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The predictive value of macaque models of preexposure prophylaxis for HIV prevention

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Abstract

Purpose of review—We review macaque models for preexposure prophylaxis (PrEP) for HIV prevention and highlight their role in advancing currently approved and novel PrEP agents.

Recent findings—The development of the repeat low dose simian HIV (SHIV) challenge models represented a significant advancement in preclinical PrEP modeling that has allowed the investigation of PrEP under conditions that better mimic HIV exposures in humans. These models incorporate relevant drug pharmacology to inform drug correlates of PrEP protection. Models of rectal, vaginal, and penile infection are now available and have been found to predict clinical efficacy of all the currently approved PrEP strategies including daily oral PrEP with the combination of emtricitabine and tenofovir disoproxil fumarate or tenofovir alafenamide, and a long-acting formulation of the integrase inhibitor cabotegravir. These models are being used to test new PrEP modalities including the nucleoside reverse transcriptase-translocation inhibitor islatravir and long-acting capsid inhibitors. The SHIV models have also been supplemented by sexually transmitted infection co-infections with Chlamydia trachomatis, Treponema pallidum or Trichomonas vaginalis to assess the impact of inflammation on PrEP efficacy.

Summary—Clinical efficacy validated current PrEP macaque models supporting their continued use to advance novel PrEP agents to improve global PrEP coverage.

Keywords

macaque models; PrEP; simian HIV (SHIV)

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Conflicts of interest

J.G.G-L and W.H. are named in US Government patents on “Inhibition of HIV infection through chemoprophylaxis”, a US Government patent on “HIV postexposure prophylaxis” and a patent application on “HIV preexposure prophylaxis”. The findings and conclusions of this manuscript are those of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

INTRODUCTION

About 1.5 million new HIV infections have occurred globally in 2020 (https://www.who.int/data/gho/data/themes/hiv-aids). While an HIV vaccine is not yet available, substantial progress has been made in the development of antiretroviral (ARV)-based strategies to prevent HIV. Preexposure prophylaxis (PrEP) with daily oral regimens containing emtricitabine in combination with tenofovir disoproxil fumarate or tenofovir alafenamide have been highly effective in preventing HIV acquisition when taken as prescribed, although inadequate adherence reduces efficacy and public health benefit [1]. Public health organizations including the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend scaling up PrEP around the world. The at-risk populations that will benefit from PrEP are diverse and generally exceed the number of HIV-infected persons. Thus, it is critical to identify PrEP modalities to accommodate different user needs to maximize coverage and public health benefit. Long-acting PrEP that does not require frequent dosing is being developed to overcome adherence challenges to daily oral PrEP. A bimonthly injectable formulation of the integrase inhibitor cabotegravir (cabotegravir long acting) was approved in late 2021 by the US Food and Drug Administration (FDA) for PrEP in men and women. Cabotegravir long acting was found to be safe and more effective than daily oral emtricitabine/tenofovir disoproxil fumarate likely reflecting the adherence advantage of long-acting PrEP [2,3].

The development of PrEP has benefited substantially from preclinical research in macaque models. These macaque models have established proof-of-concept of efficacy, informed the selection of regimens and dosage, and have now become pivotal in prioritizing PrEP products for clinical advancement. This review will provide a historical perspective of macaque models of PrEP, describe key characteristics of the models, and highlight their ability to predict clinical efficacy. The review also discusses modifications of the macaque model to investigate the impact of HIV risk factors on PrEP and discuss recent preclinical studies with novel PrEP products.

PREEXPOSURE PROPHYLAXIS TESTING USING THE REPEAT LOW DOSE MACAQUE MODEL

Early indications that antiretrovirals could work as PrEP came from macaque studies using different doses of tenofovir administered subcutaneously [4]. Although these studies provided indication of the promise of tenofovir for PrEP against intravenous exposures, they relied on the use of supratherapeutic doses of tenofovir and did not address the predominantly sexual transmission routes of HIV among humans. The development of the repeat low dose SHIV challenge model represented a significant advancement in preclinical PrEP modeling that allowed the investigation of PrEP under conditions that better mimic sexual HIV exposures in humans. Key characteristics of the model are the use of repeated virus exposures to mimic populations at high risk of HIV infection, testing conditions that incorporate more physiologic virus doses, and mucosal challenge viruses that contain R5-tropic HIV-1 envelope similar to most transmitted HIV [5–7]. The repeated virus challenge design has the additional advantage of measuring the

durability of protection and improves statistical power. The availability of rectal, vaginal, and penile models also allows the evaluation of PrEP interventions against the main routes of HIV infection [8–10]. Although these models better recapitulate transmission during sexual HIV exposure than single-high dose models, their true translational value was further refined by incorporating a strong pharmacological component in order to model clinically relevant drug doses and identify drug correlates of protection to better inform dose selection for clinical trials (Fig. 1). Pharmacokinetic studies and allometric scaling of emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide, maraviroc, and cabotegravir long-acting identified macaque doses that are equivalent to human doses and allowed assessment of PrEP efficacy at clinically relevant dosing [11–14]. At these drug doses, daily emtricitabine reduced the risk of rectal SHIV infection by 3.8-fold, whereas a non-statistically significant trend toward delayed infection was seen in animals receiving daily oral tenofovir disoproxil fumarate [10,12]. However, the combination of emtricitabine and tenofovir disoproxil fumarate provided 87% protection against rectal SHIV infection and 94%–100% protection against penile and vaginal SHIV exposures (Table 1) [12,15▪,16–18]. The tenofovir diphosphate concentration in peripheral blood mononuclear cells (PBMCs) associated with a 90% reduction in risk (EC_{90}) of rectal SHIV infection in macaques also compared well with the EC_{90} identified in men who have sex with men further highlighting the relevance of incorporating relevant drug pharmacology to the transmission component of the macaque model [19]. More recent studies with the combination of emtricitabine and tenofovir alafenamide found complete protection against rectal SHIV infection and 91% protection against vaginal exposure [13,20▪▪]. Cabotegravir long acting at doses that mimic a bimonthly injection in humans provided 90%–100% efficacy estimates against rectal, vaginal, intravenous, and penile challenges and helped identify correlates of protection by this drug [11,15▪,21–23]. Table 1 shows the available efficacy estimates in the macaque model and clinical trials. The finding of similar efficacy estimates with daily and on-demand oral emtricitabine/tenofovir disoproxil fumarate, daily oral emtricitabine/tenofovir alafenamide, and cabotegravir long acting in human PrEP trials [2,3,24–29] validates the repeat challenge macaque model further supporting its preclinical use in evaluating novel PrEP drugs and informing dosing strategies.

An important question that remains unclear is the relative contribution of PrEP drugs in mucosal tissue versus blood/PBMC (or systemic) to protection as drugs often distribute in both compartments. While there is no direct evidence from the systemic PrEP macaque model regarding this point, there are relevant data from topical PrEP that may help address this question. Data from humans and macaques show that topically applied PrEP products such as tenofovir gels result in little to no systemic drug but much higher drug concentrations in mucosal tissues compared to oral dosing [30–32]. Also, challenge studies showed that drug concentrations needed for protection from topical products far exceeds those achieved in the tissues after oral dosing [14,30,33]. Collectively, these data imply that systemic drugs in oral PrEP likely contribute to protection against sexually acquired HIV.

Novel oral on-demand PrEP regimens are also being investigated in the repeat low dose macaque model. While an on-demand PrEP option with oral emtricitabine/tenofovir disoproxil fumarate is available for men who have sex with men, this regimen requires four pills, two before sex followed by one pill at 24 h and one at 48 h post sex (2+1+1

dose schedule) [28]. Two recent macaque studies recently highlighted the promise of newer and simplified on-demand regimens that could be administered by the end-user before or after sexually viral exposure. One study using a single oral dose of emtricitabine, tenofovir alafenamide, and boosted elvitegravir provided efficacy estimates of 92% and 100% when given 4 h before or 2 h after rectal SHIV exposure, respectively, and 80%−65% when given 6–24 h post challenge. [34▪▪]. A second study with two oral doses of emtricitabine, tenofovir alafenamide and bictegravir found complete protection against rectal SHIV infection when the doses were administered 2 h before and 24 h post challenge, and 82%–90% efficacy when the two dose regimen was initiated within 24 h after exposure [35▪]. These two macaque studies document biological efficacy of a “before or after sex” HIV prevention pill that may better adapt to different needs among PrEP and PEP users.

Another drug that has been evaluated in macaques for nondaily oral PrEP is tenofovir alafenamide. Tenofovir alafenamide is very potent and achieves high intracellular concentrations of tenofovir-diphosphate in PBMCs while maintaining low concentrations of tenofovir in plasma. A recent macaque study tested the hypothesis that a once weekly dose of oral tenofovir alafenamide might be sufficient to prevent vaginal and rectal HIV acquisition, provided some dose adjustments to ensure persistent tenofovir-diphosphate in PBMCs. The study identified a weekly dose of oral tenofovir alafenamide of 27.4 mg/kg (or equivalent to ~450 mg in humans) that provided high and durable protection against vaginal SHIV infection and moderate rectal protection. These findings suggests that a clinically achievable oral tenofovir alafenamide dose might be an effective nondaily PrEP option [36].

The repeat low dose macaque model has been also used to investigate newer PrEP agents and dosing strategies. Islatravir (formerly known as EFdA (4’-ethynyl-2-fluoro-2’-deoxyadenosine)) is a first-in-class nucleoside reverse transcriptase-translocator inhibitor that is in clinical development for PrEP and treatment [37,38]. Islatravir has high antiviral potency (EC_{50} in the picomolar range) *in vitro* and *in vivo* and displays a long intracellular half-life in PBMC from macaques and humans [39,40]. The potential of islatravir for long-acting PrEP was first established in a proof-of-concept study in macaques. Treatment of macaques with a single weekly oral dose of islatravir at 3.9 mg/kg or 0.43 mg/kg fully protected the animals against repeated rectal exposures to SHIV109CP3[41▪▪]. Sequential reductions in the dose of islatravir helped define the prophylactic EC_{90} for islatravir (~24 fmols of islatravir-triphosphate per million PBMCs) which was achieved with a low 0.1 mg/kg dose. An important observation from this study was the identification of a concentration of islatravir-triphosphate of ~100 fmols/10^6 PBMC that conferred full protection in the model. These compelling findings provided the first correlate of protection by islatravir *in vivo* and highlighted the low dose requirement needed to achieve high level of PrEP protection.

The high potency of islatravir coupled with an intracellular half-life of approximately 190 h in humans also highlights the flexibility of islatravir PrEP in regard to dosing frequency and its suitability for sustained delivery [40]. In rhesus macaques, a subdermal islatravir-eluting implant achieved clinically relevant drug exposures in plasma and sustained drug release, with islatravir-triphosphate concentrations in PBMCS that were above 100 fmols/10^6 cells for 2–3 months [42]. In a recent phase 1 trial in humans, a 62 mg islatravir implant with

physical properties and dimensions similar to those of the hormonal contraceptive Implanon achieved islatravir-triphosphate concentrations above the pharmacokinetic threshold through the entire 12 weeks of study. Implants in this study were generally well tolerated with no serious adverse events or discontinuations during the implantation period [43]. At the time of writing clinical trials with oral islatravir for prevention and treatment paused enrollment of new participants due to a decrease in totally mphocyte and CD4+ T-cell counts seen in some participants treated with islatravir [44].

Another promising candidate for long-acting PrEP is lenacapavir. Lenacapavir is a first in class HIV capsid inhibitor that targets multiple stages of the HIV replicative cycle and has potent antiviral activity (EC_{50} in the picomolar range) *in vitro* and *in vivo* [45]. In a phase 1 trial, a single 900 mg subcutaneous lenacapavir formulation maintained plasma target concentrations (≥ 6xPA-IC_{95}) for 6 months supporting its use for long-acting PrEP[46]. In a recent study in rhesus macaques, a structural analog of lenacapavir (named GS-CA1) demonstrated long-lasting protection against repeated SHIV challenges, with a reduction in the risk of infection of 97% for 24 weeks [47▪▪]. Pharmacokinetic analysis also identified plasma concentrations of GS-CA1 above 2x the protein adjusted-IC_{95} associated with 100% protection. A more recent macaque study with lenacapavir showed full protection against intravenous challenge with a simian-tropic HIV (stHIV) further demonstrating the potential of lenacapavir for long-acting PrEP [48]. Two Phase 3 trials (ClinicalTrials.gov Identifier NCT04994509 and NCT04925752) are now evaluating the safety and efficacy of lenacapavir for PrEP in multiple populations at risk of HIV infection.

MACAQUE MODELING OF PREEXPOSURE PROPHYLAXIS IN THE SETTING OF HIV RISK MODIFIERS

Typical factors considered in choosing a macaque model for PrEP include animal species and gender, and the type, dose and frequency of viral challenges. However, these models not always incorporate epidemiologic risk factors that are associated with HIV in men and women and that magnify HIV risk by enhancing virus entry through vaginal, rectal or penile tissues. Examples of biologic modifiers that are known to amplify HIV risk up to six-fold include bacterial, parasitic and viral sexually transmitted infections (STI). Nonulcerative STI, such as Trichomonas vaginalis and Chlamydia trachomatis cause inflammation and discharge, whereas STI such as Treponema pallidum and Herpes simplex virus (HSV) type 2 also cause ulcers. Alterations in HIV targets and cellular and cytokine milieu can enhance HIV penetration and replication and potentially reduce the efficacy of PrEP. Such interactions are difficult to evaluate in clinical trials as subjects are carefully screened, followed and treated for STI.

Approaches for macaque modelling of STIs and PrEP include testing in presence of one or more STIs. Building on the original macaque models of vaginal Chlamydia trachomatis and Trichomonas vaginalis developed by Patton *et al.* [49,50] we developed a novel model of vaginal Chlamydia trachomatis and Trichomonas vaginalis co-infection that increased SHIV acquisition risk by ~ 2 fold [51,52]. We further developed the first vaginal Treponema pallidum model [53] and demonstrated ability to co-infect macaques with all three STI,

recapitulating typical clinical findings of inflammation, discharge, and ulcers. This “ultra-high” HIV risk model combining ulcerative and nonulcerative STIs was recently used to determine if these inflammatory conditions could diminish the efficacy of cabotegravir long acting [54▪]. All STI infected macaques treated with cabotegravir long acting remained fully protected despite 14 SHIV challenges suggesting that cabotegravir long acting is likely to protect women at the highest risk of HIV infection.

The vaginal Chlamydia trachomatis and Trichomonas vaginalis co-infection model was also used to evaluate the impact of these coinfections on the efficacy of oral emtricitabine/tenofovir disoproxil fumarate [55]. This study showed that some of the animals receiving emtricitabine/tenofovir disoproxil fumarate were infected during repeated challenges. Although the reduction of efficacy by emtricitabine/tenofovir disoproxil fumarate was modest and not statistically significant, it raised questions about potential mechanisms responsible for these effects including mucosal increases in levels of deoxynucleotide triphosphates (dNTPs) due to inflammation and cell activation. Elevated dNTP levels in activated cells may outcompete tenofovir-diphosphate or emtricitabine-triphosphates, the pharmacologically active metabolites of tenofovir and emtricitabine, during reverse transcription of HIV RNA reducing antiviral activity [56]. In contrast to nucleoside reverse transcriptase inhibitors (NRTIs), increased dNTP levels due to inflammation would have little or no impact on PrEP with cabotegravir given the different mechanism of action of integrase inhibitors. All together, these studies illustrated how the mechanism of antiviral action, and local drug concentrations can influence the impact of STIs on PrEP.

Herpes simplex virus type 2 (HSV-2) and Neisseria gonorrhea are pathogens of significant public health burden associated with increased HIV acquisition risk. However, these have been extremely challenging pathogens to establish in macaque models. For HSV-2, several groups have identified strains that can infect rhesus macaques vaginally, although the infections do not consistently recapitulate clinical HSV-2, lacking persistent shedding and ulceration [57,58]. Continued research in this field may identify strains or conditions that will generate better macaque models. In the case of Neisseria gonorrhea, many years of model development led to the conclusion that a macaque model of Neisseria gonorrhea would not be feasible [59], although recent work suggests that some clinical strains may be able to infect pigtail macaques [60].

Macaque models can also be used to evaluate multipurpose prevention technologies (MPT). A promising area of research relates to recent findings that on-demand doxycycline PEP can reduce the incidence of Chlamydia trachomatis and Treponema pallidum infection in men [61]. In this regard, models of vaginal Chlamydia trachomatis, Treponema pallidum, and SHIV could be used to determine if combinations of doxycycline and anti-HIV drugs can prevent vaginal infection with all three pathogens. The recent development of rectal Treponema pallidum and rectal Chlamydia trachomatis and lymphogranuloma venereum (LGV) models might help to investigate if doxycycline can prevent rectal infection of Chlamydia trachomatis, LGV, Treponema pallidum, and SHIV as part of an MPT [62,63]. Such studies may inform promising drug combinations, concentrations, and delivery routes and guide their clinical implementation.

CONCLUSION

By incorporating more physiologic repeat virus challenges and precise pharmacologic exposures, current macaque PrEP models can measure efficacy against all routes of sexual HIV transmission in a standardized manner. These PrEP models have to date predicted the clinical efficacy of all currently approved PrEP regimens including oral emtricitabine/tenofovir disoproxil fumarate (daily or “on demand”), oral emtricitabine/tenofovir alafenamide, and cabotegravir long acting in either men or women. This model validation will increase further if ongoing trials such as that of emtricitabine/tenofovir alafenamide in women also reproduces the high efficacy found in macaques. The availability of these models and their ability to predict clinical efficacy is pivotal to the assessment of a promising pipeline of new PrEP agents and modalities including long-acting implants and formulations. As these PrEP models become more standardized and validated, they may raise the possibility of playing a role in future product approval. Current regulatory PrEP product approval relies solely on clinical safety and efficacy conducted in both men and women in large and costly phase 3 clinical trials. Whether validated PrEP macaque models could contribute acceptable efficacy data to extend or expedite regulatory approval requires important deliberation. The concurrent availability of ulcerative and nonulcerative STI macaque models provides an additional preclinical tool to check the vulnerability of a PrEP modality to inflammation and could inform dose modification. The SHIV/STI macaque models will also be invaluable for testing multipurpose prevention products currently under development for HIV/STI prevention.

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KEY POINTS

- The repeat low dose macaque model combines repeated exposures to mimic populations at risk of HIV infection and relevant pharmacology to identify drug correlates of protection
- Studies using the repeat low dose macaque model have predicted the efficacy of the PrEP regimens that are currently approved by the Food and Drug Administration for use in humans including daily oral emtricitabine/tenofovir disoproxil fumarate, daily oral emtricitabine/tenofovir alafenamide, and cabotegravir long acting.
- Incorporation of HIV risk modifiers, such as coinfection with other sexually transmitted infections, allows the evaluation of PrEP under conditions that are difficult to test in humans.
- Macaque studies with oral tenofovir alafenamide, islatravir, and a capsid inhibitor analog of lenacapavir have identified promising new agents for long-acting PrEP.

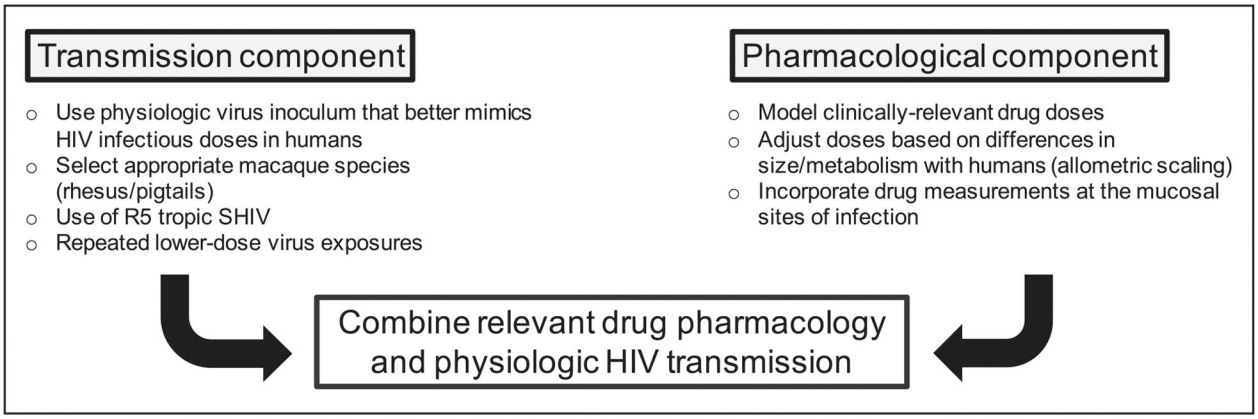

FIGURE 1.
Key considerations for evaluating preexposure prophylaxis strategies macaque models.

Table 1.

Preexposure prophylaxis efficacy estimates with oral emtricitabine/tenofovir disoproxil fumarate, oral emtricitabine/tenofovir alafenamide, and cabotegravir long acting in macaques and humans

PrEP regimen	Macaque				Human		
	Drug doses[a]	Route of SHIV exposure	Biological efficacy	Reference	Efficacy estimate (modified intention to treat)	Efficacy with detectable drug	Reference
Daily oral emtricitabine/tenofovir disoproxil fumarate	20 and 22 mg/kg	Rectal Vaginal Penile	87% 91–100% 92%	[12] [16,17] [15▪]	44–86% 71% 84%	92 −100% 85–90% 85–90%	[25,27] [24,29] [24,29]
On demand oral emtricitabine/tenofovir disoproxil fumarate (double dose)	40 and 44 mg/kg	Rectal	94–100%	[18]	86%	~100%	[28]
Daily oral tenofovir disoproxil fumarate	22 mg/kg	Rectal	57%[b]	[10]	Unknown	-	
Daily oral emtricitabine/tenofovir alafenamide	20 and 1.5 mg/kg	Rectal	100%	[13]		-	[26]
		Vaginal	91%	[20▪▪]			
Cabotegravir long acting	50 mg/kg	Rectal	100%	[11]	68% higher than emtricitabine/ tenofovir disoproxil fumarate	-	[2]
		Vaginal	90–100%	[22,23]	89% higher than emtricitabine/ tenofovir disoproxil fumarate		[3]
		Penile	93%	15▪]	Unknown		
		Intravenous	88%[c]	[21]	Unknown		

[a]Doses adjusted by macaque-human allometric scaling.

[b]$p>0.05$.

[c]Single intravenous SIV challenge.