Science Advancement & Outreach
A DIVISION OF PETA

1536 16th St. N.W., Washington, DC 20036

Feedback on Future Goals for the NIH HIV Clinical Research Enterprise

Submitted to NextNIAIDHIVNetworks@mail.nih.gov on November 15, 2024

We are writing on behalf of People for the Ethical Treatment of Animals (PETA), which has more than 9 million members and supporters globally, regarding the goals for the next networks of the National Institute of Allergy and Infectious Diseases' (NIAID's) HIV clinical research enterprise. To effectively maintain support for "core discovery and translational research to address gaps in biomedical HIV prevention and treatment, including a vaccine and therapeutic remission or cure,"[1] the Division of AIDS must divest from poorly translatable experiments on animals and fully embrace human-relevant research models. Below, we expand on our recommendations to achieve this objective.

PETA has developed a straightforward plan called the Research Modernization Deal, which utilizes cutting-edge, non-animal methods to advance biomedical research in the U.S. You can access this plan at https://www.peta.org/wp-content/uploads/2020/12/PETA-2021-Research-Modernization-Deal.pdf. Given what we know about animal sentience and the failure of experiments on animals to yield a vaccine or cure for HIV, it is unacceptable for NIAID's Division of AIDS to support, fund, and encourage the continued use of animals to fulfill its mission. The most effective way to increase knowledge about treating, curing, and preventing HIV is to focus on humans, the only species that contracts HIV and develops AIDS and the species at the center of NIH's mission.

To better support discovery and translational HIV research, the Division of AIDS must stop funding research using animals. While HIV can infect and replicate in some non-human primates, it only causes AIDS in humans. Key biological differences account for this disparity, including the human-specific structure of CD4, immune cell receptors, leukocyte antigen genes, and retrovirus restriction factor genes.[2, 3, 4, 5] As a result, experimenters instead infect monkeys with simian immunodeficiency virus (SIV), a virus

[1] Dieffenbach C. Discovery, Development and Delivery for an Increasingly Interconnected HIV Landscape. Published online September 27, 2024. Accessed November 1, 2024. https://www.niaid.nih.gov/news-events/goals-hiv-science-through-2034
[2] Humes D, Emery S, Laws E, Overbaugh J. A Species-Specific Amino Acid Difference in the Macaque CD4 Receptor Restricts Replication by Global Circulating HIV-1 Variants Representing Viruses from Recent Infection. J Virol. 2012;86(23):12472-12483. doi:10.1128/JVI.02176-12
[3] Kumar N, Chahroudi A, Silvestri G. Animal models to achieve an HIV cure. Curr Opin HIV AIDS. 2016;11(4):432-441. doi:10.1097/COH.0000000000000290
[4] Song B, Javanbakht H, Perron M, Park DH, Stremlau M, Sodroski J. Retrovirus Restriction by TRIM5α Variants from Old World and New World Primates. J Virol. 2005;79(7):3930-3937. doi:10.1128/JVI.79.7.3930-3937.2005
[5] Marshall LJ, Bailey J, Cassotta M, Herrmann K, Pistollato F. Poor Translatability of Biomedical Research Using Animals — A Narrative Review. Altern Lab Anim. 2023;51(2):102-135. doi:10.1177/02611929231157756

unique to African primates; but the genetic similarity between HIV and SIV is only 55%, and SIV is less genetically diverse than HIV.[6,7] Differences in surface proteins and other molecular markers mean that antibodies that neutralize SIV have no effect on HIV and vice versa, rendering SIV studies in primates virtually irrelevant for HIV research.[8] Consequently, while dozens of vaccine candidates have been developed using monkeys, few have reached human trials and all have failed.[9] Two clinical trials even resulted in an *increased* likelihood of infection in humans.[10, 11] The use of primates for HIV research is not a viable or reliable option, nor is the use of "humanized" mice, which have limited longevity with disease and retain their murine immune systems.[12] Humanized mice have also failed to yield useful results for clinical HIV/AIDS treatment.

The Division of AIDS must invest in human-relevant, non-animal methods of HIV/AIDS research. To develop effective interventions, drugs, and vaccines for HIV, researchers must first achieve a comprehensive understanding of HIV infection in *humans*. This necessitates testing therapeutics and prophylactics using human biology. Human cell-based models, computational modeling, bioinformatics, organ-on-a-chip technologies, and human blood sample analyses are just a few methods than can address these needs. For example, researchers worldwide are studying the immune cells of individuals labeled "HIV controllers," who become infected with HIV but can control the spread of the virus without therapeutic intervention.[13, 14, 15, 16, 17] Other examples include using interactive molecular dynamics

---

[6] Antony JM, MacDonald KS. A critical analysis of the cynomolgus macaque, Macaca fascicularis, as a model to test HIV-1/SIV vaccine efficacy. Vaccine. 2015;33(27):3073-3083. doi:10.1016/j.vaccine.2014.12.004

[7] Centlivre M, Combadière B. New challenges in modern vaccinology. BMC Immunol. 2015;16(1):18. doi:10.1186/s12865-015-0075-2

[8] Haigwood NL. Update on animal models for HIV research. Eur J Immunol. 2009;39(8):1994-1999. doi:10.1002/eji.200939576

[9] National Institute of Allergy and Infectious Diseases. History of HIV vaccine research. October 22, 2018. Accessed February 8, 2022. https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-research-history

[10] Sekaly RP. The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development? J Exp Med. 2008;205(1):7-12. doi:10.1084/jem.20072681

[11] PreEPVacc. HIV vaccines tested in PrEPVacc fail to reduce infections. July 23, 2024. Accessed October 18, 2024. https://www.prepvacc.org/news/hiv-vaccines-tested-in-prepvacc-fail-to-reduce-infections-23-july-news-release

[12] Haigwood

[13] Galperin M, Farenc C, Mukhopadhyay M, et al. CD4 + T cell–mediated HLA class II cross-restriction in HIV controllers. Sci Immunol. 2018;3(24):eaat0687. doi:10.1126/sciimmunol.aat0687

[14] Claireaux M, Robinot R, Kervevan J, et al. Low CCR5 expression protects HIV-specific CD4+ T cells of elite controllers from viral entry. Nat Commun. 2022;13(1):521. doi:10.1038/s41467-022-28130-0

[15] Etemad B, Sun X, Li Y, et al. HIV post-treatment controllers have distinct immunological and virological features. Proc Natl Acad Sci. 2023;120(11):e2218960120. doi:10.1073/pnas.2218960120

[16] Kennedy BD, Blazkova J, Justement JS, et al. Comprehensive analysis of HIV reservoirs in elite controllers. J Clin Invest. 2023;133(3):e165446. doi:10.1172/JCI165446

[17] Real LM, Sáez ME, Corma-Gómez A, et al. A metagenome-wide association study of HIV disease progression in HIV controllers. iScience. 2023;26(7):107214. doi:10.1016/j.isci.2023.107214

simulations to predict drug molecule binding to HIV proteins,[18, 19, 20, 21] novel imaging techniques to uncover aspects of HIV structure that could lead to new therapies,[22] bioinformatics analyses of specimens from individuals with viremia to identify phenotypes of HIV-susceptible cells,[23] and single-cell multi-omic analysis of healthy and HIV infected donors to identify differences in T-cell populations, protein expression, and glycan expression relevant for developing immune-targeted therapies.[24, 25, 26]

In addition to redirecting resources away from experiments on animals and towards human-relevant models, funds currently allocated to animal studies can instead support HIV prevention, training or retraining researchers in non-animal HIV methods, and systematic reviews of HIV research to ensure funding decisions address gaps in biomedical HIV prevention and treatment. Technologies for animal-free research are becoming more available and showing their efficacy.

However, academic programs still rely heavily on animal-based research despite the translation and reproducibility issues associated with HIV studies using animals. Many HIV researchers spent their formative training years learning to use animal models and lack the time, funding, and institutional support necessary to transition to new human-relevant research methods. Therefore, the Division of AIDS could collaborate with institutions to develop and offer training grants, continuing education grants, and early independence awards for early career researchers to foster the implementation of non-animal research methods for HIV studies. Additional funding streams could also be established for more senior HIV researchers to train in these newer methods, enabling them to transition their laboratories toward animal-free technologies. Opportunities for education and hands-on training in non-animal methods have

[18] Deeks HM, Walters RK, Hare SR, O'Connor MB, Mulholland AJ, Glowacki DR. Interactive molecular dynamics in virtual reality for accurate flexible protein-ligand docking. Paci E, ed. PLOS ONE. 2020;15(3):e0228461. doi:10.1371/journal.pone.0228461

[19] Baassi M, Moussaoui M, Soufi H, et al. Towards designing of a potential new HIV-1 protease inhibitor using QSAR study in combination with Molecular docking and Molecular dynamics simulations. Ghosh A, ed. PLOS ONE. 2023;18(4):e0284539. doi:10.1371/journal.pone.0284539

[20] Wang R, Zheng Q. Multiple Molecular Dynamics Simulations and Energy Analysis Unravel the Dynamic Properties and Binding Mechanism of Mutants HIV-1 Protease with DRV and CA-p2. Sinclair A, ed. Microbiol Spectr. 2022;10(2):e00748-21. doi:10.1128/spectrum.00748-21

[21] Zhang YJ, Chen L, Xu J, et al. Evaluation of novel HIV-1 protease inhibitors with DRV-resistance by utilizing 3D-QSAR molecular docking and molecular dynamics simulation. New J Chem. 2022;46(45):21885-21897. doi:10.1039/D2NJ04492G

[22] Saha I, Saffarian S. Dynamics of the HIV Gag Lattice Detected by Localization Correlation Analysis and Time-Lapse iPALM. Biophys J. 2020;119(3):581-592. doi:10.1016/j.bpj.2020.06.023

[23] Xie G, Luo X, Ma T, et al. Characterization of HIV-induced remodeling reveals differences in infection susceptibility of memory CD4+ T cell subsets in vivo. Cell Rep. 2021;35(4):109038. doi:10.1016/j.celrep.2021.109038

[24] Collora JA, Liu R, Pinto-Santini D, et al. Single-cell multiomics reveals persistence of HIV-1 in expanded cytotoxic T cell clones. Immunity. 2022;55(6):1013-1031.e7. doi:10.1016/j.immuni.2022.03.004

[25] Ma T, McGregor M, Giron L, et al. Single-cell glycomics analysis by CyTOF-Lec reveals glycan features defining cells differentially susceptible to HIV. eLife. 2022;11:e78870. doi:10.7554/eLife.78870

[26] Wang R, Li Z, Liu S, Zhang D. Global, regional, and national burden of 10 digestive diseases in 204 countries and territories from 1990 to 2019. Front Public Health. 2023;11:1061453. doi:10.3389/fpubh.2023.1061453

been created in other countries and should be replicated in the U.S. For example, in the EU, the European Commission Joint Research Center hosts a summer school on non-animal approaches.[27]

An HIV vaccine is urgently needed, regardless of the currently available therapies, such as anti-retroviral therapy (cART), which must be taken for life and are associated with morbidities.[28] Thus, a systematic review should be funded by the Division of AIDS to provide evidence on whether the animal research currently being supported is progressing toward a vaccine or cure. Systematic reviews critically analyze the breadth of available research studies and can be used to assess the effectiveness of animal use. Some countries recommend conducting systematic reviews before funding studies.[29] In addition, several U.S. funding entities, including the NIH, are members of the Ensuring Value in Research Funder Forum (EViR), an international collaboration aimed at addressing waste in clinical and preclinical research. EViR advocates that research should only be funded if existing systematic reviews for the area of study are available,[30, 31] thereby preventing unnecessary duplication and poorly designed studies that waste taxpayer dollars.[32] The evidence produced by systematic reviews can enhance scientific quality by evaluating the internal, external, or construct validity of the models used for HIV research.[33] Many resources are available for conducting systematic reviews.[34, 35] The NIH should already be conducting systematic reviews to ensure taxpayer dollars are funding robust and valuable research and not wasting funding.

PETA recently funded a systematic review on the use of non-human primates for HIV vaccine efficacy testing, comparing data from non-human primate studies to human clinical trials.[36] We expect the results in 2025 and will share them with the Division of AIDS, but additional questions about animal models for HIV research will remain. Importantly, it should not be the responsibility of non-profit advocacy organizations to fund this work. The funding bodies issuing grants for the research should take the necessary steps to confirm they do so in an evidence-based manner.

---

[27] EU Science Hub. JRC Virtual Summer School on "Non-animal approaches in science: The three r...evolution." Accessed November 1, 2024. https://joint-research-centre.ec.europa.eu/ events/jrc-summer-school-non-animal-approaches-science-3_en

[28] Marshall, *et al.*

[29] Hooijmans CR, Ritskes-Hoitinga M. Progress in Using Systematic Reviews of Animal Studies to Improve Translational Research. PLoS Med. 2013;10(7):e1001482. doi:10.1371/journal.pmed.1001482

[30] EViR Guiding principles. Published online 2021. Accessed November 1, 2024. https://evir.org/our-principles/

[31] EViR Applying the principles. Published online 2021. Accessed November 1, 2024. https://evir.org/our-principles/ applying-the-principles

[32] Hooijmans CR, IntHout J, Ritskes-Hoitinga M, Rovers MM. Meta-Analyses of Animal Studies: An Introduction of a Valuable Instrument to Further Improve Healthcare. ILAR J. 2014;55(3):418-426. doi:10.1093/ilar/ilu042

[33] Herrmann K, Jayne K, eds. Animal Experimentation: Working Towards a Paradigm Change. BRILL; 2019. doi:10.1163/9789004391192

[34] CAMARADES. Bringing Evidence to Translational Medicine. Published online 2014. Accessed November 4, 2024. http://www.dcn.ed.ac.uk/camarades/default.htm

[35] Leenaars M, Hooijmans CR, Van Veggel N, et al. A step-by-step guide to systematically identify all relevant animal studies. Lab Anim. 2012;46(1):24-31. doi:10.1258/la.2011.011087

[36] Leenaars C, Hattem A van, Struijs F, Menon J. A systematic review of the efficacy of candidate HIV vaccines in non-human primates and humans. PROSPERO. 2023. Accessed November 14, 2024. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=495529

In summary, the Division of AIDS should shift resources away from experiments on animals and toward human-relevant, non-animal HIV studies; HIV prevention research and implementation; training opportunities for researchers on non-animal HIV methods; and systematic reviews of currently funded animal studies. By doing so, the Division of AIDS will be able to confidently support discovery and translational research that effectively leads to a vaccine or therapeutic cure for HIV and reduce the incidence of HIV infection and the development of AIDS.