Antiretroviral agents against human immunodeficiency virus: an overview of current drugs and new perspectives

Agentes antiretrovirais contra o vírus da imunodeficiência humana: uma visão geral das drogas atuais e novas perspectivas

Ingrid Barcelos de Oliveira[1,2], Claudio Cesar Cirne-Santos[1,2], Caroline de Souza Barros[3], Rosa Teixeira Pinho[4], Izabel Christina Nunes de Palmer Paixão[1,2]

ABSTRACT

Introduction: Since its discovery in the 1980s, the human immunodeficiency virus (HIV) has been the target of many studies. Nowadays, estimates show that 36.7 million people are infected with HIV worldwide. In Brazil, HIV infection overcomes 840 thousand people. Globally, only 53% of the HIV infected people are under antiretroviral therapy. Significant advances in antiretroviral therapy have been made since the introduction of zidovudine in 1987. **Objective:** To advance the discoveries of the available antivirals demonstrating their functional specificities. **Methods:** We performed a systematic review with a bibliographic survey in the Index Medicus/MEDLINE and PubMed databases for periodical and indexed articles, from 2013 to 2018 that reported on antiretrovirals used or not in the clinical practice. **Results:** Currently, there are six classes of antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), entry inhibitors (CCRIs), and HIV integrase strand transfer inhibitors (INIs or INSTIs). In summary, several antiretroviral agents under development make HIV entry, reverse transcription, integration, and maturation emerging drug become targets. **Conclusion:** A multifaceted approach to antiretroviral therapy, using combinations of inhibitors that target different steps of the viral life cycle, has the best potential for long-term control of HIV infection.

Keywords: AIDS; HIV; antiretroviral therapy, highly active.

RESUMO

Introdução: Desde sua descoberta na década de 1980, o vírus da imunodeficiência humana (HIV) tem sido alvo de muitos estudos. Atualmente, as estimativas mostram que 36,7 milhões de pessoas estão infectadas pelo HIV em todo o mundo. No Brasil, a infecção pelo HIV supera 840 mil pessoas. Globalmente, apenas 53% das pessoas infectadas pelo HIV estão sob terapia antirretroviral. Avanços significativos na terapia antirretroviral (TARV) foram feitos desde a introdução da zidovudina (AZT) em 1987. **Objetivo:** O objetivo deste estudo foi descrever a descoberta dos antivirais disponíveis atualmente, demonstrando suas especificidades funcionais. **Métodos:** Foi realizada uma revisão sistemática com levantamento bibliográfico nas bases de dados Index Medicus/MEDLINE e PubMed para artigos periódicos e indexados, no período de 2013 a 2018, que relataram antirretrovirais utilizados ou não na prática clínica. **Resultados:** Atualmente, existem seis classes de medicamentos antirretrovirais: inibidores nucleosídeos da transcriptase reversa (NRTIs), inibidores não-nucleosídeos da transcriptase reversa (NNRTIs), inibidores da protease (IPs), inibidores de fusão (FIs), inibidores de entrada (CCRIs) e transferência da cadeia da integrase do HIV inibidores (INIs ou INSTIs). Em resumo, vários agentes antirretrovirais em desenvolvimento fazem da entrada do HIV, da transcrição reversa, da integração e da maturação, alvos dos medicamentos emergentes. **Conclusão:** Uma abordagem multifacetada para a TAR, usando combinações de inibidores que visam diferentes etapas do ciclo de vida viral, tem o melhor potencial para o controle da infecção pelo HIV a longo prazo.

Palavras-chave: AIDS, HIV, terapia antirretroviral

INTRODUCTION

HIV is the etiologic agent of acquired immunodeficiency syndrome (AIDS). This syndrome is characterized by a decrease in the total number of T CD4$^+$ cells, as well as an increase in the incidence of opportunistic infections and progressive failure of the immune system. The first report of AIDS occurred in the early 1980s, with cases of homosexuals with depletion of circulating T lymphocytes in Los Angeles, United States[1].

HIV-1 is a single-stranded RNA virus inserted on the *Retroviridae* family. Its particle possesses 100 to 150 nanometers of diameter with a lipid envelope that contains spike-form glycoproteins[2,3]. HIV can infect some immune system cells that express CD4 receptors, such as CD4$^+$ T helper cells, macrophages, and dendritic cells. Typically, HIV-1 infection is characterized by an initial phase of high-level viremia, followed by a long period of persistent virus replication at a lower level. Viral persistence occurs despite specific antiviral immune responses, which include the generation of neutralizing antibodies[4]. The progression of HIV infection can be divided into three phases: acute or primary, persistent chronic phase, and AIDS. The markers of AIDS progression, which clinically define these steps, are the CD4$^+$ T cell count, the plasma viral load, and the presence or absence of clinical manifestations[5].

Three decades and a half after its discovery and recognition, HIV has emerged as a global epidemic present in all continents, despite the massive campaigns of prevention and growing treatment strategies. The 2017 statistics showed that there were about 36.7 million people living with HIV in 2016[6]. Since 1980 until 2016, 842,710 people have been HIV infected in Brazil, and in terms of access to antiretroviral therapy, a total of 495.275 individuals are under treatment[7]. Studies have indicated that morbidity and mortality from HIV

[1]Post-Graduation in Science and Biotechnology Program, Institute of Biology, Universidade Federal Fluminense – Niterói (RJ), Brazil.
[2]Laboratory of Molecular Virology, Department of Cellular and Molecular Biology, Universidade Federal Fluminense – Niterói (RJ), Brazil.
[3]Department of Immunobiology, Universidade Federal Fluminense – Niterói (RJ), Brazil.
[4]Laboratory of Clinical Immunology, Department of Immunology, Instituto Oswaldo Cruz – Rio de Janeiro (RJ), Brazil.

infection have decreased since the introduction of ART. Although the decrease in statistics is evident, the lack of effective treatment and/or protective vaccine and strategies capable of inhibiting the virus replication are still the significant challenges of scientists[8,9].

OBJECTIVE

The aim of this study is to address the importance of less toxic compounds with higher antiviral activity that can reduce the morbidity and mortality of HIV infection. In addition, it aimed to produce a correlation between azidothymidine (AZT) and other drugs that even though are available for clinical use, have high levels of toxicity.

METHODS

We conducted a research in Index Medicus/MEDLINE and PubMed databases on articles that reported the currently available antiretrovirals. For this analysis, we used the keywords "AIDS", "HIV" and "antiretroviral therapy" in the database to find articles from the last five years (from 2013 and 648 articles), evaluated and followed our exclusion criteria that are articles that fully descriptively address compounds in clinical use or compounds that are in the preclinical (experimental) phase. In addition, the compounds have established toxicity and mechanism of action data. Therefore, only 38 articles were selected to compose this paper.

RESULTS

Forty-five articles from indexed journals and 38 selected for this review work were evaluated. We observed that since the discovery of AZT as the first drug available for use in the HIV infection treatment that shows great results, several substances have been studied and made available to make up the current treatment, which has been very effective.

DISCUSSION

Antiretroviral therapy

After 35 years from HIV discovery, many studies have been done and achieved for creating anti-HIV drugs. There is still no cure for such disease; therefore, once the highly active antiretroviral therapy (HAART) — the treatment currently used for HIV seropositive individuals — has been initiated, it must be continued throughout the patient's life[10]. The HIV-1 reverse transcriptase (RT), protease (PR) and integrase (IN) enzymes, as well as the main steps of the replicative cycle, are the main targets of antiretroviral therapy.

HAART consists of a combination of drugs that aim to inhibit enzymes and/or fusion/entry mechanisms of the virus into the cell during the steps of the HIV replicative cycle. A remarkable effect of HAART is the regeneration of $CD4^+$ and $CD8^+$ T cells and re-establishment of the immune function stably at long term. Therapy acts to reduce viral load in blood plasma, promoting higher survival to individuals[11-13]. Initially, the use of two nucleoside RT inhibitors (NRTI) and one non-nucleoside RT inhibitor (NNRTI) or two NRTIs and a third drug, either an integrase inhibitor or the protease inhibitor as HAART standard approach, is recommended for the treatment of AIDS[14,15].

There are 28 available drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV infection, including: eight nucleoside reverse transcriptase inhibitors (NRTIs); five non-nucleoside reverse transcriptase inhibitors (NNRTIs); ten protease inhibitors (PIs); one fusion inhibitor (FI); one entry inhibitor (CCRI); three integrase inhibitors (INIs or INSTIs), as see in **Table 1**[16-18].

Despite the continued developments in AIDS treatment and virus combat, infected individuals remain susceptible to viral and bacterial infections, such as influenza and pneumococcus, which can raise the level of morbidity and mortality. Therefore, alternative strategies and new targets need to be considered to combat the increasing AIDS pandemic[19].

Table 1 – Antiretroviral drugs currently used in the HIV infection treatment.

Drug Class Mode of action	Generic name	Year of approval
Nucleoside reverse transcriptase inhibitors (NRTIs) They are phosphorylated by cellular enzymes; competitively inhibit viral DNA synthesis or cause DNA chain termination	zidovudine (ZDV, azidothymidine, AZT)	1987
	didanosine (ddI, dideoxyinosine)	1991
	zalcitabine (ddC, dideoxycytidine)	1992
	stavudine (d4T)	1994
	lamivudine (3TC)	1995
	abacavir (ABC)	1998
	tenofovir (TDF)	2001
	emtricitabine (FTC)	2003
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) They are non-competitive inhibitors of viral DNA synthesis; directly connect the enzyme	nevirapine (NVP)	1996
	delavirdine (DLV)	1997
	efavirenz (EFV)	1998
	etravirine (ETR)	2008
	rilpivirine (RPV)	2011
Protease inhibitors (PIs) They bind to the active site of protease, thereby inhibiting enzyme function	saquinavir (SQV)	1995
	indinavir (IDV)	1996
	ritonavir (RTV)	1996
	nelfinavir (NFV)	1997
	amprenavir (APV)	1999
	lopinavir (LPV)	2000
	fosamprenavir (FOS-APV)	2003
	atazanavir (ATV)	2003
	tipranavir (TPV)	2005
	darunavir (DRV)	2006
Fusion inhibitors (FI) They bind to HR1 region of envelope glycoprotein gp41	enfuvirtide (T-20)	2003
Entry inhibitors – CCR5 co-receptor antagonist (CCRI) They inhibit the interaction of glycoprotein gp120 with CCR5 chemokine receptor	maraviroc (MVC)	2007
HIV integrase strand transfer inhibitors (INI or INSTI) They block integrase, preventing the insertion of viral DNA into the host DNA	raltegravir (RAL)	2007
	elvitegarvir (EVG)	2012
	dulotegravir (DTG)	2013

Source: adapted from Pau and George[16], da Cunha, Maselli[17], FDA[18].

Pharmacokinetic enhancer

Most of HIV protease inhibitors need a pharmacokinetic enhancer to assure their efficiency. Although ritonavir is a protease inhibitor, it is commonly used as a pharmacokinetic enhancer. Due to high daily doses and some side effects related to ritonavir use, the administration of cobicistat has become more frequent. In addition, cobicistat (COBI) inhibits cytochrome CYP3A more selectively than ritonavir[20].

COBI is a pharmacokinetic enhancer (pharmacoenhancer) that inhibits the metabolism of the atazanavir and darunavir antiretrovirals HIV-1 protease inhibitors (PIs) and is known for prolonging their effects. It was first approved by the US Food and Drug Administration (FDA) in 2012 combined with other drugs (elvitegravir/emtricitabine/tenofovir). Then, its single use was approved in 2014. More recently, in 2015, its use combined with atazanavir (ATV/COBI) and darunavir (DRV/COBI) was approved for use in treatment-naive and treatment-experienced adults in combination with other ARV agents[21].

COBI possesses a structure analog to ritonavir. Synthesized from ritonavir, it is an inhibitor of human cytochrome P-450 (CYP) 3A and is used to increase the systemic exposure of antiretrovirals metabolized by CYP3A enzymes, in other words, it helps to optimize the activity of these antiretrovirals[20,21].

COBI inactivates CYP3A like ritonavir, in a concentration- and time-dependent manner. However, unlike ritonavir, COBI has no anti-HIV activity, which is essential to develop no resistance to antiretrovirals. Moreover, it does not disrupt the antiviral activity of PIs and several other ARVs against HIV. As a nonselective CYP3A inhibitor, the use of ritonavir becomes difficult in patients receiving multiple medications. COBI has demonstrated high efficacy. It can be compared and is considered non-inferior to standard RTV as a pharmacoenhancer. Hence, COBI offers an alternative to ritonavir boosting, with efficacy and safety in treatment-naive and -experienced adults[22,23].

Microbicides

Microbicides are experimental products containing drugs that could be inserted into the vagina or rectum to safely block sexual transmission of HIV. A microbicide would deliver an anti-HIV agent to the mucous membranes, lining the surface of the vagina or rectum through a substance, such as a gel, intravaginal ring, or film. A safe, effective, desirable, and affordable microbicide against HIV could help to prevent many new infections. Microbicide development is a challenge due to many factors, such as: no precedent that guarantees the strategy success, difficulty of achieving secure therapeutic levels, lack of markers, among others[24].

There are some essential characteristics for prioritizing microbicide development. They are safety, efficacy, cost, acceptability, appropriate drug delivery, long-term effectiveness, potential for resistance and impact on therapy, prioritization of best-in-class products[25].

Women are two to four times more susceptible than men to acquire sexually transmitted HIV infection, and recent research from the Joint United Nations Programme on HIV/AIDS (UNAIDS) show that 51% of people living with HIV worldwide are women. Moreover, AIDS-related illnesses remain the leading cause of death among women at reproductive age (15–49 years) in the world[26,27].

Microbicides currently used for pre-exposure prophylaxis strategy to prevent the sexual transmission of HIV are astodimer, dapivirine, and tenofovir[28].

Astodimer

Astodimer or VivalGel is a topical microbicide that is applied to the vagina, rectum, or used in condoms during a sexual intercourse. Studies have demonstrated the antiviral and antibacterial activities of the active principle. Astodimer belongs to a class of drugs that inhibits virus entry into the cell through polyanion, electrostatically creating an environment that prevents adsorption[25,29].

Dapivirine

Dapivirine is a non-nucleoside reverse transcriptase inhibitor that prevents the conversion of viral RNA to pro-viral DNA. It is also used as a topic pre-exposure prevention. One study evaluated the distribution of drug concentration of vaginal canal of women who used a silicone ring containing 25 mg of Dapivirine. The concentration was higher in the entire length of ectocervix than in endocervix[28].

Tenofovir

Tenofovir is a nucleoside reverse transcriptase inhibitor that was developed as a pre-exposure prophylaxis. Tenofovir clinical trials have shown promising results, with low anal and vaginal mucosal irritability. A study evaluated the use of 1% tenofovir vaginal gel for 30 months. There was an increase in cases of mild and self-limiting diarrhea, except for the group receiving the gel compared to the placebo group[30].

MARINE NATURAL PRODUCTS IN THE REPLICATION OR INFECTIVITY OF HIV AS A CANDIDATE FOR NEW ANTIRETROVIRALS

Marine organisms, as well as their derivatives, are sources of biologically active compounds. The Brazilian coast has a great marine biodiversity, with a broad range of resource of compounds with potential anti-HIV-1 activity[31]. Researchers' interest in investigating marine natural products is because the current antiretroviral therapy provides an emergence increase of drug resistance. Thus, it is important for the identification of new drugs with inhibitory action of both reverse transcriptase and other viral enzymes. Literature has demonstrated that the compounds have promising antiviral activity.

Studies have shown many compounds with rich chemical diversity and high biological activity against different microorganisms, especially HIV. A study of 257 pure compounds showed that at least four had an interesting potential to induce the production of latent proviruses, which may be an interesting combination strategy and may generate a more efficient low-dose combined effect[32]. Other studies with marine compounds had high repercussion and showed significant results, as flavonoids isolated from Caribbean seagrass acting as integrase inhibitors[33]. Nanotechnology active compounds with superior pharmacokinetics for site-specific delivery appear to be an interesting strategy for the use in more deadly diseases, such as cancer, HIV/AIDS, and neurological disorders. However, a large number of active compounds against HIV can be removed from the marine environment, such as polysaccharides, lectins, Aspernigrins with

anti-HIV-1 activities and Manzamine, although the best strategy is possibly for compounds that act directly on the virus[34].

In 2004, Pereira and Leão-Ferreira[35] demonstrated antiviral activity of two diterpenes isolated denominated hydroxidictiodial and dictiodial from brown alga *Dictyota menstrualis* against HIV-1. Values between 40 and 70 μM of EC_{50} in PM-1 cells were obtained. The diterpenes also inhibited the synthesis of pro-viral DNA, and reverse transcriptase was inhibited in a dose-dependent manner with the maximal inhibitory effect varying from 70 to 95% by both compounds. Cirne-Santos et al.[36] showed that diterpene 8,10,18-trihydroxy-2, 6-dolabelladiene (dolabelladienetriol) isolated from marine brown alga *Dictyota pfaffii* inhibits the HIV-1 infection. Dolabelladienetriol was able to inhibit the activity of RT enzyme in a dose-dependent manner, reaching the value of 16.5 μM of IC_{50}. Infected peripheral blood mononuclear cells (PBMCs) and macrophages presented EC_{50} of 8.4 and 1.85 μM, respectively. These results show that the diterpene can be a candidate to a new antiretroviral, including for viral reservoirs.

After those and other results, Paixão[37] proposed the formulation of a microbicide gel for women with active principles obtained from isolated products of *Dictyota menstrualis* and *Dictyota pfaffii* algae, which act inside the cell preventing HIV replication and inhibiting enzymes of virus life cycle[37].

In 2014, Pardo-Vargas et al.[38] reported three new dolabellane diterpenes isolated from Brazilian brown alga *Dictyota pfaffii* with antiviral activity against HIV-1 in MT-2 cells. They presented high values of CC_{50}, varying between 1345 and 1,456 μM. Compounds also inhibited 52, 69 and 83% of the HIV-1 replication, suggesting that these diterpenes could be considered potential new agents for HIV-1 therapy.

Isolated compounds of another brown alga, *Canistrocarpus cervicornis*, demonstrated inhibitory activity against HIV-1 replication and low cytotoxic effect in cell culture. Marine dolasthanes and secodolastane diterpenes inhibit virus replication in a dose-dependent manner. Diterpenes also showed excellent performance to reduce the infective capacity of HIV, which suggests the existence of a mechanism that prevents virus adsorption in the host cell. The promising results of algae extracts in combating HIV-1 replication and its potential virucidal effect require further studies, such as pharmacodynamic tests and *in vitro* and *in vivo* models[39].

Nogueira et al.[40] demonstrated the antiviral effect of extracts from red alga *Acanthophora spicifera* on HIV-1 replication. PBMCs were used to evaluate the cytotoxicity (CC_{50}) of dichloromethane, ethyl acetate, acetone, and methanol extracts. The respective values were: 31, 45, 38, and 179 μg/mL. The antiviral activity showed that ethyl acetate extract inhibited 60% of viral replication in infected cells, whereas the maximum inhibition was 79% for RT. The results evidence the promising use of *A. spicifera*, especially as a RT inhibitor.

Pioneer studies on the potential antiviral to develop microbicides as a preventive and topical use in genital mucosa are being developed, mainly the use of explant technology due to its easy study of the human mucosal tissue. Stephens et al.[41] determined the pretreatment effect with the compound extracted from brown alga *Dictyota pfaffii* dolabelladienetriol in inhibition of HIV-1 replication, and the protective effect of this compound in *ex vivo* explant model. The compound showed high inhibitory activity in PBMCs, achieving from 60 to 80%, and prevented HIV-1 replication macrophages. Tests with explant model (stratified squamous tissue) confirmed the low cytotoxicity of dolabelladienetriol and inhibited viral replication from 21 to 95%, maintaining the viability of the tissue, producing a protective effect on it. These findings indicate the need for further studies to the development of new antiretrovirals.

CONCLUSIONS

The current available antiretroviral therapy is composed of highly effective drugs that have improved morbidity and mortality of infected individuals, although many have significant toxic effects. The search for new antiretrovirals that have high activity and low toxicity is undoubtedly an important strategy to increase the arsenal of drugs for effective treatment and control of HIV infection. This fact can still be fundamental, especially considering that there are no vaccines available for HIV infection.

Participation of each author

Ingrid Barcelos de Oliveira, Doctoral student, worked on writing the review article. Claudio Cesar Cirne-Santos is the co-advisor and worked on article review. Caroline de Souza Barros worked on the article review. Rosa Teixeira Pinho worked on the article review. Izabel Christina Nunes de Palmer Paixão is project coordinator.

Funding

The authors are grateful to *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) for their financial support and Productivity Fellowships to I.C.N.P.P. (443930/2014-7 and 304070/2014-9). I.C.N.P.P. (E-26/201.442/2014) also thanks the *Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro* (FAPERJ) for the *Cientista do Nosso Estado* Fellowship. C.C.C.S. thanks to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the Postdoc fellowship, and C.S.B. thanks FAPERJ for the Postdoc fellowship (E-26/201.344/2016), in the Postgraduate Program in Sciences and Biotechnology of *Universidade Federal Fluminense* (PPBI-UFF).

Conflict of interests

The authors declare no conflict of interests.

REFERENCES

1. De Cock KM, Jaffe HW, Curran JW. The evolving epidemiology of HIV/AIDS. Aids. 2012;26(10):1205-13. https://doi.org/10.1097/QAD.0b013e328354622a
2. Tagliamonte M, Tornesello ML, Buonaguro FM, Buonaguro L. Conformational HIV-1 envelope on particulate structures: a tool for chemokine coreceptor binding studies. J Transl Med. 2011;9(Suppl. 1):S1. https://dx.doi.org/10.1186%2F1479-5876-9-S1-S1
3. Collier LKP, Oxford J. Retroviruses HIV-1 and -2 and HTLV. In: Press OU, editor. Human Virology. 5th edition. 2016. p. 273-87.
4. Wyatt R, Sodroski J. The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens. Science. 1998;280(5371):1884-8. https://doi.org/10.1126/science.280.5371.1884
5. Coffin J, Swanstrom R. HIV pathogenesis: dynamics and genetics of viral populations and infected cells. Cold Spring Harb Perspect Med. 2013;3(1):a012526. https://dx.doi.org/10.1101%2Fcshperspect.a012526

6. Akbari M, Fararouei M, Haghdoost AA, Gouya MM, Kazerooni PA. Survival and associated factors among people living with HIV/AIDS: A 30-year national survey in Iran. J Res Med Sci. 2019;24:5. https://dx.doi.org/10.4103%2Fjrms.JRMS_630_18
7. Brasil. Ministério da Saúde. Boletim Epidemiológico HIV/AIDS. Brasília: Ministério da Saúde, Secretaria de Vigilância em Saúde, PN de DST e AIDS; 2017. Ano V, n. 1.
8. Cardoso SW, Luz PM, Velasque L, Torres T, Coelho L, Freedberg KA, et al. Effectiveness of first-line antiretroviral therapy in the IPEC cohort, Rio de Janeiro, Brazil. AIDS Res Ther. 2014;11:29. https://doi.org/10.1186/1742-6405-11-29
9. Pang X, Liu Z, Zhai G. Advances in non-peptidomimetic HIV protease inhibitors. Curr Med Chem. 2014;21(17):1997-2011. https://doi.org/10.2174/09298673216661402171159 51
10. Sarafianos SG, Marchand B, Das K, Himmel DM, Parniak MA, Hughes SH, et al. Structure and function of HIV-1 reverse transcriptase: molecular mechanisms of polymerization and inhibition. J Mol Biol. 2009;385(3):693-713. https://doi.org/10.1016/j.jmb.2008.10.071
11. Agrawal L, Lu X, Jin Q, Alkhatib G. Anti-HIV therapy: current and future directions. Curr Pharm Des. 2006;12(16):2031-55. https://doi.org/10.2174/138161206777442100
12. Ramkumar K, Serrao E, Odde S, Neamati N. HIV-1 integrase inhibitors: 2007–2008 update. Med Res Rev. 2010;30(6):890-954. https://doi.org/10.1002/med.20194
13. De Luca L, Gitto R, Christ F, Ferro S, De Grazia S, Morreale F, et al. 4-[1-(4-Fluorobenzyl)-4-hydroxy-1H-indol-3-yl]-2-hydroxy-4-oxobut-2-enoic acid as a prototype to develop dual inhibitors of HIV-1 integration process. Antiviral Res. 2011;92(1):102-7. https://doi.org/10.1016/j.antiviral.2011.07.005
14. Nanfack AJ, Agyingi L, Noubiap JJN, Ngai JN, Colizzi V, Nyambi PN. Use of amplification refractory mutation system PCR assay as a simple and effective tool to detect HIV-1 drug resistance mutations. J Clin Microbiol. 2015;53(5):1662-71. https://doi.org/10.1128/JCM.00114-15
15. Murray AJ, Kwon KJ, Farber DL, Siliciano RF. The latent reservoir for HIV-1: how immunologic memory and clonal expansion contribute to HIV-1 persistence. J Immunol. 2016;197(2):407-17. https://doi.org/10.4049/jimmunol.1600343
16. Pau AK, George JM. Antiretroviral therapy: current drugs. Infect Dis Clin North Am. 2014;28(3):371-402. https://doi.org/10.1016/j.idc.2014.06.001
17. da Cunha J, Maselli LMF, Stern ACB, Spada C, Bydlowski SP. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old and new drugs. World J Virol. 2015;4(2):56-77. https://doi.org/10.5501/wjv.v4.i2.56
18. FDA. Approved HIV Medicines [Internet]. FDA; 2019 [cited on Mar. 21, 2019]. Available from: https://aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets/21/58/fda-approved-hiv-medicines
19. Cribbs SK, Lennox J, Caliendo AM, Brown LA, Guidot DM. Healthy HIV-1-infected individuals on highly active antiretroviral therapy harbor HIV-1 in their alveolar macrophages. AIDS Res Hum Retroviruses. 2015;31(1):64-70. https://doi.org/10.1089/AID.2014.0133
20. Kakuda TN, Crauwels H, Opsomer M, Tomaka F, van de Casteele T, Vanveggel S, et al. Darunavir/cobicistat once daily for the treatment of HIV. Expert Rev Anti Infect Ther. 2015;13(6):691-704. https://doi.org/10.1586/14787210.2015.1033400
21. Sherman EM, Worley MV, Unger NR, Gauthier TP, Schafer JJ. Cobicistat: review of a pharmacokinetic enhancer for HIV infection. Clin Ther. 2015;37(9):1876-93. https://doi.org/10.1016/j.clinthera.2015.07.022
22. Gallant JE, Koenig E, Andrade-Villanueva J, Chetchotisakd P, DeJesus E, Antunes F, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1–infected patients: week 48 results. J Infect Dis. 2013;208(1):32-9. https://doi.org/10.1093/infdis/jit122
23. Deeks ED. Cobicistat: a review of its use as a pharmacokinetic enhancer of atazanavir and darunavir in patients with HIV-1 infection. Drugs. 2014;74(2):195-206. https://doi.org/10.1007/s40265-013-0160-x
24. Singh K, Flores J, Kirby K, Neogi U, Sonnerborg A, Hachiya A, et al. Drug resistance in non-B subtype HIV-1: impact of HIV-1 reverse transcriptase inhibitors. Viruses. 2014;6(9):3535-62. https://doi.org/10.3390/v6093535
25. Shattock RJ, Rosenberg Z. Microbicides: topical prevention against HIV. Cold Spring Harb Perspect Med. 2012;2(2):a007385. https://dx.doi.org/10.1101%2Fcshperspect.a007385
26. Wang L, Wang L, Smith KM, Li L-M, Ming S, Lü J, et al. Heterosexual transmission of HIV and related risk factors among serodiscordant couples in Henan province, China. Chin Med J (Engl). 2013;126(19):3694-700.
27. UNAIDS. Global AIDS update 2017. Geneva: UNAIDS; 2017. 198p.
28. Nel A, Haazen W, Nuttall J, Romano J, Rosenberg Z, van Niekerk N. A safety and pharmacokinetic trial assessing delivery of dapivirine from a vaginal ring in healthy women. Aids. 2014;28(10):1479-87. https://doi.org/10.1097/QAD.0000000000000280
29. Fletcher PS, Wallace GS, Mesquita PM, Shattock RJ. Candidate polyanion microbicides inhibit HIV-1 infection and dissemination pathways in human cervical explants. Retrovirology. 2006;3:46. https://doi.org/10.1186/1742-4690-3-46
30. Karim QA, Karim SSA, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168-74. https://doi.org/10.1126/science.1193748
31. Berlinck RG, Hajdu E, da Rocha RM, de Oliveira JH, Hernández IL, Seleghim MH, et al. Challenges and rewards of research in marine natural products chemistry in Brazil. J Nat Prod. 2004;67(3):510-22. https://doi.org/10.1021/np0304316
32. Richard K, Williams D, de Silva E, Brockman M, Brumme Z, Andersen R, et al. Identification of novel HIV-1 latency-reversing agents from a library of marine natural products. Viruses. 2018;10(7). https://doi.org/10.3390/v10070348
33. Martins BT, Correia da Silva M, Pinto M, Cidade H, Kijjoa A. Marine natural flavonoids: chemistry and biological activities. Nat Prod Res. 2019;33(22):3260-72. https://doi.org/10.1080/14786419.2018.1470514
34. Parimala S, Begum A. A review on anti hiv agents from marine sources. World J Pharm Res. 2019;8(6).
35. Pereira H, Leão-Ferreira L, Moussatché N, Teixeira V, Cavalcanti D, Costa L, et al. Antiviral activity of diterpenes isolated from the Brazilian marine alga Dictyota menstrualis against human immunodeficiency virus type 1 (HIV-1). Antiviral Res. 2004;64(1):69-76. https://doi.org/10.1016/j.antiviral.2004.06.006
36. Cirne-Santos CC, Teixeira VL, Castello-Branco LR, Frugulhetti IC, Bou-Habib DC. Inhibition of HIV-1 replication in human primary cells by a dolabellane diterpene isolated from the marine algae Dictyota pfaffii. Planta Med. 2006;72(4):295-9. https://doi.org/10.1055/s-2005-916209
37. Paixão TV. A Cura que Vem do Mar (The Cure that Comes from the Sea). DST - Jornal Brasileiro de Doenças Sexualmente Transmissíveis. 2008.
38. Pardo-Vargas A, de Barcelos Oliveira I, Stephens P, Cirne-Santos C, de Palmer Paixão I, Ramos F, et al. Dolabelladienols A–C, new diterpenes isolated from Brazilian brown alga Dictyota pfaffii. Mar Drugs. 2014;12(7):4247-59. https://dx.doi.org/10.3390%2Fmd12074247
39. de Souza Barros C, Cirne-Santos CC, Garrido V, Barcelos I, Stephens PRS, Giongo V, et al. Anti-HIV-1 activity of compounds derived from marine alga Canistrocarpus cervicornis. J Appl Phycol. 2016;28:2523-7. http://doi.org/10.1007/s10811-015-0776-1
40. Nogueira CCR, Paixão ICNP, Santos CCC, Stephens PRS, Villaça RC, Pereira HS, et al. Anti-HIV-1 activity in human primary cells and Anti-HIV-1 RT inhibitory activity of extracts from the red seaweed Acanthophora spicifera. J Med Plants Res. 2016;10(35):621-5. http://doi.org/10.5897/JMPR2016.6208
41. Stephens PRS, Cirne-Santos CC, de Souza Barros C, Teixeira VL, Carneiro LAD, Amorim LSC, et al. Diterpene from marine brown alga Dictyota friabilis as a potential microbicide against HIV-1 in tissue explants. J Appl Phycol. 2017;29(2):775-80. http://doi.org/10.1007/s10811-016-0925-1

Address for correspondence:
IZABEL CHRISTINA NUNES DE PALMER PAIXÃO
Outeiro de São João Batista, s/n, Campus do Valonguinho – Centro
Niterói (RJ), Brazil
CEP: 24020-140
E-mail: izabeluff@gmail.com

Received on: 05.10.2019
Approved on: 07.11.2019