovir, particularly when the mucosal route of virus inoculation was used, or when animals had some pre-existing antiviral immune responses that by themselves were not protective (Metzner et al., 2006; Van Rompay et al., 2000). In addition, several studies in infant and adult macaques have demonstrated that short or intermittent pre-exposure prophylaxis (PrEP) regimens of tenofovir (with or without emtricitabine coadministration) consisting of one dose before and one dose after each virus inoculation were highly effective in reducing infection rates after oral or intrarectal SIV or SHIV inoculation (Garcia-Lerma et al., 2008; Van Rompay et al., 1998a, 2001).

The demonstration that antiretroviral drugs can prevent infection in macaque models has provided the rationale to administer anti-HIV drugs to humans to reduce the likelihood of infection in several clinical settings. Antiviral drugs are now recommended, usually administered as a combination of several drugs, to reduce the risk of HIV infection after occupational exposure (e.g., needlestick accidents of health care workers) and non-occupational exposure (e.g., sex or injection-drug use) (Centers for Disease Control and Prevention, 1996, 2005). In addition, drug regimens containing particularly zidovudine and nevirapine have proven to be highly effective to reduce the rate of mother-to-infant transmission of HIV, including in developing countries (Connor et al., 1994; Gaillard et al., 2004; Guay et al., 1999). Because the short nevirapine regimen that is given to pregnant women at the onset of labor frequently induces drug resistance mutations in the mother (Eshleman et al., 2001), tenofovir's prophylactic efficacy in the infant macaque model has instigated clinical trials in which a short tenofovir-containing regimen was added to existing perinatal regimens to reduce the occurrence of resistance mutations and/or further lower the intra-partum transmission rate (Chi et al., 2007, 2008; Hirt et al., 2009).

Because an efficacious HIV vaccine has so far not been identified, the concept of using PrEP also as a possible HIV prevention strategy in adults has gained rapid momentum in recent years. The promis-

ing prophylactic data of tenofovir (with or without emtricitabine) in the macaque model, combined with the favorable pharmacokinetics, safety profile, drug resistance pattern and therapeutic efficacy of these drugs in HIV-infected people, have made these compounds the leading candidates in ongoing PrEP clinical trials that investigate whether uninfected adult persons who engage in high-risk behavior will have a lower infection rate by taking a once daily tablet of tenofovir or tenofovir plus emtricitabine. An overview of the design, status and challenges of these ongoing trials which are held at several international sites and target different high-risk populations is reviewed elsewhere (AIDS Vaccine Advocacy Coalition, August 2008; PrEP Watch).

5.3. Therapy: Treatment of infection

Numerous studies in the macaque model have demonstrated that even when infection was not prevented, early drug treatment delayed or reduced the peak of acute viremia that occurs during the first weeks of infection, enhanced antiviral immune responses and delayed disease progression (Böttiger et al., 1992c; Hazuda et al., 2004; Hodge et al., 1999; Joag et al., 1997; Le Grand et al., 1994, 2000; Lifson et al., 2000; Lori et al., 1997; Lundgren et al., 1991; Martin et al., 1993; McClure et al., 1990; Mori et al., 2000; Rausch et al., 1995; Rosenwirth et al., 2000; Smith et al., 2000; Spring et al., 2001; Tsai et al., 1993; Uberla et al., 1995; Van Rompay et al., 1995, 1999b; Watson et al., 1997a; Wyand, 1992). The demonstration that early treatment not only suppressed acute viremia but also improved disease-free survival in the SIV-macaque model was at that time very important as proof-of-concept, because the initial human trials did not demonstrate any difference in survival between immediate administration of zidovudine monotherapy versus deferred initiation of therapy (Joint Concorde and Opal Coordinating Committee, 1998); in hindsight, this result was likely because in these human studies, the acute viremia stage was missed and zidovudine monotherapy was rather weak during the chronic stage of HIV infection. Since then, however, the availability of better drug regimens and improved diagnosis of early infection has led to increased recognition of the benefits of early treatment, which were translated into the growing recommendations for early initiation of antiretroviral therapy (Berrey et al., 2001; Hammer et al., 2008; Hecht et al., 2006; Kassutto and Rosenberg, 2004; Kinloch-de Loës et al., 1995; Lafeuillade et al., 1997; Rosenberg et al., 2000).

When acute viremia in animals was suppressed by antiretroviral regimens, the durability of its benefits following treatment withdrawal depended on the virus isolate. With pathogenic env-SHIV isolates, short-term suppression of acute viremia was usually effective to induce strong antiviral immune responses that controlled virus replication and delayed disease for an extended time in the absence of drug treatment (Hazuda et al., 2004; Igarashi et al., 2001; Smith et al., 2000). In contrast, animals infected with virulent SIV isolates (such as SIVmac251) generally had a gradual increase in viremia when treatment was stopped, similarly to observations in most HIV-infected humans (Daar et al., 1998; Davey et al., 1999; Feinberg and Moore, 2002; Hel et al., 2000; Lifson and Martin, 2002; Lori and Lisziewicz, 2001; Markowitz et al., 2002; Spring et al., 2001).

When macaques with chronic SIV infection were started on antiretroviral drugs, the results were variable and generally more disappointing than those observed with early treatment. Initial studies with zidovudine were not very successful in reducing viremia of established SIV infection (Böttiger et al., 1992b; Van Rompay et al., 1992, 1995). Because zidovudine-resistant SIV mutants emerged slowly (Van Rompay et al., 1997), these results were consistent with the relative poor efficacy of zidovudine monotherapy in humans (Eron et al., 1995). Lamivudine (3TC) and emtricitabine ((−)-FTC) treatment of SIVmac251-infected infant macaques also had little effect on viremia and disease progression; yet, there was rapid emergence of drug-resistant mutants with the M184V mutation in RT, indicating that drug levels were sufficient to inhibit replication of wild-type virus (Van Rompay et al., 2002). The CCR5 inhibitor CMPD 167 reduced viremia 4- to 200-fold in chronically SIV-infected macaques, but in some animals this effect was transient (Veazey et al., 2003). Similarly, efavirenz reduced viremia in RT-SHIV-infected macaques, and selection for drug-resistant mutants led in some animals to viral rebound (Hofman et al., 2004). The integrase inhibitor L-870812 reduced viremia only transiently in SHIV-89.6P-infected macaque that had high virus levels and low CD4+ cell counts (Hazuda et al., 2004).

Tenofovir has generally been quite effective in suppressing viremia during established SIV infection (Nowak et al., 1997; Silvera et al., 2000; Tsai et al., 1995b, 1997; Van Rompay et al., 1996). A combination of tenofovir with lamivudine and efavirenz was also effective in suppressing RT-SHIV viremia without detectable emergence of drug-resistant mutants (North et al., 2005). All these studies with tenofovir in macaques have contributed to its clinical development and have been predictive of tenofovir's efficacy in HIV-infected humans (Barditch-Crovo et al., 2001; Deeks et al., 1998; Schooley et al., 2002).

During prolonged tenofovir monotherapy of infected macaques, the emergence of K65R viral mutants with reduced *in vitro* susceptibility did not necessarily lead to a rebound in viremia, as some animals maintained undetectable or low viremia for currently as long as 12 years of tenofovir monotherapy (Van Rompay et al., 1996, 2004d, 2007, 2008). In some studies, tenofovir therapy was not effective in suppressing viremia despite the presence of drug-susceptible virus at the onset of treatment; such poor virologic response was especially observed when tenofovir therapy was initiated when viremia was high and animals were immunosuppressed (Igarashi et al., 2001; Magierowska et al., 2004; Silvera et al., 2000; Tsai et al., 1997; Van Rompay et al., 2004c, 2007). All these observations indicated that the success of antiviral drug therapy is more than just a combination of sufficient drug levels and susceptible virus, and have led to the development of a model of viral dynamics during drug therapy that also incorporates the role of the immune system (see further).

The demonstration that antiretroviral drugs can be effective in SIV-infected macaques has sparked many other studies over the past decade, because these compounds can now be used as tools to acquire a better understanding of disease pathogenesis and drug therapy, to develop immunotherapeutic strategies, and to investigate novel hypotheses. Such studies include the demonstration of the beneficial effects of early antiretroviral therapy on gut-associated lymphoid tissue (GALT) (George et al., 2005; Mattapallil et al., 1999), immune responses against other organisms such as Mycobacterium (Shen et al., 2001), and viral reservoirs (Shen et al., 2003). The model has also been used to test the effect of administration of a CCR5 inhibitor (CMPD 167) in animals that were dually infected with R5 and X4 viruses. While CCR5-using virus levels decreased, an unexpected finding was that most animals demonstrated a transient increase in X4-virus which was, however, not sustained throughout the period of therapy; the reasons and clinical implications of this are unclear (Wolinsky et al., 2004).

Antiretroviral drugs have been combined with other strategies with the aim of restoring the immune system or enhancing antiviral immune responses so that when drug treatment was stopped, viremia was controlled better. These immunotherapeutic strategies include structured treatment interruption, the combination of antiviral therapy with active immunization (including strategies that target dendritic cells), cytokine administration, and immune reconstitution via administration of autologous CD4+ T cells collected prior to SIV infection (Beq et al., 2006; Boyer et al., 2002; Fuller et al., 2006; Hel et al., 2001, 2002; Lisziewicz

et al., 2005; Lori et al., 2000; Nacsa et al., 2003; Shimada et al., 2009; Tryniszewska et al., 2002; Uberla et al., 2007; Van Rompay et al., 2006b; Villinger et al., 2002). While most of these studies observed some effect, the benefits were variable or transient, or the strategy was technically complicated and therefore needs to be simplified before it can be applied to a large human population. Accordingly, prolonged suppression of viremia in SIV-infected macaques to undetectable or very low levels generally still requires daily administration of antiretroviral drugs, similar to observations in humans (DART Trial Team, 2008; Van Rompay et al., 2008).

5.4. The role of primate models in studying drug resistance

Although the goal of HAART is to indefinitely suppress virus replication, many HIV-infected individuals do not experience this desired outcome. While factors such as compliance and variability in pharmacokinetics also contribute to reduced efficacy of HAART, a major limiting factor is the emergence of viral mutants with reduced *in vitro* susceptibility to antiviral drugs, or so-called drug-resistant mutants (Richman, 2001).

Several studies have evaluated the emergence of drug-resistant viral mutants in drug-treated macaques. Similarly to observations in HIV-infected humans, nevirapine and efavirenz treatment of RT-SHIV-infected macaques resulted in mutations at codons 103 and 181 in RT (Ambrose et al., 2007; Hofman et al., 2004; Zuber et al., 2001); lamivudine or emtricitabine treatment of SIVmac251-infected infant macaques induced mutants with a methionine-to-valine mutation at codon 184 of RT (M184V)(Van Rompay et al., 2002); and tenofovir treatment of SIVmac251-infected macaques resulted in the emergence of K65R RT viral mutants (Magierowska et al., 2004; Margot et al., 2003; Ruane and Luber, 2004; Valer et al., 2004; Van Rompay et al., 1996). Interestingly, tenofovir treatment of RT-SHIV-infected macaques gave transiently rise to K70E mutants within 4 weeks of therapy which were then replaced rapidly by K65R mutants (Van Rompay et al., 2007).

A zidovudine-treated SIVmac-infected macaque developed a glutamine-to-methionine substitution at codon 151 of RT (Q151M), associated with high-level (>100-fold) *in vitro* resistance to zidovudine (Van Rompay et al., 1995, 1997). The Q151M mutation has not been found in HIV-1 infected patients during zidovudine monotherapy, but only during sequential or combination therapy with dideoxynucleoside analogues (Schmit et al., 1996; Shafer et al., 1996). However, the Q151M mutation is found frequently in HIV-2 infected patients receiving NRTI therapy including zidovudine (Descamps et al., 2004), which suggests that due to much sequence homology, SIV and HIV-2 have similar mutational pathways that are sometimes distinct from those of HIV-1.

While the observation of the emergence of drug-resistant mutants in treated macaques is informative and an important first step, the true value of the animal models lies in their ability to take the study of drug resistance to higher levels. While the correlation between specific mutations in the viral genome and *in vitro* reduced susceptibility has been documented extensively for most antiviral compounds, it is important to remember that the terms "drug resistance" and "reduced susceptibility" are *in vitro* measures. Many unanswered questions remain regarding the relative virulence and exact clinical implications of these drug-resistant variants *in vivo,* and thus, how to use such information to make treatment decisions. In other words, if drug resistance means that the drug is no longer effective, then the compound can as well be withdrawn; but if there is still a partial response, then it will be counterproductive to discontinue drug administration unless better alternatives can be offered (Darby and Larder, 1992; Deeks, 2001; Deeks et al., 2005, 2007; Richman, 1992).

One question about drug-resistant mutants concerns their replicative fitness and virulence in comparison to wild-type virus. Because the drug resistance mutations are at very low frequency or undetectable in the absence of drug treatment, these mutations are expected to reduce the ability of the virus to replicate. However, primary drug resistance mutations are often followed by compensatory mutations to improve replicative fitness, and it is often unclear whether the final result is full virulence (i.e., able to cause disease) or significant attenuation so that the purpose of continuing drug therapy would be to prevent reversion to the more virulent wild-type form. Studies in the SIV-macaque model have repeatedly demonstrated a weak correlation between *in vitro* markers of replication (replication fitness, cell tropism and cytopathogenicicy) and *in vivo* replication and virulence, which is determined by complex pharmacologic, viral and host factors (Borda et al., 2004; Kestler et al., 1991; Lohman et al., 1994).

Some information regarding the relative replication fitness and stability of drug-resistant HIV mutants *in vivo* can be gathered from case reports, such as those documenting primary infection with drug-resistant HIV-1, as well as those monitoring the reversion of drug-resistant virus to wild-type following discontinuation of drug treatment (Deeks et al., 2001; Gandhi et al., 2003; Izopet et al., 2002). An animal model, however, allows approaches which are impossible to do in humans, but which are the most direct ways to study the virulence and clinical implications of drug-resistant virus: animals can be inoculated with drug-resistant viral mutants or their wild-type counterparts, and the outcome can be compared in drug-treated versus untreated animals.

Inoculation of newborn macaques with a zidovudine-resistant Q151M SIVmac isolate demonstrated that this mutation did not significantly reduce viral replication and viral virulence; the Q151M mutation (which is the result of two base changes) was also very stable in the absence of zidovudine treatment (Van Rompay et al., 1997).

Because M184V mutants of HIV-1 have impaired replication kinetics *in vitro* (Back et al., 1996; Miller et al., 1999), a study was designed to investigate the impact of this mutation on SIV *in vivo*. A SIVmac239 clone with the M184V mutation was found to have slightly reduced replication fitness compared to wild-type SIVmac239, as demonstrated by lower virus levels 1 week after inoculation, and its reversion to wild-type sequence in untreated animals. However, this reduced replication fitness was not sufficient to affect viral virulence, because the viremia (from 2 weeks after infection onward) and disease course in animals inoculated with M184V virus and treated with emtricitabine (to prevent reversion) was indistinguishable from that of wild-type virus (Van Rompay et al., 2002).

The SIV and RT-SHIV macaque model has been used extensively to study the clinical implications of K65R viral mutants during tenofovir treatment. Following the emergence of K65R mutants, two outcomes were possible during continued tenofovir therapy (i) K65R viremia was reduced and could remain very low or undetectable with prolonged disease-free survival (>3–12 years; (ii) viremia remained or became high (>10^6–10^7 RNA copies/ml plasma), but with continued tenofovir treatment, survival was increased significantly more than predicted based on viral RNA levels and CD4+ T cell counts) (Van Rompay et al., 1996, 1999a, 2004c,d, 2007, 2008). To investigate whether this observation of suppressed viremia in some tenofovir-treated animals despite K65R virus was caused by an attenuating effect of the K65R mutation on viral replication fitness and virulence, K65R SIV isolates were inoculated into new animals. In the absence of tenofovir treatment, K65R SIV isolates were as fit and virulent as wild-type virus based on their ability to induce high viremia and rapid disease ($\leq$4 months) in newborn macaques (Van Rompay et al., 1999a). In contrast, in the presence of prolonged tenofovir treatment, the disease course of K65R virus-

infected animals was changed, with the same therapeutic benefits (suppressed viremia or high viremia with prolonged disease-free survival) as described above (Van Rompay et al., 1999a). In the tenofovir-treated animals with low viremia of K65R viral mutants, withdrawal of tenofovir therapy led to an increase in viremia (Van Rompay et al., 2004d, 2007); while this need for continued therapy suggests partial antiviral effects of tenofovir against these mutants which have a 5-fold reduced *in vitro* susceptibility, additional factors were found to play a role in suppressing viremia (see further). In summary, although the ultimate goal of therapy is to suppress viremia in 100% of the subjects to undetectable levels, these studies demonstrated that at least for tenofovir, the presence of "drug-resistant" virus did not mean that the animal was resistant to the clinical benefits of tenofovir therapy.

These findings of continued therapeutic benefits of continued tenofovir therapy in the presence of "drug-resistant" virus in the macaque models are consistent with some observations in HIV-infected humans where studies, including those utilizing drug interruptions, have demonstrated that some drug regimens can still provide therapeutic virologic and/or immunologic benefits in the presence of drug-resistant virus (Barbour et al., 2002; Bélec et al., 2000; Deeks, 2001; Deeks et al., 2000, 2001, 2002, 2004; Hunt et al., 2003; Mezzaroma et al., 1999; Miller et al., 2002; Monpoux et al., 2004).

5.5. The role of the immune system on the efficacy of drug therapy

Viral kinetics during drug therapy are believed to depend on viral replication fitness, the drug susceptibility of the virus and the potency of the drug (Bonhoeffer et al., 1997; Perelson, 2002; Wodarz and Nowak, 2002). When virus levels in plasma are reduced rapidly following the onset of drug therapy, the antiviral drugs are lauded for their potency, while antiviral immune responses during drug therapy are generally given less credit and receive attention mainly as a backup plan to try to contain viremia whenever drug treatment is withdrawn or drug-resistant virus would emerge (Lori and Lisziewicz, 2001). Recently, however, a growing body of evidence from human and primate studies demonstrates that antiviral immune responses play a previously unrecognized role during drug therapy that merits proper credit (Buseyne et al., 2005; Deeks et al., 2004; Hazuda et al., 2004; Van Rompay et al., 2004c,d).

Drug studies in macaques have demonstrated the concept that antiviral drugs require the assistance of immune responses to reach full effectiveness in reducing viremia, both at the onset of treatment when the virus has wild-type susceptibility, as well as during prolonged treatment in the presence of drug-resistant mutants (Hazuda et al., 2004; Van Rompay et al., 2004c,d, 2007).

A major role of the immune system during antiviral drug therapy was identified by experiments to further explain the observations with tenofovir described above. Several key studies used experimental depletion of CD8+ cells *in vivo* (through administration of anti-CD8 monoclonal antibody). When tenofovir treatment was started during acute viremia with wild-type SIVmac251, the efficacy of tenofovir to suppress acute viremia with wild-type SIVmac251 was significantly reduced in the absence of CD8+ cells (Van Rompay et al., 2004d). These observations indicated that the otherwise rapid decline of productively infected cells (with half-life of ~1–2 days) after the onset of drug therapy was due to CD8+ cell-mediated killing or inhibition, rather than the death rate determined by the cytopathogenicity of the virus (Van Rompay et al., 2004d). In this model of drug therapy (Fig. 3), CD8+ cell-mediated antiviral immune responses contribute significantly to the antiviral effects of anti-HIV drugs by reducing the burst of virus replication in productively infected cells via cytolytic or noncytolytic pathways. In the absence of CD8+ cells, productively infected cells were found to have a long half-life, suggesting that virulent SIV, during concomitant tenofovir treatment, was not highly cytopathic (Van Rompay et al., 2004d). This beneficial interaction between antiretroviral drugs and antiviral immune responses is likely to be bi-directional; potent antiviral drugs like tenofovir may promote the development of effective antiviral immune responses by reducing the virus-induced immunosuppression and/or via other immunomodulatory effects (Van Rompay et al., 2004b,d).

As described earlier, even after the emergence of K65R SIV or RT-SHIV mutants, some tenofovir-treated animals reached and maintained undetectable viremia for years (Van Rompay et al., 1996, 2004d, 2007). A tempting explanation for this observation, especially if made in tenofovir-treated humans, would be to ascribe it to (i) a severe reduction in replication fitness caused by the K65R

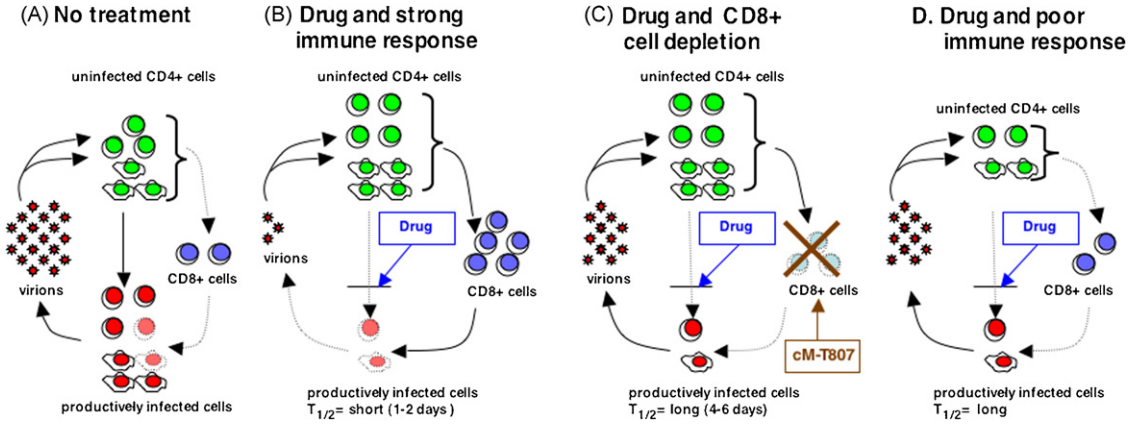

Fig. 3. Model of viral dynamics during antiretroviral drug therapy: (modified from references Van Rompay (2005), Van Rompay et al. (2004d)). (A) Without drug treatment, virulent virus replicates to high titers because of high infection rates of CD4+ T helper cells and antigen presenting cells which are unable to provide sufficient assistance to CD8+ cell-mediated immune responses to contain virus replication. (B) A potent drug regimen reduces the number of CD4+ T helper cells and antigen presenting cells that become newly infected. Potent CD8+ cell-mediated immune responses reduce the half-life of and thus the burst size of viral progeny for those cells that already became infected. The combined antiviral activities of drug and antiviral CD8+ cells are efficient to induce and maintain low viremia, even after the emergence of drug-resistant viral mutants (as shown for tenofovir in the macaque model (Van Rompay et al., 2004d, 2007)). (C) During artificial CD8+ cell depletion, productively infected cells survive longer and produce more progeny virus, resulting in higher viremia (Van Rompay et al., 2004d). (D) During immunodeficiency, the reduced function of antigen presenting cells and CD4+ T helper cells results in insufficient assistance to antiviral CD8+ cells to remain active, especially at lower levels of viremia. Even when infection of new cells is reduced by an efficient drug regimen, the half-life of the productively infected cells is long, resulting in a slower decrease of viremia (see Fig. 4A). Without sufficient immune restoration, the emergence of drug-resistant mutants is likely to lead to a rebound in viremia (Hazuda et al., 2004; Van Rompay et al., 2004c, 2007).

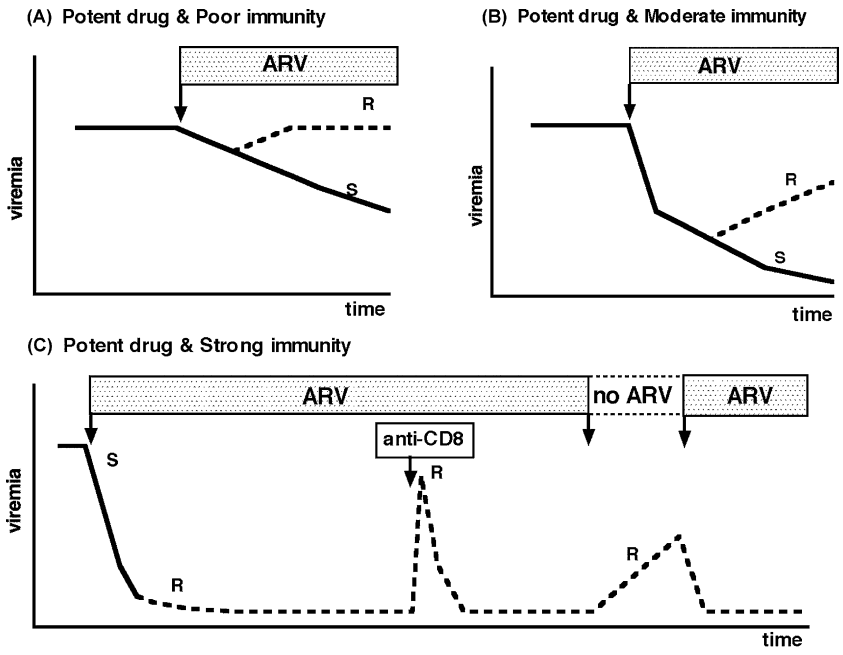

Fig. 4. Model of viremia patterns during antiviral drug therapy: the role of antiviral immune responses (modified from reference Van Rompay (2005)). Several scenarios are presented, which all use a potent antiretroviral (ARV) regimen (i.e., complete prevention of infection of new cells with drug-susceptible virus) while the antiviral immune responses have variable strength. R indicates the emergence of drug-resistant mutants with good replication fitness, while S indicates susceptible wild-type virus (or drug-resistant mutants with severely reduced replication fitness). Please note that intermediate levels of viral fitness or drug potency are possible but not shown. (A) Without effective antiviral immune responses (e.g., SIV- or SHIV-infected macaques with severe immunodeficiency, or when CD8+ cells are depleted at the start of therapy) (Hazuda et al., 2004; Van Rompay et al., 2002, 2004c,d), treatment with an otherwise highly potent drug regimen does not result in a rapid reduction of viremia despite the presence of wild-type virus. Without restoration of antiviral immune responses, the emergence of drug-resistant mutants leads inevitably to a rebound in viremia. (B) Starting drug treatment at a moment of moderate immunity (e.g., most HIV-infected patients with chronic infection) leads to a first phase of rapid decline in viremia, followed by phases of slower decline. These phases, generally believed to reflect distinct populations of infected cells (Perelson, 2002), may alternatively also reflect antiviral immune responses that, without sufficient assistance of antigen presenting cells or T-helper cells, become less active at lower levels of antigen (Arnaout et al., 2000). Without sufficient immune restoration, the emergence of drug-resistant virus leads to increased viremia. (C) In this model, which is supported by observations of tenofovir-treated SIV-infected macaques (Van Rompay et al., 2004d, 2007), a potent drug regimen combined with strong antiviral immune responses rapidly reduces viremia, which can remain low or undetectable even after the emergence of replication-fit drug-resistant virus. When such chronically treated animals were depleted of CD8+ cells (while drug treatment is continued), viremia of drug-resistant virus increased rapidly but returned to baseline values upon return of CD8+ cells. However, these CD8+ cells are not sufficient to control viremia, because withdrawal of drug treatment leads to slow increase in viremia. Thus, these experiments demonstrated that drug or CD8+ cell-mediated immune responses alone were not sufficient, but both were required to maintain maximal suppression of viremia (Van Rompay et al., 2004d).

mutation (which, as discussed earlier, is not the case for K65R SIV isolates) (Van Rompay et al., 1999a), and/or (ii) sufficient residual inhibitory effect of tenofovir against these viral mutants (with ~5-fold reduced *in vitro* susceptibility). However, *in vivo* CD8+ cell depletion experiments, which are not feasible in humans, revealed that the suppressed viremia of K65R SIV and RT-SHIV mutants during prolonged tenofovir treatment of macaques was largely due to strong CD8+ cell-mediated antiviral immune responses. When CD8+ cells were transiently depleted during continued tenofovir treatment, a transient dramatic increase of K65R viremia was observed, indicating that (i), these K65R viral mutants were very replication-competent (ii) tenofovir treatment alone was insufficient to inhibit these K65R viral mutants *in vivo* (Van Rompay et al., 2004d, 2007) (Fig. 4). In subsequent experiments, when CD8+ cells were restored, tenofovir withdrawal led to a slow increase in viremia, indicating the importance of continued tenofovir therapy (Van Rompay et al., 2004d, 2007). Thus, both tenofovir and effective CD8+ cells were required to maximally suppress replication of virulent K65R virus in this animal model (Van Rompay et al., 2004d). These observations of reduced viremia of K65R SIV mutants associated with strong antiviral immune responses in tenofovir-treated macaques may explain observations that viremia in persons with detectable K65R HIV-1 mutants can be suppressed by tenofovir-containing regimens (Chappell et al., 2007) and are consistent with clinical observations of strong antiviral immune responses in HIV-1 infected people who are receiving HAART and have low-level viremia with drug-resistant virus (Alatrakchi et al., 2005; Deeks et al., 2004).

Additional support for this model in which antiviral immune responses assist anti-HIV drugs in reducing viremia is provided by observations in SIV- or SHIV-infected macaques that drug regimens that were highly effective during acute viremia were less effective when therapy was started later in infection, particularly with more virulent isolates, in the presence of high viremia and immunodeficiency, even though the virus was fully drug-susceptible at the onset of treatment (Hazuda et al., 2004; Igarashi et al., 2001; Magierowska et al., 2004; Silvera et al., 2000; Tsai et al., 1997; Van Rompay et al., 2004c) (Fig. 3). Also in humans, lower CD4+ cell counts and higher pre-treatment virus levels have generally been associated with a slower virological response to therapy (Egger et al., 2002; Moore et al., 2003; Phillips et al., 2001). In the absence of effective antiviral immune responses, antiviral drugs face a more daunting task to control viremia as already infected cells survive longer and produce more viral progeny (Fig. 3D) (Van Rompay et al., 2004c,d).

Incorporating the role of the host immune system in the way we interpret viral dynamics during drug therapy is useful, because the variability in the strength of antiviral immune responses among individuals and among study cohorts helps to explain the different patterns of viremia that are seen in drug-treated SIV-infected macaques and HIV-infected infants and adults (Ghaffari et al., 2004; Huang et al., 2001; Wu et al., 2005) (Fig. 4).

It is important to remember that the effects of antiviral immune responses during drug therapy are not mutually exclusive of effects of altered replication fitness or diversity of mutant virus, and/or residual drug activity. In particular, even a relatively minor decrease

in replication fitness or viral heterogeneity, or a partial inhibition of virus replication by the drug regimen can have a major impact on viremia if it provides more opportunity for effective antiviral immune responses to kill productively infected cells prior to the major viral burst; in contrast, in the absence of effective antiviral immune responses (such as during late-stage disease), a small difference in replication fitness or residual drug activity may not translate in any significant difference in viremia and clinical outcome (Frost et al., 2000; Van Rompay et al., 2002, 2004d).

As discussed earlier, studies in SIV-infected macaques have shown that improvement of immunological control of viremia is possible with various immunotherapeutic strategies that are administered during chronic drug therapy (Boyer et al., 2002; Hel et al., 2001, 2002; Lisziewicz et al., 2005; Lu et al., 2003; Nacsa et al., 2003; Tryniszewska et al., 2002; Villinger et al., 2002). The demonstration in SIV-infected macaques that antiviral immune responses also contribute significantly to reducing viremia at the onset of drug therapy (Figs. 3 and 4) provides a scientific rationale to explore also immunotherapeutic strategies that target the onset of antiviral drug therapy, instead of assuming that such interventions should wait until viremia has already reached lower levels.

6. Looking into the future: The ultimate goal of stopping HAART

Considering the bleak prognosis for HIV-infected patients during the early years of the epidemic, our current ability to manage HIV infection with antiretroviral drugs represents a triumph of modern medicine. However, because even the newer drugs are still relatively expensive and carry some risk of toxicity (which may be cumulative after decades of treatment), the ultimate goal remains to have a strategy that would allow permanent withdrawal of HAART, either by gaining long-term immunological control (discussed earlier), or by purging out viral reservoirs and totally curing HIV infection. While there were early mathematical projections that several years of HAART may perhaps be able to cure infection (Perelson et al., 1997), the much slower decay rates of some viral reservoir compartments and/or evidence of some ongoing low-level virus replication have dashed such hopes, because treatment interruptions invariably result in a rebound of virus replication (Ho, 1998). Thus, novel strategies have to be developed to achieve this goal of curing infection. The available evidence suggests that viral persistence during HAART can be caused by different mechanisms, of which the relative importance is still being debated. Thus, it is likely that all of these mechanisms need to be targeted simultaneously in order to achieve success (Hamer, 2004). First of all, evidence of very low levels of virus replication during HAART with ongoing replenishment of the reservoirs suggests the need to develop even more effective antiretroviral drug regimens or gene therapy-based approaches, such as si-RNA's (Martinez, 2009; Palmer et al., 2008). While current drugs focus on inhibiting the structural proteins, novel strategies can also target the regulatory and accessory proteins (Tat, Ref, Nef, Vif, Vpu, Vpr). Secondly, to reduce the latent viral reservoirs, agents are needed to activate HIV gene expression (Richman et al., 2009). Thirdly, because viral gene expression and viral replication by itself may not result in the death of the infected cell, approaches that can selectively and effectively destroy the HIV-infected cells in the reservoirs are needed; such strategies include immunological approaches such as immunotoxins that target HIV proteins, genetically engineered cytotoxic lymphocytes, or anti-HIV microbes (Hamer, 2004).

Many strategies aimed at reactivating virus and eradicating viral reservoirs are likely to carry a risk of adverse effects, such as toxicity or, in case of incomplete eradication, a rebound of viremia upon withdrawal of HAART, which may affect future treatment options. Without proof of concept, only few people who fare well on a stable HAART regimen may be interested to volunteer for such clinical trials. Therefore, animal models can play an important role in better understanding viral persistence and testing novel concepts aimed at elimination or permanent control. As mentioned, because HIV can persist through a variety of mechanisms and in a variety of cell types, a combination of strategies is probably necessary to target all of them. In a step-wise approach to understand our ability to manipulate the individual components, some pilot studies have already been performed in animal models with some relative success.

Studies in the SCID-hu mouse model have focused on reactivating virus in latently infected thymocytes, and have demonstrated that strategies including prostratin and interleukin-7 (IL-7) were able to reactivate latent virus, and when used in conjunction with a gp120-directed immunotoxin, reduced the latent viral reservoirs (Brooks et al., 2003; Korin et al., 2002; Scripture-Adams et al., 2002). However, because the latently infected cells in this model resemble more naive T-cells, it may not accurately represent memory CD4+ T cells that are one of the predominant cell types harboring the latent reservoir in infected humans (Han et al., 2007). Because SIV infection of macaques also results in establishment of a reservoir in resting T cells (Shen et al., 2003), this model will also be useful to test such strategies.

Several studies have targeted macrophages/monocytes as one of the viral reservoirs. Because of its ability to cause macrophage depletion, clodronate was evaluated in a murine model of AIDS, in which LP-BM5 retroviral complex-infected C57BL/6 mice received oral administrations of antiretroviral drugs with our without clodrenate (Serafini et al., 2009). In another study, tenofovir-treated SIV-infected sooty mangabeys were treated with fludarabine-loaded red blood cells which selectively targets infected macrophages/monocytes via a pSTAT1-dependent pathway. Both studies found a delay in viral rebound upon withdrawal of the antiretroviral drug regimen.

Although none of these strategies have been effective in eradicating infection, their relative success in reducing viral rebound after HAART withdrawal represents an important step in the right direction. Accordingly, these animal models will continue to be useful to explore additional compounds and combinations.

7. Conclusions

During the past two decades, the gradually better understanding of disease pathogenesis and the development of better resources (reagents, assays, and drugs) have improved the usefulness of animal models to evaluate novel prophylactic and therapeutic drug strategies, and to test hypotheses that cannot be mimicked appropriately by *in vitro* experiments and are difficult to explore in humans. Although each animal model has its limitations, the ongoing comparison of results obtained in animal models and human studies will be useful to further validate and improve these animal models so they can continue to provide a solid foundation to advance our scientific knowledge and to guide clinical trials.

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