Opinion

Microbiology

Can We Realize a Functional Cure of HIV?

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Despite significant advances in antiretroviral therapy (ART), which have transformed HIV from a fatal disease into a manageable chronic condition, a definitive cure remains elusive. Functional cure, defined as durable viral remission without ongoing therapy, represents a realistic yet ambitious goal that could drastically reduce global morbidity, mortality, and transmission. Achieving this requires addressing the complex challenges posed by viral reservoirs, immune evasion, and viral latency. Recent advances in gene editing, immunotherapy, and latency-reversing agents offer promising avenues, yet each approach faces scientific, logistical, and ethical hurdles. This article argues that while a sterilizing cure—complete eradication of the virus—is currently impractical, a functional cure may be attainable through coordinated strategies that combine ART, immune modulation, and innovative biomedical interventions. By critically examining current research and emerging technologies, we can envision a future in which HIV is controlled without daily therapy, reshaping both clinical practice and global public health strategies.

Keywords: HIV; Functional Cure; Antiretroviral Therapy; Viral Reservoirs; Immunotherapy

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THE HUMAN immunodeficiency virus (HIV) remains one of the most formidable public health challenges of the modern era. Since its identification in the early 1980s, significant progress has been made in understanding its pathogenesis, transmission dynamics, and treatment. Antiretroviral therapy (ART) has transformed HIV infection from an almost universally fatal disease into a chronic condition compatible with long-term survival (Deeks et al., 2013). Patients on consistent ART can achieve viral suppression, immune reconstitution, and a dramatically reduced risk of transmission, a concept now summarized as "undetectable equals untransmittable" (Eisinger et al., 2019). Yet, ART is not a cure: treatment must be lifelong, adherence challenges persist, and residual viral reservoirs remain a source of latent infection and viral rebound upon therapy cessation (Siliciano & Siliciano, 2016). In this context, the concept of a *functional cure*—sustained viral remission

without ongoing ART—has emerged as a pragmatic and clinically meaningful goal.

The challenge in realizing a functional cure lies in the unique biology of HIV. Unlike many other viruses, HIV establishes latent reservoirs early in infection. These reservoirs, composed primarily of resting memory CD4+ T cells and other long-lived cellular compartments, harbor replication-competent virus that is transcriptionally silent and therefore invisible to immune surveillance and unaffected by ART (Chun et al., 2015; Siliciano & Siliciano, 2016). Even in individuals with decades of viral suppression, these reservoirs can rapidly reignite infection if therapy is interrupted (Pitman et al., 2018). Functional cure strategies must therefore eliminate these reservoirs, permanently silence proviral transcription, or enable immune-mediated control sufficient to prevent viral rebound (Cillo & Mellors, 2016). Understanding reservoir dynamics, tissue distribution, and persistence remains central to cure research.

One promising avenue for achieving a functional cure involves immune modulation and enhancement. Broadly neutralizing antibodies (bNAbs) have demonstrated the ability to suppress viral replication, delay viral rebound following ART interruption, and enhance immune-mediated clearance of infected cells in both animal models and human studies (Barouch et al., 2013; Caskey et al., 2015). These antibodies may be administered passively or induced through vaccination strategies. In parallel, chimeric antigen receptor (CAR) T cell therapies—adapted from cancer immunotherapy—are being explored as a means of redirecting cytotoxic immune responses toward HIV-infected cells with high specificity (Liu et al., 2016). By combining immune enhancement with ART or latency-targeting strategies, researchers aim to enable the immune system to autonomously maintain viral suppression, a defining feature of a functional cure.

Latency-reversing agents (LRAs) represent another major pillar in functional cure research. These agents are designed to induce transcription of latent provirus, thereby exposing infected cells to immune-mediated elimination while ART prevents new rounds of infection—a strategy commonly described as "shock and kill" (Archin et al., 2014; Margolis et al., 2016). Although preclinical and early clinical studies have demonstrated that LRAs can induce viral transcription, meaningful reductions in reservoir size have been limited (Pitman et al., 2018). Heterogeneity in latency mechanisms, immune exhaustion, and off-target toxicities complicate implementation (Margolis et al., 2016). Nevertheless, LRAs may still play a role as part of combination approaches that reduce reservoir size below a threshold compatible with durable immune control.

Gene-editing technologies offer a particularly compelling, though complex, pathway toward functional cure. CRISPR/Cas9-based approaches have been used experimentally to excise or inactivate proviral DNA and to modify host genes essential for viral entry, such as the CCR5 co-receptor (Saayman et al., 2015; Xu et al., 2019). The cases of the "Berlin patient" and the "London patient," who achieved long-term HIV remission following CCR5Δ32/Δ32 hematopoietic stem cell transplantation, provide proof of principle that eliminating CCR5-expressing target cells can lead to sustained viral control (Hütter et al., 2009; Gupta et al., 2019). However, these interventions involved high-risk procedures not scalable to the broader population. Advances in in vivo gene delivery, precision editing, and safety optimization may eventually enable less invasive strategies capable of conferring functional resistance to HIV.

While these biomedical strategies are promising, achieving a functional cure will almost certainly require integrated, combinatorial approaches. Monotherapies have thus far proven insufficient given HIV's resilience and adaptability (Pitman et al., 2018). Rational combinations of ART, immune modulation, latency reversal, and gene editing may offer synergistic benefits capable of sustaining viral remission (Lewin et al., 2020). Importantly, functional cure research must prioritize global applicability. Interventions must be safe, affordable, and feasible in low- and middle-income countries, where the burden of HIV remains highest (UNAIDS, 2023).

Ethical considerations are central to the pursuit of a functional cure. Experimental interventions such as gene editing and immune-based therapies carry inherent risks, particularly when tested in otherwise clinically stable individuals on effective ART. Ethical trial design requires rigorous risk–benefit assessment, informed consent, and long-term monitoring (Tucker et al., 2018). Additionally, cure research must avoid exacerbating stigma or inequities by limiting access to certain populations or regions. Social, cultural, and structural dimensions of HIV care are inseparable from biomedical innovation.

It is essential to recognize that a functional cure does not imply eradication of HIV. Unlike a sterilizing cure, which seeks to eliminate all replication-competent virus, a functional cure accepts the persistence of residual virus while maintaining it below clinically significant thresholds. This reframing shifts the goal of HIV research toward durable remission, reduced treatment burden, preserved quality of life, and prevention of transmission—outcomes with substantial individual and public health benefits (Deeks et al., 2013).

The timeline for achieving functional cures remains uncertain. Although advances in immunotherapy, gene editing, and virology are rapid, translating these discoveries into safe, scalable, and affordable interventions will require sustained investment, interdisciplinary collaboration, and careful long-term evaluation (Lewin et al., 2020). Monitoring viral rebound, immune competence, and late adverse effects will be critical in determining whether functional cure strategies deliver durable benefit.

In conclusion, while a sterilizing cure for HIV remains elusive, a functional cure represents a realistic and transformative objective. By integrating ART with immune enhancement, latency-targeting strategies, and emerging gene-editing technologies, durable viral remission without continuous therapy may be achievable (Siliciano & Siliciano, 2016). Achieving this goal will require scientific rigor, ethical vigilance, and equitable implementation. If successful, the functional cure paradigm could redefine HIV care, transforming a lifelong pharmacological dependency into a condition controllable through sustained biological remission and bringing the global community closer to ending the HIV epidemic. ■

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References

Archin, N. M., Sung, J. M., Garrido, C., Soriano-Sarabia, N., & Margolis, D. M. (2014). Eradicating HIV-1 infection: Seeking to clear a persistent pathogen. Nature Reviews Microbiology, 12(11), 750–764. DOI: https://doi.org/10.1038/nrmicro3352

Barouch, D. H., Whitney, J. B., Moldt, B., et al. (2013). Therapeutic efficacy of potent neutralizing HIV-1–specific monoclonal antibodies in SHIV-infected rhesus monkeys. Nature, 503(7475), 224–228. DOI: https://doi.org/10.1038/nature12744

Caskey, M., Klein, F., Lorenzi, J. C. C., et al. (2015). Viraemia suppressed in HIV-1–infected humans by broadly neutralizing antibody 3BNC117. Nature, 522(7557), 487–491. DOI: https://doi.org/10.1038/nature14411

Chun, T. W., Moir, S., & Fauci, A. S. (2015). HIV reservoirs as obstacles and opportunities for an HIV cure. Nature Immunology, 16(6), 584–589. DOI: https://doi.org/10.1038/ni.3152

Cillo, A. R., Mellors, J. W. (2016). Which therapeutic strategy will achieve a cure for HIV-1? Current Opinion in Virology, 18, 14–19. DOI: https://doi.org/10.1016/j.coviro.2016.02.003

Deeks, S. G., Lewin, S. R., & Havlir, D. V. (2013). The end of AIDS: HIV infection as a chronic disease. The Lancet, 382(9903), 1525–1533. DOI: https://doi.org/10.1016/S0140-6736(13)61809-7

Eisinger, R. W., Dieffenbach, C. W., & Fauci, A. S. (2019). HIV viral load and transmissibility of HIV infection: Undetectable equals untransmittable. JAMA, 321(5), 451–452.DOI: https://doi.org/10.1001/jama.2018.21167

Finzi, D., Blankson, J., Siliciano, J. D., et al. (1999). Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1. Nature Medicine, 5, 512–517. DOI: https://doi.org/10.1038/8394

Gupta, R. K., Abdul-Jawad, S., McCoy, L. E., et al. (2019). HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. Nature, 568(7751), 244–248. DOI: https://doi.org/10.1038/s41586-019-1027-4

Hütter, G., Nowak, D., Mossner, M., et al. (2009/long-term follow-up relevance). Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. New England Journal of Medicine, 360(7), 692–698. DOI: https://doi.org/10.1056/NEJMoa0802905

Lewin, S. R., Attoye, T., Bansbach, C., Doehle, B., Dubé, K., Dybul, M., SenGupta, D., Jiang, A., Johnston, R., Lamplough, R., McCune, J. M., Nabel, G. J., Ndung'u, T., Pottage, J., Ripin, D., Rooney, J. F., Sikazwe, I., Nsubuga, M., Warren, M., Deeks, S. G., … Sunnylands 2019 Working Group (2021). Multi-stakeholder consensus on a target product profile for an HIV cure. The lancet. HIV, 8(1), e42–e50. DOI: https://doi.org/10.1016/S2352-3018(20)30234-4

Liu, B., Zou, F., Lu, L., Chen, C., He, D., Zhang, X., Tang, X., Liu, C., Li, L., & Zhang, H. (2016). Chimeric Antigen Receptor T Cells Guided by the Single-Chain Fv of a Broadly Neutralizing Antibody Specifically and Effectively Eradicate Virus Reactivated from Latency in CD4+ T Lymphocytes Isolated from HIV-1-Infected Individuals Receiving Suppressive Combined Antiretroviral Therapy. Journal of virology, 90(21), 9712–9724. DOI: https://doi.org/10.1128/JVI.00852-16

Margolis, D. M., Garcia, J. V., Hazuda, D. J., & Haynes, B. F. (2016). Latency reversal and viral clearance to cure HIV-1. Science, 353(6297), aaf6517. DOI: https://doi.org/10.1126/science.aaf6517

Pitman, M. C., Lau, J. S. Y., McMahon, J. H., & Lewin, S. R. (2018). Barriers and strategies to achieve a cure for HIV. The Lancet HIV, 5(6), e317–e328. DOI: https://doi.org/10.1016/S2352-3018(18)30039-0

Saayman, S. M., Lazar, D. C., Scott, T. A., et al. (2015). Potent and targeted activation of latent HIV-1 using the CRISPR/dCas9 activator complex. Molecular Therapy, 24(3), 488–498. DOI: https://doi.org/10.1038/mt.2015.202

Siliciano, J. D., & Siliciano, R. F. (2014). Recent developments in the search for a cure for HIV-1 infection: targeting the latent reservoir for HIV-1. The Journal of Allergy and Clinical Immunology, 134(1), 12–19. DOI: https://doi.org/10.1016/j.jaci.2014.05.026

Tucker, J. D., Rennie, S., & Sugarman, J. (2018). Social and ethical implications of HIV cure research. Journal of the International AIDS Society, 21(1), e25072. DOI: https://doi.org/10.1002/jia2.25072

UNAIDS. (2023). Global AIDS update 2023: The path that ends AIDS. https://www.unaids.org

Xu, L., Yang, H., Gao, Y., et al. (2019). CRISPR/Cas9-mediated CCR5 ablation in human hematopoietic stem/progenitor cells confers HIV-1 resistance in vivo. Molecular Therapy, 27(11), 1785–1796. DOI: https://doi.org/10.1016/j.ymthe.2019.08.004.