SUPPLEMENT ARTICLE

Efficacy of HIV Postexposure Prophylaxis: Systematic Review and Meta-analysis of Nonhuman Primate Studies

Cadi Irvine,[1] Kieren J. Egan,[2] Zara Shubber,[3] Koen K. A. Van Rompay,[4] Rachel L. Beanland,[1] and Nathan Ford[1]

[1]Department of HIV/AIDS, World Health Organization, and [2]Department of Mental Health and Psychiatry, University Hospitals of Geneva, Switzerland; [3]Department of Infectious Disease Epidemiology, Imperial College London, United Kingdom; and [4]California National Primate Research Center, University of California, Davis

Background. The efficacy of antiretrovirals as postexposure prophylaxis (PEP) to prevent viral acquisition was demonstrated in nonhuman primate models of human immunodeficiency virus (HIV) in the early 1990s. To complement the evidence base for efficacy of HIV PEP in humans, we systematically reviewed the published data on PEP efficacy across animal studies.

Methods. PubMed, Web of Science, and Embase were searched from inception to 31 May 2014 for randomized and nonrandomized studies reporting seroconversions among uninfected animals exposed to HIV or simian immunodeficiency virus, irrespective of route of exposure. Seroconversion risk data were pooled using random-effects models, and associations explored through meta-regression.

Results. Twenty-five studies (408 primates) were included for review. The risk of serconversion was 89% lower among animals exposed to PEP compared with those that did not receive PEP (odds ratio, 0.11 [95% confidence interval, .05–.23]). Heterogeneity was low ($I^2 = 0.0\%$). In meta-regression, a significant association was found between timing of PEP and seroconversion and the use of tenofovir compared with other drugs.

Conclusions. This review provides further evidence of the protective benefit of PEP in preventing HIV acquisition, and the importance of initiating PEP as early as possible following virus exposure.

Keywords. HIV/AIDS; nonhuman primate; postexposure prophylaxis; transmission.

The efficacy of antiretroviral drugs as postexposure prophylaxis (PEP) to prevent viral infection was first demonstrated in nonhuman primate models in the early 1990s [1, 2], and subsequently shown in humans by a case-control study in 1997 [3]. Because of the ethical difficulties involved in carrying out further studies in humans, subsequent controlled studies of PEP efficacy have been conducted in primate models, especially simian immunodeficiency virus (SIV) infection of macaques [4].

A systematic review of PEP for human occupational human immunodeficiency virus (HIV) exposure concluded that a formal systematic review of all relevant animal studies was warranted because the rationale for PEP is partly based on results from individual primary animal studies [5]. To complement the evidence base for HIV PEP, we systematically reviewed the published data on PEP efficacy across nonhuman primate studies.

METHODS

This systematic review was conducted according to a study protocol following the requirements of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [6].

Search Strategy and Selection Process

We searched online databases (PubMed, Web of Science, and Embase) from inception to 31 May 2014, using a highly sensitive search strategy for each database

Correspondence: Nathan Ford, PhD, Department of HIV/AIDS, World Health Organization, 20 Avenue Appia, 1211 Geneva, Switzerland (fordn@who.int).

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following a predefined study protocol. Randomized and nonrandomized studies were included if they reported seroconversions among uninfected animals exposed to HIV or SIV irrespective of route of exposure and at least 1 animal was subsequently given 1 or more antiretroviral drugs as PEP. Only nonhuman primate studies were included in the final review. Human studies, in vitro studies, and studies where outcomes were not reported were excluded. No date, geographic, or language restrictions were applied.

Data were extracted independently and in duplicate by 2 authors (C. I., Z. S.) using a standardized data extraction form on key study variables including the following outcome variables: number of animals exposed to virus, type, timing and duration of intervention, and number seroconverting. Study quality was assessed using an adapted version of the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies quality checklist, as follows: (1) publication in a peer-reviewed journal, (2) allocation concealment, (3) randomization to treatment or control group, (4) blinded assessment of outcome, (5) sample size calculation, (6) statement of compliance with regulatory requirements, and (7) statement regarding possible conflicts of interest [7].

Data Analysis

To assess the efficacy of the antiretrovirals in preventing virus acquisition, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for each study comparing seroconversion among animals in the intervention group (receiving antiretrovirals) with those who are in the control group (receiving placebo, or untreated controls). In the case of zero outcome events in one arm, the Haldane method was applied, adding 0.5 to each arm [8]. Estimates were pooled using a DerSimonian–Laird random-effects model [9]. Cumulative meta-analysis was used in which the pooled estimates of each study is pooled each time the results of a new study are published to display the accumulation of evidence over time [10]. Heterogeneity was assessed using the I^2 statistic [11]. The potential difference of running a fixed-effects model was explored in sensitivity analysis. Sources of potential study heterogeneity were explored through a preplanned subgroup analysis to assess the influence of number of drugs and duration of PEP on odds of seroconversion. The influence of timing of PEP initiation and type of drug was evaluated through meta-regression. For those animals receiving the intervention, the proportion seroconverting was estimated together with corresponding 95% CIs, and data were transformed to stabilize the variance in the raw proportions prior to meta-regression [12, 13]. Publication bias was assessed for the primary outcome of treatment discontinuation by funnel plot and the Egger's test for small study effects [14]. All analyses were conducted using Stata software, version 12 (StataCorp, College Station, Texas), with a P value <.05 considered to be statistically significant.

RESULTS

From a total of 2517 titles screened, 25 studies were taken through for full review, providing data on 408 primates exposed to HIV or SIV (Figure 1) [1, 15–37]. Studies were conducted across 5 countries (United States, France, Japan, Sweden, and China), between 1990 and 2014 (average, 2002). The main species used were rhesus macaques (10 studies) or cynomolgus monkeys (5 studies). The main route of virus exposure was intravenous exposure (17 studies). The main route of drug administration was subcutaneous administration (10 studies). Three studies were randomized [24, 33,

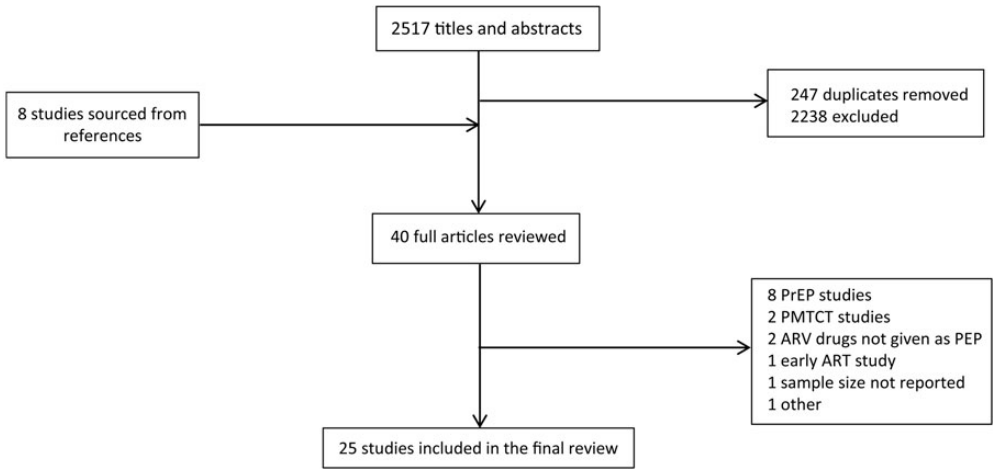

Figure 1. Study selection process. Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; PEP, postexposure prophylaxis; PMTCT, prevention of mother-to-child transmission; PrEP, preexposure prophylaxis.

34], but none reported allocation concealment, blinded assessment of outcomes, or sample size calculations.

Sixteen studies provided evaluable data for the assessment of PEP efficacy comparing PEP (180 primates) against controls (103 primates). The risk of serconversion was 89% lower among animals exposed to PEP compared with those that did not receive PEP (OR, 0.11 [95% CI, .05–.23]). Heterogeneity was low ($I^2 = 0.0\%$). Individual study estimates and pooled results are shown in Figure 2. This result did not differ if a fixed-effects model was used (OR, 0.10 [95% CI, .05–.20]; $I^2 = 0.0\%$). We did not identify evidence of publication bias ($P = .12$).

In subgroup analysis, there was no difference in the odds of seroconversion by number of drugs ($P > .05$); however, this comparison is limited by the fact that the majority of studies (n = 13) administered a single antiretroviral agent as part of PEP. In univariate meta-regression, a significant association was found between timing of PEP and seroconversion (β coefficient < 0.01 [95% CI, <.01–.01]; $P = .03$) Lower seroconversion was also associated with the use of tenofovir compared with other drugs (β coefficient −0.23 [95% CI, −.42 to −.38]; $P = .02$).

DISCUSSION

This work provides the first systematic review and meta-analysis of PEP studies in nonhuman primate models of HIV. We were able to pool data across 18 studies, increasing the confidence in the estimate of the effect of PEP in preventing SIV or HIV acquisition, and found evidence supporting the importance of initiating PEP as early as possible following virus exposure. These findings also demonstrate the growing trend in efficacy as over time studies began to use more potent drugs (eg, tenofovir instead of zidovudine) with more favorable pharmacokinetics, and lower doses of SIV infection that more closely resemble natural HIV infection.

Strengths of this review include a broad search strategy that evaluated >2000 titles, and compliance with standard approaches to limit potential errors and biases that can be introduced in the conduct of systematic reviews. Although we have made every attempt to systematically and robustly explore these data, there are a number of limitations that should be considered. The overall quality of the included studies was relatively low and no study performed a sample size calculation, and as such, our review may include studies that are underpowered.

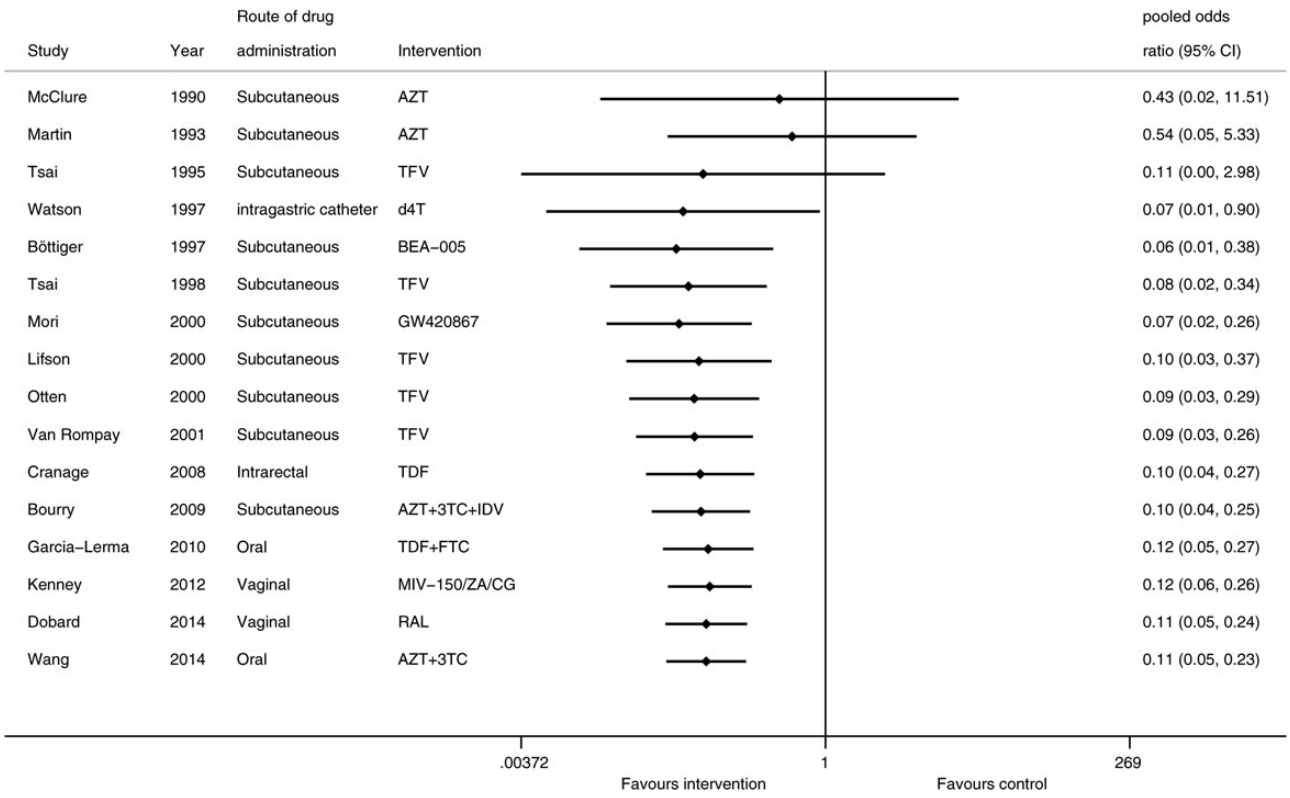

Figure 2. Cumulative meta-analysis of the pooled odds of seroconversion. Abbreviations: 3TC, lamivudine; AZT, azidothymidine; BEA-005, 2′,3′-dideoxy-3′-hydroxymethyl cytidine; CG, carregeenan gel; CI, confidence interval; d4T, stavudine; FTC, emtricitabine; IDV, indinavir; RAL, raltegravir; TDF, tenofovir disoproxyl fumarate; TFV, tenofovir; ZA, zinc acetate.

In addition, previous animal review work has suggested that an absence of blinding or randomization can have an impact on observed outcomes [38]. The inconsistency in reporting of data across studies limited our ability to assess other outcomes that could potentially inform clinical practice, notably duration of treatment and number or class of antiretroviral. Although we would have liked to perform a sensitivity analysis for the impact of study quality, it was not possible in the described dataset. Finally, only studies in the public domain are included in this review and although our analyses did not suggest publication bias it is still feasible that reporting and publication bias exist within this literature.

The estimated protective benefit of PEP in this meta-analysis (OR, 0.11 [95% CI, .05–.23]) was greater and more precise than that reported in the case-control study in humans (OR, 0.19 [95% CI, .06–.52]) [3]. These differences may partly be the result of the larger sample size in our study, and may suggest a greater protective efficacy than previously reported, although any inferences derived from animal studies should be interpreted with caution. This emphasis on timing of PEP is in line with the early biological mechanisms of infection illustrating a narrow window of opportunity descriptive of the early stages of viral replication that occur locally before the virus disseminates systemically [39].

Animal models can help to obtain critical pathophysiological information that cannot always be gleaned from human studies. The strengths of the primate model in the case of HIV PEP include (1) the window it provides on critical events that precede the earliest time clinical signs and symptoms of HIV type 1 (HIV-1) infection disease are manifest; (2) ability to control the virus strain and inoculum dose to achieve infection of a high proportion of animals within a known number of exposures; (3) access to relevant tissues in a relevant time frame, which increases chances to directly observe virus–host cell interactions and critical events; and (4) similarities in anatomy, physiology, and immunology of the rhesus macaques to humans, and the general similarities of pathogenic SIV infection to HIV-1 infection in CD4 T-cell depletion, pathology, and AIDS [40].

Beyond informing proof-of-concept of an intervention strategy that can be translated into clinical practice, the purpose of animal model studies can be to prove a hypothesis in a biological system, or to provide a platform for future research. Despite the many similarities of animals models, inherent differences in route of inoculation, virus titer, drug dose, and duration of intervention, as well as innate biological differences, all caution against absolute inferences from animal to human studies. Previous studies [41] have suggested that approximately one-third of highly cited animal research translates at the level of human clinical trials, but in some specific animal model fields there have been suggestions that there is too much noise in the animal data to extrapolate findings directly to clinical trials [42]. Data from animal models—despite their limitations—can guide human clinical trials; however, the results of such trials must also feed back continuously into the animal model, so that the animal models can be further improved to increase their relevance and predictability for subsequent clinical trials.

In conclusion, the findings of this review provide further evidence supporting the use of PEP to reduce the risk of HIV infection following exposure to HIV.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest.

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