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Immunogenetic features of HIV-infection and allergy comorbidity

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Abstract

Today, the comorbidity of infection caused by the human immunodeficiency virus (HIV) is an important problem due to the complexity of the selection of the optimal antiretroviral therapy and the diagnosing of associated pathological conditions. The study of the comorbidity of HIV-infection and allergy is an important area of research. This article presents a literature review on different types of comorbidity. Special attention is paid to the development of allergic reactions to antiretroviral drugs. The presence of an allergic reaction in a patient can cause low adherence to therapy and subsequent development of HIV resistance to the treatment. The review provides information on the possible causes of the development of hypersensitivity in HIV-infected patients. The data on the development of hypersensitivity reactions in response to treatment with the main classes of antiretroviral drugs (nucleoside and non-nucleoside reverse transcriptase inhibitors, synthesis inhibitors, protease inhibitors, integrase inhibitors, cysteine-cysteine chemokine receptor 5 inhibitors) are presented. The most common allergic reactions to these drug classes are itching and rash, as well as increasing hepatic transaminase levels and cough. The existing scientific data on allergic reactions to drugs prescribed for other concurrent conditions (tuberculosis, fungal diseases) is also considered. The examples of studies reflecting the relevance of using immunogenetic and molecular genetic approaches in the study of comorbidity of HIV-infection and allergy are given. The identification of immunogenetic markers of the development of the hypersensitivity to therapy will optimize the diagnostic and treatment algorithms, especially in complex comorbid conditions.

Keywords: HIV-infection, comorbidity, hypersensitivity, immunogenetics.

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Introduction. Human immunodeficiency virus (HIV) infection is an acute socially significant problem. It is a chronic infection primarily caused by HIV type 1 (HIV-1). A much smaller number of cases are associated with HIV type 2 (HIV-2), which is registered mainly in West Africa and is less pathogenic than HIV-1 [1].

However, HIV infection is rarely limited to a single disease. In HIV infection, polymorbidity is often noted, manifested by the presence of concomitant tuberculosis [2], hepatitis C [3, 4], hepatitis B [5], diabetes mellitus [6, 7], hypertension [7], allergies [8–10], and other pathological conditions. Each form of polymorbidity has several characteristics that are important to consider not only in the diagnostics of HIV infection but also in the selection of antiretroviral therapy and management of patients.

The problem of HIV infection and allergy comorbidity is under-investigated. However, comprehension of the mechanisms of the concurrence of these types of pathologies can improve understanding of the pathogenetic aspects of the course of HIV infection and optimize diagnostic and treatment algorithms.

Critical analysis of modern views on HIV infection and allergy comorbidity. An allergic reaction usually proceeds according to the following scenario. At the initial contact of an allergen with a macroorganism, the allergen comes into contact with an antigen-presenting cell that processes and presents the allergen to type 2 T-helpers. The activation of the latter leads to the active synthesis of interleukins-4 and 10, which ensure the differentiation of naive B-cells and the production of class E immunoglobulins specific to the presented allergen. The synthesis of interleukin-4 inhibits the activity of type 1 T-helpers, which leads to a decrease in the activity of the cellular link of immunity and resistance of the macroorganism to the intracellular parasites [10].

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Table 1. Hypersensitivity reactions to some antiretroviral drugs.

Group of drugs	Representatives of the group	Described hypersensitivity reactions
Nucleoside reverse-transcriptase inhibitors	Abacavir	Maculopapular and urticarial rash (2.3%–9% of cases) [22]
	Tenofovir	Maculopapular and vesicular rash (5%–7% of cases) [23], photodermatitis [24]
Non-nucleoside reverse-transcriptase inhibitors	Nevirapine	Maculopapular rash (15%–32% of cases) [25]
	Efavirenz	Mild-to-moderate skin rash [23]
Protease inhibitors	Atazanavir	Rash, hyperbilirubinemia (6% of cases) [27]
	Darunavir	Rash, increased hepatic aminotransferase levels (6.7% of cases) [28]
	Lopinavir	Rash, increased hepatic aminotransferase levels (2%–4% of cases) [29]
Fusion inhibitors	Enfuvirtide	Extremely rare (<1% of cases), isolated cases have been described [30]
Inhibitors of the cysteine–cysteine-receptor of chemokine 5	Maraviroc	Extremely rare, possible rash, and cough [31, 32]
Integrase inhibitors	Raltegravir	Increased sweating (4% of cases), pruritus (2.3%–6.7% of cases) [22]
	Dolutegravir	Drug hypersensitivity reactions are extremely rare (<1% of cases) [33]
	Elvitegravir	Rare allergic reactions [34, 35]

The development of allergic reactions in patients with HIV infection can be associated with several causes. The main cause is the chronic nature of HIV infection. Long-term persistence of HIV in the human body can become a specific trigger for the development of allergies [8].

Moreover, allergies in patients with HIV infection may be caused by a genetic predisposition to the development of allergic reactions. Researchers have found several significant genetic predictors of allergy development [11–13], such as the *R576* (IL-4α) mutant allele, *IL4RA* (IL-4 receptor) polymorphism, and the *ADAM33*, *PHF11*, *DPP10*, and *GPRA* genes.

There is also an assumption that allergic reactions in patients with HIV infection can result from helminthic invasion [8, 14, 15]. This is confirmed by a study that indicated the presence of eosinophilia in such patients and symptoms of eosinophilic inflammation of various localizations [10].

The study of HIV infection and helminthic invasion comorbidity is the subject of a separate review; however, several important aspects should be noted. A high helminthic load correlates with a high viral load of HIV, and successful anthelminthic treatment leads to a significant decrease in the HIV viral load [16]. Moreover, anthelmintic therapy in patients with HIV infection does not lead to a significant improvement in immune status indicators and is not mandatory in non-endemic areas [17, 18]. Allergic syndrome with helminthic invasion often manifests as urticaria, pruritus, and eruption [19].

In the context of HIV infection and allergy comorbidity, it is important to investigate the manifestations of drug hypersensitivity in response to antiretroviral therapy. Thus, more than 50% of patients with HIV infection develop skin eruption of varying severities in response to antiretroviral therapy [20] and other forms of allergic reactions to certain antiretroviral drugs [21]. Several groups of antiretroviral drugs are used to treat HIV infection, namely, nucleoside and non-nucleoside reverse-transcriptase inhibitors, protease inhibitors, synthesis inhibitors, integrase inhibitors, and inhibitors of the cysteine–cysteine receptor of chemokine 5. Table 1 presents information on the main reactions to antiretroviral drugs.

Nucleoside reverse-transcriptase inhibitors can cause allergic reactions manifested as maculopapular or urticarial rash. These phenomena are more common with the use of abacavir and tenofovir [22, 23]. Cases of photodermatitis have been described for tenofovir [24].

Nevirapine can cause maculopapular rash, which emerges in the period from 10 days to 6 weeks from the start of drug administration, which usually has a mild course and resolves independently without withdrawal of the drug [25, 26]. Efavirenz is often included in antiretroviral therapy,

and it can cause a skin rash that appears on week 2 of drug intake, with possible itching. The above-described characteristics of a mild-to-moderate rash do not require drug withdrawal, and it resolves after 4 weeks of taking antihistamines or glucocorticoids [23]. Nevirapine and efavirenz are the most commonly used representatives of non-nucleoside reverse-transcriptase inhibitors.

Protease inhibitors are also used in antiretroviral therapy. Atazanavir can cause rash and hyperbilirubinemia [27]. Darunavir can cause rash and elevated hepatic aminotransferase levels [28]. Lopinavir is an antiretroviral coformulated drug that can cause rash and elevated hepatic aminotransferase levels [29].

Fusion inhibitors rarely cause allergic reactions. Cases of hypersensitivity to the administration of enfuvirtide in the presence of hepatotoxic syndrome have been described [30]. Generally, inhibitors of the cysteine–cysteine-receptor chemokine 5 (maraviroc) do not cause allergic reactions; however, there were reports of rash and coughing with maraviroc intake [31, 32].

Patients taking raltegravir have presented increased sweating and itching in rare cases [22]. The intake of dolutegravir does not induce allergic reactions (less than 1% of drug hypersensitivity cases were noted when dolutegravir was also included in the treatment regimen [33]). Elvitegravir is used as a component of antiretroviral complex of drugs. Its allergic reactions develop two times less frequently than with regimens containing efavirenz [34, 35].

In addition to antiretroviral drugs, other drugs used in comorbid conditions can cause hypersensitivity reactions. Antibacterial drugs are used in the prevention and treatment of tuberculosis, which, with the history of allergic conditions, can cause severe allergic reactions in patients with HIV infection. In the past, thioacetazone was used to treat tuberculosis, and its study revealed the development of hypersensitivity reactions in patients with HIV infection compared with patients with seronegative results (22% vs. 1% of cases, respectively) [36].

With the prophylactic use of isoniazid, adverse reactions may occur in 0.25% of cases, including pruritic eruptions in 4.3%–8.3% of cases [37]. Isolated cases of drug-induced erythroderma while taking isoniazid were described [38]. When pyrazinamide is prescribed to patients with eosinophilia, an allergic rash may occur [39]. These adverse events were described without taking into account the comorbidities of HIV infection.

When prescribing therapy for patients with HIV infection, the doctor should remember the possibility of allergic reactions in response to antifungal drugs. Thus, fluconazole may induce maculopapular rash, diffuse erythema, angioderma, and Stevens–Johnson syndrome [40], which is important to consider when prescribing therapy for patients with HIV infection.

The study of HIV infection comorbidities is an important and promising field of scientific research that should be performed using molecular genetic and immunogenetic methods. Research on HIV infection and allergic reaction comorbidity in the context of molecular genetics is promising to identify causally significant genetic markers.

A study [41] showed a relationship between the development of hypersensitivity reactions in response to abacavir and the rs2395029 (*57:01) variant in the *HLA-B* gene [41]. Another study revealed that hypersensitivity to nevirapine is associated with HLA-Cw8 and HLA-B14 antigens [42]. In patients taking nevirapine and efavirenz, a relationship was established between the HLA-DRB101*01 allele and rash appearance [43].

Conclusion. Comorbid conditions in HIV infection remain an urgent scientific problem requiring detailed investigation. HIV infection and allergy comorbidity may be caused by the long-term presence of the virus in the body, genetic predictors of allergy development, and concomitant helminthic invasion. The phenomenon of drug allergy should be closely monitored, which manifests itself in the use of antiretroviral therapy and must be taken into account when choosing therapy for patients with HIV infection. Allergic reactions are also possible when taking drugs for other conditions associated with HIV infection.

The scientific community is showing particular interest in investigating hypersensitivity reactions in HIV infection, since solving the problem of HIV infection and allergy comorbidity will optimize diagnostics and treatment of HIV infection and other combined pathological conditions.

The use of immunogenetic and molecular genetic methods is promising in identifying markers of the development of hypersensitivity in patients with HIV infection and various comorbidities. These methods were used in some of the articles mentioned in this review.

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REFERENCES

1. Marlink R., Kanki P., Thior I., Travers K., Eisen G., Siby T., Traore I., Hsieh C.C., Dia M.C., Gueye E.H., Hellinger J., Guèye-Ndiaye A., Sankalé J.-L., Ndoye I., Mboup S., Essex M. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science*. 1994; 265 (5178): 1587–1590. DOI: 10.1126/science.7915856.

2. Duarte R., Lönnroth K., Carvalho C., Lima F., Carvalho A.C.C., Muñoz-Torrico M., Centis R. Tuberculosis, social determinants and co-morbidities (including HIV). *Pulmonology*. 2018; 24 (2): 115–119. DOI: 10.1016/j.rppnen.2017.11.003.

3. Rockstroh J.K., Spengler U. HIV and hepatitis C virus co-infection. *Lancet Infect. Dis*. 2004; 4 (7): 437–444. DOI: 10.1016/S1473-3099(04)01059-X.

4. Kupin W.L. Viral-associated GN: Hepatitis C and HIV. *Clin. J. Am. Soc. Nephrol*. 2017; 12 (8): 1337–1342. DOI: 10.2215/CJN.04320416.

5. Barreiro P., Martín-Carbonero L., García-Samaniego J. Hepatitis B en pacientes con infección por el virus de la inmunodeficiencia humana. *Enferm. Infecc. Microbiol. Clin*. 2008; 26 (Suppl. 7): 71–79. (In Spanish.) DOI: 10.1016/s0213-005x(08)76522-4.

6. Duncan A.D., Goff L.M., Peters B.S. Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study. *PLoS One*. 2018; 13 (3): e0194199. DOI: 10.1371/journal.pone.0194199.

7. Getahun Z., Azage M., Abuhay T., Abebe F. Comorbidity of HIV, hypertension, and diabetes and associated factors among people receiving antiretroviral therapy in Bahir Dar city, Ethiopia. *J. Comorb*. 2020; 10: 2235042X19899319. DOI: 10.1177/2235042X19899319.

8. Мокроносова М.А., Мац М.А. Инфекция и аллергия: две стороны одной медали. *Астма и аллергия*. 2015; (4): 9–12. [Mokronosova M.A., Mats A.N. Infection and allergies: two sides of the same coin. *Astma i allergiya*. 2015; (4): 9–12. (In Russ.)]

9. Akhmedzhanova Z.I. The incidence of allergic diseases in HIV-infected. *Meditsinskaya immunologiya*. 2009; 11 (4–5): 380. (In Russ.)

10. Nora S.A., Arkhipov G.S., Kropachev I.G., Arkhipova E.I. Role of allergies in diagnostics and treatment of HIV-infection. *Vestnik Novgorodskogo gosudarstvennogo universiteta*. 2021; (1): 67–70. (In Russ.) DOI: 10.34680/2076-8052.2021.1(122).67-70.

11. Freidin M.V., Puzyrev V.P. Genomic bases of susceptibility to atopic diseases. *Molekulyarnaya meditsina*. 2007; (3): 26–35. (In Russ.)

12. Hershey G.K.K., Friedrich M.F., Esswein L.A., Thomas M.L., Chatila T.A. The association of atopy with a gain of function mutation in the α-subunit of the interleukin 4 receptor. *New Eng. J. Med*. 1997; 337: 1720–1725. DOI: 10.1056/NEJM199712113372403.

13. Mitsuyasu H., Yanagihara Y., Mao X.Q., Gao P.S., Arinobu Y., Ihara K., Takabayashi A., Hara T., Enomoto T., Sasaki S., Kawai M., Hamasaki N., Shirakawa T., Hopkin J.M., Izuhara K. Dominant effect of Ile50Val variant of the human IL-4 receptor α-chain in IgE synthesis. *J. Immunol*. 1999; 162: 1227–1231. PMID: 9973373.

14. Simonov R.O., Valishin D.A., Yapparov R.G. Acute allergies in HIV-infected patients against the background of helminthic invasion. In: *Diagnostika i lechenie glaznykh proyavleniy infektsionnykh i sistemnykh zabolevaniy.* (Diagnostics and treatment of ocular manifestations of infectious and systemic diseases.) 2018; 98–105. (In Russ.)

15. Brown M., Mawa P.A., Kaleebu P., Elliott A.M. Helminths and HIV infection: epidemiological observations on immunological hypotheses. *Parasite Immunol*. 2006; 28 (11): 613–623. DOI: 10.1111/j.1365-3024.2006.00904.x.

16. Wolday D., Mayaan S., Mariam Z.G., Berhe N., Seboxa T., Britton S., Galai N., Landay A., Bentwich Z. Treatment of intestinal worms is associated with decreased HIV plasma viral load. *J. Acquir Immune Defic. Syndr*. 2002; 31 (1): 56–62. DOI: 10.1097/00126334-200209010-00008.

17. Means A.R., Burns P., Sinclair D., Walson J.L. Antihelminthics in helminth-endemic areas: effects on HIV disease progression. *Cochrane Database Syst. Rev*. 2016; 4 (4): CD006419. DOI: 10.1002/14651858.CD006419.pub4.

18. Walson J., Singa B., Sangaré L., Naulikha J., Piper B., Richardson B., Otieno P.A., Mbogo L.W., Berkley J.A., John-Stewart G. Empiric deworming to delay HIV disease progression in adults with HIV who are ineligible for initiation of antiretroviral treatment (the HEAT study): a multi-site, randomised trial. *Lancet Infect. Dis*. 2012; 12 (12): 925–932. DOI: 10.1016/S1473-3099(12)70207-4.

19. Chernikova E.A., Drynov G.I. Helminthiasis in the practice of an allergist. *Astma i allergiya*. 2016; (1): 27–32. (In Russ.)

20. Davis C.M., Shearer W.T. Diagnosis and management of HIV drug hypersensitivity. *J. Allergy Clin. Immunol*. 2008; 121 (4): 826–832.e5. DOI: 10.1016/j.jaci.2007.10.021.

21. Peter J., Choshi P., Lehloenya R.J. Drug hypersensitivity in HIV infection. *Curr. Opin. Allergy Clin. Immunol*. 2019; 19 (4): 272–282. DOI: 10.1097/ACI.0000000000000545.

22. Borrás-Blasco J., Navarro-Ruiz A., Borrás C., Casterá E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. *J. Antimicrob. Chemother*. 2008; 62 (5): 879–888. DOI: 10.1093/jac/dkn292.

23. Yunihastuti E., Widhani A., Karjadi T.H. Drug hypersensitivity in human immunodeficiency virus-infected patient: challenging diagnosis and management. *Asia Pac. Allergy*. 2014; 4 (1): 54–67. DOI: 10.5415/apallergy.2014.4.1.54.

24. Verma R., Vasudevan B., Shankar S., Pragasam V., Suwal B., Venugopal R. First reported case of tenofovir-induced photoallergic reaction. *Indian J. Pharmacol*. 2012; 44 (5): 651–653. DOI: 10.4103/0253-7613.100407.

25. Temesgen Z., Beri G. HIV and drug allergy. *Immunol. Allergy Clin. North Am*. 2004; 24 (3): 521–531. DOI: 10.1016/j.iac.2004.03.006.

26. Montessori V., Press N., Harris M., Akagi L., Montaner J.S. Adverse effects of antiretroviral therapy for HIV infection. *CMAJ*. 2004; 170 (2): 229–238. PMID: 14734438.

27. Squires K., Lazzarin A., Gatell J.M., Powderly W.G., Pokrovskiy V., Delfraissy J.F., Jemsek J., Rivero A., Rozenbaum W., Schrader S., Sension M., Vibhagool A., Thiry A., Giordano M. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J. Acquir Immune Defic. Syndr*. 2004; 36 (5): 1011–1019. DOI: 10.1097/00126334-200408150-00003.

28. Madruga J.V., Berger D., McMurchie M., Suter F., Banhegyi D., Ruxrungtham K., Norris D., Lefebvre E., de Béthune M.P., Tomaka F., De Pauw M., Vangeneugden T., Spinosa-Guzman S.; TITAN study group. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. *Lancet*. 2007; 370 (9581): 49–58. DOI: 10.1016/S0140-6736(07)61049-6.

29. Corbett A.H., Lim M.L., Kashuba A.D. Kaletra (lopinavir/ritonavir). *Ann. Pharmacother*. 2002; 36 (7–8): 1193–1203. DOI: 10.1345/aph.1A363.

30. Shahar E., Moar C., Pollack S. Successful desensitization of enfuvirtide-induced skin hyper-sensitivity reaction. *AIDS*. 2005; 19 (4): 451–452. DOI: 10.1097/01.aids.0000161779.23191.e5.

31. Gulick R.M., Lalezari J., Goodrich J., Clumeck N., DeJesus E., Horban A., Nadler J., Clotet B., Karlsson A., Wohlfeiler M., Montana J.B., McHale M., Sullivan J., Ridgway C., Felstead S., Dunne M.W., van der Ryst E., Mayer H.; MOTIVATE Study Teams. Maraviroc for previously treated patients with R5 HIV-1 infection. *N. Engl. J. Med*. 2008; 359 (14): 1429–1441. DOI: 10.1056/NEJMoa0803152.

32. Dubois E.A., Cohen A.F. Maraviroc and raltegravir. *Br. J. Clin. Pharmacol*. 2009; 68 (5): 651–652. DOI: 10.1111/j.1365-2125.2009.03503.x.

33. Walmsley S.L., Antela A., Clumeck N., Duiculescu D., Eberhard A., Gutiérrez F., Hocqueloux L., Maggiolo F., Sandkovsky U., Granier C., Pappa K., Wynne B., Min S., Nichols G.; SINGLE Investi-gators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N. Engl. J. Med*. 2013; 369 (19): 1807–1818. DOI: 10.1056/NEJMoa1215541.

34. Lee F.J., Carr A. Tolerability of HIV integrase inhibitors. *Curr. Opin. HIV AIDS*. 2012; 7 (5): 422–428. DOI: 10.1097/COH.0b013e328356682a.

35. Al Soub H., Al-Khal A.L.M., Alsoub D., Awouda W. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in the treatment of HIV-infected patients: Experience with the first 100 patients from Qatar. *Can. J. Infect. Dis. Med. Microbiol*. 2020; 2020: 1597839. DOI: 10.1155/2020/1597839.

36. Nunn P., Brindle R., Wasunna K., Gilks C., Omwega M., Were J., Med M., Nunn P., Kibuga D., Gathua S., Imalingat A., Nunn P., Wasunna K., Lucas S., McAdam K., Brindle R., Lucas S., Gilks C., Omwega M., Were J. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet*. 1991; 337 (8742): 627–630. DOI: 10.1016/0140-6736(91)92447-a.

37. Grant A.D., Mngadi K.T., van Halsema C.L., Luttig M.M., Fielding K.L., Churchyard G.J. Adverse events with isoniazid preventive therapy: experience from a large trial. *AIDS*. 2010; 24 (Suppl. 5): 529–536. DOI: 10.1097/01.aids.0000391019.10661.66.

38. Garg Y., Gore R., Jain S., Kumar A. A rare case of isoniazid-induced erythroderma. *Indian J. Pharmacol*. 2015; 47 (6): 682–684. DOI: 10.4103/0253-7613.169575.

39. Savintseva E.V., Zelenina A.O., Shadieva S.V. Unwanted side effects and factors contributing to their development, in the treatment of patients with first-time pulmonary tuberculosis. *Sinergiya nauk*. 2018; (24): 1224–1230. (In Russ.)

40. Craig T.J., Peralta F., Boggavarapu J. Desensitization for fluconazole hypersensitivity. *J. Allergy Clin. Immunol*. 1996; 98 (4): 845–846. DOI: 10.1016/s0091-6749(96)70136-7.

41. McLaren P.J., Fellay J. HIV-1 and human genetic variation. *Nat. Rev. Genet*. 2021; 22: 645–657. DOI: 10.1038/s41576-021-00378-0.

42. Littera R., Carcassi C., Masala A., Piano P., Serra P., Ortu F., Corso N., Casula B., La Nasa G., Contu L., Manconi P.E. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. *AIDS*. 2006; 20 (12): 1621–1626. DOI: 10.1097/01.aids.0000238408.82947.09.

43. Vitezica Z.G., Milpied B., Lonjou C., Borot N., Ledger T.N., Lefebvre A., Hovnanian A. HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. *AIDS*. 2008; 22 (4): 540–541. DOI: 10.1097/QAD.0b013e3282f37812.