Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Editorial: Anti-infective 2020: HIV—From pathogenesis to treatment

Leonor Huerta

Current Opinion in Pharmacology 2020, **54:**x–xii

This review comes from a themed issue on **Anti Infectives**

Edited by **Leonor Huerta**

https://doi.org/10.1016/j.coph.2020.12.001

1471-4892/

Leonor Huerta
Instituto de Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico
*Corresponding author. Huerta, Leonor
e-mail: leonorhh@biomedicas.unam.mx

Dr. Leonor Huerta is an immunologist and virologist from the Instituto de Investigaciones Biomédicas of the Universidad Nacional Autónoma de México (UNAM). She received a Doctoral degree in Basic Biomedical Research in 2004 under the direction of Dr. Carlos Larralde. Currently she is a full-time assistant investigator of the Department of Immunology at the same institution. She is also a member of the National System of Investigators. Her main research interests are the biology of the HIV envelope-dependent cell–cell fusion, the antibody immune response in the HIV infection, the inhibition of HIV replication by small compounds, and the mathematical modeling of T-lymphocyte function. She has conducted research involving HIV$^+$ individuals and has obtained financial support from the Consejo Nacional de Ciencia y Tecnología de México. She is author of research articles and book chapters and thesis advisor for graduated students.

In spite of the success of a number of vaccines in controlling or eradicating infectious diseases, global social conditions remain as effective breeding grounds for the emergence of new pathogens, as has been shown by the epidemics of HIV and SARS-Cov-2, the virus causing the coronavirus disease 2019 (COVID-19), to cite those viral infections that have affected a significant number of people [1,2]. Although strategies for effective, organized surveillance, and prevention measures should be routinely implemented, there is a constant need for new forms of treatment.

HIV is an enveloped virus that has a special tropism by cells of the immune system, in which it replicates. The virus produces an acute infection that subsequently persists as a mostly asymptomatic disease in the majority of HIV$^+$ individuals, while causing cumulative deleterious effects on immune function. Key findings that relate to the mechanism of AIDS pathogenesis frame the search for new therapeutic approaches and include the following list.

i) Gut mucosal immunity is seriously damaged early in the infection by HIV replication and direct viral cytopathic effects, resulting in the loss of the gut barrier integrity and leading to permeability to microbial products and dysbiosis. The appearance in the circulation of translocated bacterial products is closely linked to the systemic chronic immune activation that drives disease pathogenesis and chronic inflammation, even in patients under antiretroviral therapy (ART) [3,4]
ii) HIV viral particle retention in lymphoid tissues induces local innate and adaptive immune responses to HIV. The sustained activation causes damage to the lymphoid tissue architecture by scarring [5,6], limiting the access of these cells to essential homeostatic factors. This process contributes to immune cell loss and is related to the failure of antiretroviral therapy (ART) to meaningfully increase CD4(+) T-cell populations [7].
iii) The HIV genome is established as a latent virion in different cell types and tissues early in infection. The persistence of latent virus in these reservoirs is perhaps the major barrier to virus eradication [8].

The 2020 Anti-Infective Section of *Current Opinion in Pharmacology* covers established and new approaches to HIV treatment, factors associated with therapeutic efficacy, and the processes favoring replication and persistence of the virus in the organism despite the ART approach. It also includes clinical and preclinical aspects associated with improving treatment. After almost four decades of development, ARTs have proven effective in inducing the long-term suppression of HIV plasma viremia and in increasing patient life expectancy when combined with improvements in health care [9,10]. A treatment regimen against HIV is composed of three or four drugs, commonly referred to as ART or combined antiretroviral therapy (cART). To date, 10 of 23 Food and Drug Administration—approved anti-HIV medicines target the HIV reverse transcriptase (RT) [11]. These are divided into two categories, nucleoside RT inhibitors (NRTIs) and non-NRTIs(NNRTIs).

The review by Vanangamudi et al. [12] from the Vigneshwaran Namasivayam group at the Rheinische Friedrich-Wilhelms-Universität in Bonn, Germany, recapitulates features of clinically available NNRTI drugs and combination regimens, with focus in their pharmacokinetic profiles. Likewise, the review from Shuang-Xi et al. [13] at the Wuhan Institute of Technology, China, compiles research on both NRTIs and NNRTIs and noteworthy drug candidates in different developmental stages, responding to the continuous need of development of new inhibitors to overcome viral genetic resistance to drugs and secondary effects.

While ART is a very significant achievement for treatment of HIV infection, the persistence of the virus in tissues reservoirs remains as the main barrier for cure [8]. Evidence from clinical, cerebrospinal fluid, neuroimaging, and neuropathological data has shown that virus can persist in the central nervous system even in patients under ART who may have undetectable levels of virus in blood. Likewise, approximately 50% of people living with HIV on suppressive antiretroviral therapy are estimated to have some form of HIV-associated neurocognitive disorders. The review by Fletcher et al. [14] from the University of Nebraska Medical Center College of Pharmacy, USA, discusses the physiological and pharmacological features of clinically approved antiretrovirals, with emphasis on organ penetration, association with neurocognitive disorders, and persistence of the infections in pharmacological sanctuaries. Importantly, it proposes particular pharmacological features of drugs that may positively improve sustained viral suppression in the brain and suggests strategies of therapeutic approaches to improve ART activity.

Deficient adherence may lead to the appearance of resistant mutant strains. Long-acting antiretroviral formulations would improve adherence while also helping to prevent transmission of HIV. The results from two Phase III clinical trials, ATLAS-2M and FLAIR, were presented this year in the Conference on Retroviruses and Opportunistic Infections (CROI 2020) and showed the exciting possibility of application of injectable long-acting formulations that were reported as well-tolerated and efficacious. These advances are summarized by Sang et al. [15] from the Fener Chen laboratory at the Harbin Institute of Technology, Harbin, China, along with other modalities of long-acting medication with great potential to prevent the risk of virologic failure, based on sustained drug release such as implants, vaginal rings, and nanotherapies.

RNA interference (RNAi) is a conserved mechanism of gene regulation that has been extensively explored as a therapeutic alternative for viral infections. RNAi therapeutics developed for acute infections (respiratory syncytia virus, Ebolavirus, coronavirus, and bornavirus) have utilized the transient, classic cytoplasmic mRNA degradation mechanism. Instead, novel RNAi mediates epigenetic modifications at the transcriptional levels in the nucleus, to ensure constitutive alteration of the expression of viruses causing chronic infections (HIV-1, human cytomegalovirus, hepatitis B and Epstein—Barr viruses). The review by Kelleher et al. [16] from the Ahlenstiel group at the Kirby Institute, University of New South Wales, Sydney, Australia, compiles basic and applied aspects of RNAi therapeutics for treating acute and chronic viral infections, accompanied by an update on current antiviral RNAi therapeutic clinical trials. The authors also assess the delivery challenges through different presentation and administration routes to get effectiveness (mucosal, respiratory, transdermal, oral or systemic), thus emphasizing the translational aspect of this research field.

The genetic diversity of HIV in a single individual is reflected in the integrated proviral reservoir. The review by Wilson and Lynch [17] *f*rom the Lynch laboratory in the Department of Microbiology, Immunology and Tropical Medicine at George Washington University, Washington DC, USA, summarizes current understanding of the diversity and complexity of the viral reservoir in ART-treated patients and its manifestations after analytical treatment interruption studies, which demonstrated that viremia re-emerges quickly after ART cessation [18,19]. In principle, broadly neutralizing antibodies, which target conserved epitopes of the virus and are highly effective against most circulating strains *in vitro*, represent an alternative to confront the rebound. This promising strategy includes antibody combinations, prescreening individuals for bNAb sensitivity, focusing on low-diversity individuals, and targeting of host proteins.

The equilibrium between the gut microbiota, the intestinal barrier and the mucosal immune system is altered by HIV early in the infection. Local and systemic

inflammatory events are key features of untreated HIV infection and are only partially reversed by ART. Modest results have been obtained when aiming at restoring the mucosal immune system. The review by Rosel-Pech et al. [20] from the Cardoso group at the Instituto Nacional de Enfermedades Respiratorias, Mexico City, México, discusses the current evidence supporting a role for microbial dysbiosis in HIV pathogenesis. The authors show that after controlling for sexual preference [21] and gender, gut microbiota alterations present in HIV infection are linked to metabolic syndromes. Therapeutic approaches using fecal microbiota transplantation to restore the mucosal immune system and the gut barrier by increasing the abundance of bacteria with immunomodulatory properties, however, remain at an early stage of investigation.

The topic of HIV is an outstanding example of cooperative efforts to contain a chronic disease with drug combinations and approaches targeted to the pathogenic mechanisms. It is hoped that this collation of reviews on key milestones in the search for AIDS therapies may guide researchers in other chronic disease areas.

References

1. WHO: *Coronavirus disease (COVID-19) dashboard*. 2020. https://covid19.who.int/?gclid=Cj0KCQjw8rT8BRCbARIsALWiOvR0EkrY4m-FfTaVmJq37nPdJepwGSdT9NLFcmOxmMQRpGLhSFJWhLcaAsHeEALw_wcB.
2. HIV/AIDS, data and statistitics. 2020. https://www.who.int/hiv/data/en/.
3. Mehandru Saurabh, Poles Michael A, Tenner-Racz Klara, Manuelli Victoria, Jean-Pierre Patrick, Lopez Peter, Shet Anita, Low Andrea, Mohri Hiroshi, Boden Daniel, Racz Paul, Markowitz Martin: **Mechanisms of gastrointestinal CD4$^+$ T-cell Depletion during acute and early human immunodeficiency virus type 1 infection**. *J Virol* 2006, **81**:599–612.
4. Brenchley J, Price D, Schacker T, *et al.*: **Microbial translocation is a cause of systemic immune activation in chronic HIV infection**. *Nat Med* 2006, **12**:1365–1371.
5. Schacker TW, Brenchley JM, Beilman GJ, Reilly C, Pambuccian SE, Taylor J, Skarda D, Larson M, Douek DC, Haase AT: **Lymphatic tissue fibrosis is associated with reduced numbers of naive CD4+ T cells in human immunodeficiency virus type 1 infection**. *Clin Vaccine Immunol* 2006, **13**:556–560.
6. Huang L, Deng J, Xu W, Wang H, Shi L, Wu F, Zhou X: **CD8+ T cells with high TGF-β1 expression cause lymph node fibrosis following HIV infection**. *Mol Med Rep* 2018, **18**:77–86.
7. Lorenzo-Redondo R, Fryer HR, Bedford T, Kim EY, Archer J, Pond SLK, Chung YS, Penugonda S, Chipman J, Fletcher CV, Schacker TW, Malim MH, Rambaut A, Haase AT, McLean AR, Wolinsky SM: **Persistent HIV-1 replication maintains the tissue reservoir during therapy**. *Nature* 2016, **530**:51–56.
8. Pitman MC, Lau JSY, McMahon JH, Lewin SR: **Barriers and strategies to achieve a cure for HIV**. *Lancet HIV* 2018, **5**:e317–e328.
9. Antiretroviral Therapy Cohort Collaboration: **Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies**. *Lancet HIV* 2017, **4**:e349–e356.
10. Katz IT, Maughan-Brown B: **Improved life expectancy of people living with HIV: who is left behind?** *Lancet HIV* 2017, **4**:e324–e326.
11. *FDA-Approved HIV Medicines*. September 28, 2020. HIVinfo.NIH.gov. https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines.
12. Vanangamudi, *et al.*: **Non-nucleoside reverse transcriptase inhibitors (NNRTIs): a brief overview of clinically approved drugs and combination regimens**. *Curr Opin Pharmacol* 2020 [THIS ISSUE].
13. Shuang-Xi Gu, *et al.*: **Recent discoveries in HIV-1 reverse transcriptase inhibitors**. *Curr Opin Pharmacol* 2020 [THIS ISSUE].
14. Courtney V Fletcher and colleagues: **Pharmacologic approaches to HIV-associated neurocognitive disorders**. *Curr Opin Pharmacol* 2020 [THIS ISSUE].
15. Sang, *et al.*: **Design strategies for long-acting anti-HIV pharmaceuticals**. *Curr Opin Pharmacol* 2020 [THIS ISSUE].
16. Kelleher, *et al.*: **RNAi therapeutics: an antiviral strategy for human infections**. *Curr Opin Pharmacol* 2020.
17. Wilson, Lynch: **Embracing diversity: how can broadly neutralizing antibodies effectively target adverse HIV-1 reservoir?** *Curr Opin Pharmacol* 2020 [THIS ISSUE].
18. Rothenberger MK, Keele BF, Wietgrefe SW, Fletcher CV, Beilman GJ, Chipman JG, Khoruts A, Estes JD, Anderson J, Callisto SP, *et al.*: **Large number of rebounding/founder HIV variants emerge from multifocal infection in lymphatic tissues after treatment interruption**. *Proc Natl Acad Sci USA* 2015, **112**:E1126–E1134.
19. Colby DJ, Trautmann L, Pinyakorn S, Leyre L, Pagliuzza AXL, Kroon EXN, Rolland M, Takata H, Buranapraditkun S, Intasan J, *et al.*: **Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection**. *Nat Med* 2018, **24**:923–926.
20. Rosel-Pech, *et al.*: **Therapeutic avenues for restoring the gut microbiome in HIV infection**. *Curr Opin Pharmacol* 2020 [THIS ISSUE].
21. Noguera-Julian M, Rocafort M, Guillén Y, Rivera J, Casadellà M, Nowak P, Hildebrand F, Zeller G, Parera M, Bellido R, Rodríguez C, Carrillo J, Mothe B, Coll J, Bravo I, Estany C, Herrero C, Saz J, Sirera G, Torrela A, Navarro J, Crespo M, Brander C, Negredo E, Blanco J, Guarner F, Calle ML, Bork P, Sönnerborg A, Clotet B, Paredes R: **Gut microbiota linked to sexual preference and HIV infection**. *EBio Med* 2016, **5**:135–146.