Trakia Journal of Sciences, No 3, pp 271-279, 2024

Available online at:
https://trakia-uni.bg

ISSN 1313-3551 (online) doi:10.15547/tjs.2024.03.011

Review

MODULATING AND STIMULATING THE IMMUNE SYSTEM THERAPY IN PEOPLE WITH HIV/AIDS - ADVANTAGES AND POSSIBILITIES - REVIEW OF THE LITERATURE WITH SHARING OF OWN EXPERIENCE

L. Pekova[1,2*], S. Angelova[1], P. Parusheva[1,2], B. Bureva[1,2], M. Mitev[3]

[1]Department of Hygiene, Epidemiology, Microbiology, Parasitology and Infectious Diseases, Medical Faculty, Trakia University, Stara Zagora, Bulgaria
[2]Clinic of Infectious Diseases, University Hospital for Active Treatment "Prof. Stoyan Kirkovich"-AD, Stara Zagora, Bulgaria
[3]Department of Medical Physics, Biophysics, X-ray and Radiology Medical Faculty, Trakia University, Stara Zagora, Bulgaria

ABSTRACT

The immune system in people living with HIV can range from normal to severely dysfunctional, depending on the timing of ART initiation and adherence. The use of immunostimulating and immunomodulating drugs in HIV/AIDS still hides many unknowns. Various types of immunotherapy, including monoclonal antibodies, interferon, cytokines, immunomodulatory drugs, allogeneic hematopoietic stem cell transplantation, and most importantly ART adherence, have shown efficacy in HIV-associated opportunistic infections and neoplasms. The beneficial effect of immunotherapy in autoimmune, inflammatory and oncological diseases in the course of HIV/AIDS is based on reducing the pathological damage of the immune system and modifying the disease processes by interfering with cellular metabolism and nucleic acid synthesis, as well as the production of antagonist molecules of inflammation. While most known immunomodulators reduce pathological disorders of the immune system, newer "checkpoint inhibitors" have been developed to improve immune surveillance in oncological diseases. Some cancer immunotherapies can affect HIV latency and HIV-specific immunity. Knowing the benefits of immunotherapy in people with HIV/AIDS and opportunistic diseases will improve their clinical care, providing a unique opportunity to gain insight into the mechanisms of HIV eradication. We present two cases of AIDS and Pneumocystis jirovecii pneumonia where we administered immunomodulators concurrently with ART and specific etiologic therapy. One patient died.

Key words: immunomodulatory drugs, HIV/AIDS, Pn. jirovecii pneumonia

BACKGROUND

Immunomodulatory drugs (IMD) alter the immune response by increasing or decreasing the production of serum antibodies (1). Immunostimulators are prescribed to enhance immunity against infectious diseases, tumours, primary or secondary immunodeficiency, and alterations in antibody transfer, among others (2).

Immunosuppressive drugs are used to reduce the immune response against transplanted organs and treat autoimmune diseases, such as pemphigus, lupus, or allergies (3). IMDs have altered the morbidity associated with debilitating autoimmune and inflammatory conditions, such as rheumatoid arthritis, psoriasis and psoriatic arthritis, and inflammatory bowel disease (4).

The mechanisms of action of IMDs involve various responses by which immunological pathways are triggered to alter disease processes. This is done by affecting cellular metabolism and nucleic acid synthesis, antagonizing molecules in inflammatory areas, impact on protein structures and depletion of certain cells (5-7).

Most IMDs reduce the pathological

***Correspondence to:** *Professor Liliya Pekova, PhD, Section of Infectious diseases, Dept. of Hygiene, Epidemiology, Microbiology, Parasitology and Infectious diseases. Medical faculty, Trakia University, 11, Armeyska Str. Stara Zagora, Bulgaria ORCID.org/0000-0001-5866-6890, e-mail: dr.pe_kova@abv.bg, GSM +359 899946450*

manifestations of the immune system, while newer ones known as "checkpoint inhibitors" have been developed to stimulate the immune system in oncological diseases. IMDs can be used alone or in combination (8). The term *immunomodulator* is more commonly used than *immunostimulant* for a substance that causes measurable changes in immune function. The action of IMDs can be specific and non-specific (9).

Four most commonly used types of IMDs are known:
* checkpoint inhibitors
*cytokines
* agonists and
* adjuvants (10).

Checkpoint inhibitors work by blocking immune checkpoints—the “brakes” of the immune system. Cytokines are messenger molecules that regulate immune cell maturation, growth, and responsiveness. Agonists activate pathways that promote adaptive immune responses, either by helping to activate “killer” T cells. Adjuvants activate pathways involved in the innate immune system that can stimulate general immune responses and ultimately promote adaptive immune responses. There is a growing concern that immunomodulatory therapy may be associated with an increased risk of infectious complications (11). Checkpoint inhibitors are thought to be capable of reversing HIV-1 latency (12). The definition of viral breakthrough is a condition in which a previously undetectable HIV RNA viral load is followed by a detectable result in plasma. The concept of virological failure characterizes the inability to achieve an HIV RNA below 200 copies/mL and to maintain this level despite adherence to ART. (13). Data on the outcomes of IMDs use in people living with HIV and AIDS are limited (14). Generally, these people have been excluded from the approval studies of these agents. Although there are case reports of their use in people lived with HIV (PLWH), the literature is likely biased due to selective reporting of certain outcomes, including successful treatment or unanticipated complications. For this reason, no firm conclusions can be drawn regarding the use of IMDs in HIV/AIDS in real practice (14). Peluso MJ et al. conducted a study using IMDs in 77 patients with persistent HIV infection with incident CD4+ values <200/mm^3 and previous opportunistic infections with *Pn. jirovecii*, Candida, invasive Herpesvirus infections (CMV, VZV, HSV1,2), mycobacterial diseases (pulmonary TBC, mycobacterium avium complex adenitis) and AIDS-related Kaposi's sarcoma in 26%. At the end of the study, infectious complications such as *E. coli* sepsis, bacterial pneumonia, and bacterial pneumonia sepsis, disseminated aspergillosis, *Clostridium difficile*-associated diarrhea were reported in 11.8%. An infectious complication was defined as any documented infection or infectious syndrome (e.g., sepsis syndrome) after initiation of an immunomodulator. No correlation was found between their occurrence and the levels of CD4+ cells, as well as the number of previous opportunistic infections. The authors concluded that despite more frequent viral blips and less frequent infectious complications, IMDs can be used in PLWH. The same authors allow that it is possible to grow clinically insignificant viral blips with the use of checkpoint inhibitors, which can reverse HIV-1 latency according to some other authors (15). The published data on severe infectious complications, incl. skin and soft tissue infections in PLWH treated with IMDs require further studies to fully understand the infectious risk of IMDs in the setting of HIV infection (16).

Intravenous immunoglobulin (IVIG) is not HIV-specific but is safe and temporarily reduces the HIV reservoir in chronic HIV infection (15). IVIG is a pooled antibody and biologic agent used to manage a variety of immunodeficiency states and numerous other conditions, including autoimmune, infectious, and inflammatory conditions. The ultimate goal of this therapy is to normalize a compromised immune system (17). Immunoglobulins are glycoprotein molecules produced by plasma cells in response to various antigenic stimuli involved in various physiological and pathological processes. Immunoglobulins function primarily in the adaptive arm (although "natural immunoglobulins" function in the innate arm) of the immune system and are subdivided based on the heavy chains they contain into different classes, viz. IgM, IgG, IgD, IgA and IgE (18). The indications for IVIG administration based on the mechanism of action and the type of conditions they treat are as follows:

- replacement therapy for immunodeficiencies
- immunomodulatory and anti-inflammatory therapy (immunomodulation in hematological

and organ-specific autoimmune diseases and anti-inflammatory in rheumatic inflammatory conditions, infectious and neurological diseases)
- As hyperimmune therapy against specific infectious agents (17).

According to some authors, IVIG therapy can be beneficial in HIV-infected children by reducing the number of recurrent bacterial infections, especially of the respiratory system (19, 20). Mofenson LM et al. conducted a double-blind, placebo-controlled trial in 372 HIV-infected children with IVIG at a dose of 0.4 g/kg. Children with CD4+ >200/mm^3 show a significantly long interval without co-infections and respectively the need for hospitalizations. No statistically significant difference was found with the placebo group (21). Evidence in favor of IVIG therapy in adult patients with HIV is still scarce. Saint-Marc et al. reported in 24 AIDS patients receiving or not receiving IVIG therapy (0-2g/kg/month) a significant reduction in mortality. Compared to the placebo group, they had fewer episodes of bacterial or viral infections (22). Administration of IVIG at a dose of 1-2 g/kg for 2-4 weeks in adult patients with HIV and idiopathic thrombocytopenic purpura had shown an improvement in platelet levels and a reduction in bleeding tendency. Indirect data indicate that IVIG is also effective in the treatment of *Pn. jirovecii* pneumonia in HIV (23). Administration of IVIG is effective in preventing further deterioration of cellular immunity and progression from asymptomatic to AIDS-related complex infection in patients with hemophilia (24).

IVIG administered to a patient with HIV and parvovirus infection leading to anemia has shown excellent results (25). Attempts have been made to improve the immune status of HIV+ individuals with the transfusion of human plasma containing a high concentration of anti-HIV antibodies (26). There are also trials with hyperimmune anti-HIV immunoglobulin preparations of human or porcine origin (27, 28).

Hague et al. for a period of 12 months administered IVIG in HIV infected children with heterogeneous clinical symptoms. However, they proved a significant improvement in the condition of the children by reporting weight gain, reduction in the number of infectious episodes and hospital stay (29).

Inosine pranobex (IP), or Isoprinosine, positively affects the host immune system by increasing the proliferation of T-cell lymphocytes and the activity of natural killer cells, as well as the levels of pro-inflammatory cytokines, thereby supporting the immune response in immunosuppressed patients. Some authors hypothesize that IP may affect viral RNA levels and therefore inhibit the growth of some viruses (30). It is approved in several countries for the treatment of viral infections (31). In patients with AIDS-related complex and persistent generalized lymphadenopathy, IP enhances T-cell proliferative responses and natural killer cell activity (32). In a study by De Simone C, et al., co-administration of IP with zidovudine in HIV+ patients was reported to increase zidovudine plasma levels, prolonging the mean half-life of the antiretroviral drug. According to the authors, this co-administration allows the use of a lower dose of zidovudine and prolongation of the intervals between drug administrations and is a prerequisite for obtaining sustained plasma levels as well as the potential to improve immune function (33).

REPORT OF TWO CASES

Case 1. A 17-year-old patient had been sick for about a month with progressive fatigue, lack of appetite, profuse night sweats and weight loss. There was a cough with infrequent discharge of small, highly viscous sputum, pains in the large joints and bones of the lower legs. He reported no past illnesses. For three years there had been promiscuous homosexual relationships. He was hospitalized with X-ray proven pneumonia in a pediatrics clinic, from where, after a positive result for HIV, he was transferred to an infectious diseases clinic. He was admitted in a severely damaged general condition with evidence of respiratory failure - weakened vesicular breathing bilaterally, tachydyspnea, BF=40/min., intercostal and epigastric circulation, SAT 88%. Cardiac activity is slightly increased, 90/min, RR=117/78. The abdomen is painless with hepatomegaly 1.5-2-2 cm and moderately active peristalsis. CT of the lung visualized bullous emphysema, a bilateral interstitial inflammatory process with striated-reticular and small-spotted changes in the lung parenchyma. **Figure 1.** On the 10^{-th} day of the hospital stay, the patient developed a total pneumothorax on the right, which necessitated thoracentesis, placement of a drainage intercostal catheter, and transfer to the intensive care unit. There, the condition worsened with

temperature up to 40˚C, dyspnea unresponsive to O2 treatment and need of artificial pulmonary ventilation (APV). Laboratory tests revealed leukocytosis, with extreme left shift, elevated amynotransferases, and LDH. *Pn. jirovecii* was found positive in sputum by the National Reference Laboratory (NRL) for Parasitoses, National Center for Infectious and Parasitic Diseases (NCIPD), Sofia. *Candida glabrata* was isolated from nasal discharge, *Candida albicans* from rectal discharge. The TB-gold-spot test was negative as well as markers for viral hepatitis. Data from immunological studies can be seen in **Table 1.** Given the severity of the condition, etiologic-specific therapy for suspected *Pn. jirovecii* pneumonia was started early, as was ART immediately after receiving the HIV positive result. **Table 2.** On the 19th day, the patient had a present cardiac arrest and exitus.

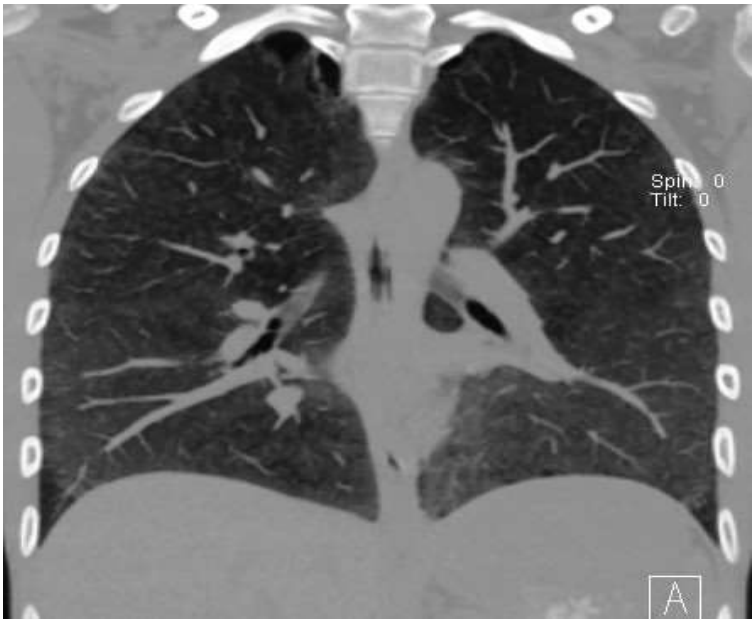

Figure 1. CT of the lungs in **Case 1**. Coronary reconstruction diffusely in all lung segments bilaterally, pronounced frosted glass type zones are visible. Bilateral apical presence of emphysema bullae, the largest up to 24 mm on the right. The hiluses are of normal structure. Single enlarged paratracheal lymph node up to 7 mm.

Table 1. *Laboratory studies in both patients*

Parameters	**CASE 1**				**CASE 2**			
Leuc.10^9/L	16,77	18,76	22,17	10,60	12,4	11,59	9,39	6,87
Sg%	92,9	73,9	95,4	82,3	83,8	91,5	92,0	75,1
Ly%	3,3	9,2	2,8	5,9	9,6	6,1	5,1	16,5
Hb g/L	134,1	129,0	120,6	121,1	100,0	87,0	95,0	123,0
CRP mg/L	0,6	2,2	25,0	47,8	338,2	335,9	121,1	3,8
Total protein g/L	58,0	61,3	54,8	50,4	62,7	71,1	58,4	62,1
Albumin g/L	29,5	31,2	24,3	22,1	20,4	38,5	30,2	31,8
AST IU/L	39,4	63,3	78,2	143,9	74,4	69,1	79,2	90,1
ALT IU/L	42,5	56,2	83,8	104,3	26,7	21,1	17,2	18,9
GGT IU/L	61,2	62,0	59,1	152,3	107,6	94,7	56,2	43,0
LDH IU/L	1141,0	1614,0	2397,2	2713,7	1938,2	2299,4	1509,3	550,9
Na+ mmol/L	134,2	127,7	127,5	129,1	131,1	135,4	127,3	134,5
K+ mmol/L	3,8	4,2	2,1	3,0	3,4	4,3	4,0	3,8
CD4+.10^6/L		107	76		11			112
CD8+.10^6/L		1019	879		150			498
CD4+/CD8+		0,10	0,8		0,07			0,22
VL c/ml		5242972				2138242		

Table 2. *Therapy in both patients*

Medication	**Case 1**	**Duration (days)**	**Case 2**	**Duration (days)**
Ceftriaxon	2x2.0 IV	2		3
Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide (Symtuza)	X 1 tabl. PO	11		21
Trimethoprim/Sulfamethoxazole	4x960 mg IV	5	4x960 mg IV,	
Clarithomycin	2x 500 mg IV	6		21
Methylprednisolone	2x40 mg IV with subsequent reduction according to the scheme	11	2x40 mg IV with subsequent reduction according to the scheme	18
Diflucan	x 1 fl. IV,	10	x 1 fl. IV	10
IVIG	x 10 amp. IV	5 consecutive days	x 10 amp. IV	5 consecutive days
Inosine Pranobex	4x 1000 mg PO	11	4x1000 mg PO	42
FTC/TDF, Darunavir, Ritonavir			x 1 tabl. PO,	Till now
Meropenem			3x2.0 IV	18
Pathogenetic and symptomatic agents	+		+	20

Case 2. A 20-year-old patient presented with a 4-month history of severe fatigue, cough without expectoration, progressively deepening dyspnea, and a weight loss of 20 kg. In the last week, his temperature began to rise to 39˚C. Ambulatory proven carrier of *S. aureus* from nasal secretion and *C. albicans* from oral secretion. No past illnesses. Epidemiologically reported homosexual contacts. He was admitted to the pulmonology department with a diagnosis of pneumonia, confirmed radiographically as extensive areas of ground-glass consolidation bilaterally, striated-reticular and fine-macular opacities, and axillary lymphonodulomegaly. **Figure 2.** Cardiovascular system – no changes. The abdomen was soft, painless with hepatomegaly of 2-2-2 cm below the costal arch. Consulted an infectious disease specialist and tested positive for HIV, then was transferred to an infectious disease clinic. Due to deterioration of the condition with constant shortness of breath, BF 52/min., SAT 78%, heartbeat 120/min., RR 100/60, the patient was transferred to an ICU, where he was placed on an APV for 5 days. From the laboratory tests, in addition to data on inflammation, anemia and electrolyte disorders are also observed. **Table 1.** An endotracheal aspirate showed the presence of *Pn. jirovecii* in the NRL on Parasitosis, NCIPD, Sofia. *C. albicans* was isolated from esophageal secretions. Tests for Influenza, TBC, HBV, HCV, CMV, EBV and syphilis were negative. Therapy can be seen in the **Table 2**.

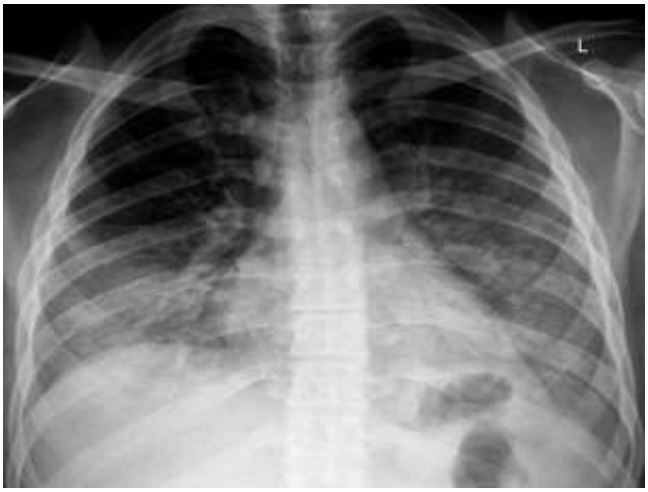

Figure 2. Frontal chest X-ray in **Case 2**. Bilateral basally reduced porosity of the parnechyma with ground-glass type changes and the presence of small-speckled, not sharply defined shadows in the lungs basally, paracardially and perihilarly

In the course of inpatient treatment, which lasted 23 days, the patient's condition began to improve. Subsequent studies by the CD panel and VL confirmed this. The patient is currently doing well, taking his therapy regularly.

DISCUSSION

Both presented cases concern *Pn. jirovecii* pneumonia as an opportunistic indicator infection in newly diagnosed HIV infection. In both cases, it concerns young men with homosexual orientation. From the described two cases, it is clear that these patients are late presenters, in advanced stage C of AIDS with opportunistic infections - *Pn. jirovecii* pneumonia and candidal infections. In the second case, the data from the immunological tests are worse than the first one, but on the other hand, the viral load is lower. In both patients, we used immunostimulators - Immunovenin intact and Isoprinosine. The classic clinical manifestations in both patients followed the combination of fever, nonproductive cough and dyspnea as described in the literature (34). Instrumental methods of diagnosis in both cases show the typical lung changes - bilateral, symmetrical interstitial or granular changes of the "frosted glass" type. Although relatively rare, pneumothorax is a complication that often requires prolonged ARV treatment (35).

Case 1 had a right-sided pneumothorax, after which tachy-dyspnea worsened and endotracheal intubation was required. In case 2, such complication was not visualized. Both pneumothorax and pleural effusions are rare findings associated with a severe course of *Pn. jirovecii* (35). The proof of *Pn. jirovecii* in induced sputum or broncho-alveolar lavage by means of PCR is a classical diagnostic method [36]. Both of our patients were investigated in this way. PCR as a method for proving the diagnosis *Pneumocystis jirovecii* pneumonia provides enhanced sensitivity over conventional methods, with meta-analyses demonstrating a sensitivity of ≥97% and negative predictive value (NPV) ≥ 99% (36). Trimethoprime/Sulfometoxazole is the first-line agent of choice for PJP in HIV-infected patients with mild, moderate, and severe cases (37). In patients without HIV infection, response to treatment should begin within 4-5 days, while in patients with HIV, this usually takes longer, but should occur within the first 8 days. In the absence of improvement within the expected time, an appropriate alternative regimen should be used (38). This is what we did in Case 1 by adding Clarithromycin to the therapy. Therapeutic failure with TMP-SMX occurs in up to 20% of cases and cannot be solely attributable to gene mutations (39). The presence of *Pn. jirovecii* resistance can be discussed in Case 1 where the use of Trimethoprim/Sulfamethoxazole alone was not effective. The addition of intravenous Clarithromycin should have shown a beneficial result, however, such an effect was not achieved. In addition, corticosteroids are recommended concurrently with antibacterial agents in patients with moderate to severe clinical disease. This is necessitated by the risk of further inflammation by provoking a severe inflammatory response in the lungs as a result of increased microbial degradation and clearance (40). Multivariate analysis showed that the probability of a favorable in-hospital outcome of PJP depended on age, status after bone marrow transplantation, immediate need for oxygen use, placement of mechanical ventilation, and delay in initiation of treatment (41). Pneumocystis pneumonia in HIV infection, as well as after solid organ transplantation, rarely has an unfavorable outcome. The mortality ratio of non-AIDS patients to those with AIDS is 27% to 4%; $p<0.0001$ (42). Delayed therapy is the only predictor of adverse disease outcome (43). In both patients, the high levels of LDH, which appear as a marker for the degree of lung damage, are striking. They are elevated in 90% of patients with PJP who are infected with HIV. Their reduction is the key to successful therapy (44).

CONCLUSION

We believe that the administration of immunostimulants such as IVIG and Isoprinosine in parallel with antibiotic, corticosteroid and other pathogenetic and symptomatic therapy in patients with advanced AIDS in the third stage with opportunistic infections, regardless of the lethal outcome in one patient, does not carry the risk of an unfavorable outcome.

ACKNOWLEDGEMENTS

We thank all the doctors, nurses, laboratory staff and patients who participated in this work. We thank the staff of the Infectious Diseases Clinic of University Multiprofile Hospital for Active Treatment, Stara Zagora for their medical care and treatment.

Funding statement: This research did not receive any specific grant from funding

agencies in the public, commercial, or not-for-profit sectors.

REFFERENCES

1. Avorn J. Learning about the Safety of Drugs. A Half-Century of Evolution. *N Engl J Med*. 2011;365:2151–3
2. Asherson RA, Gunter K, Daya D, Shoenfeld Y. Multiple Autoimmune Diseases in a Young Woman: Tuberculosis and Splenectomy as Possible Triggering Factors? Another Example of the "Mosaic" of Autoimmunity. *J Rheumatol*. 2008;35:1224–7
3. Chan LS. Ocular and oral mucous membrane pemphigoid (cicatricial pemphigoid) *Clin Dermatol*. 2012;30:34–7
4. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol* 2015; 12(9):537–545
5. Cronstein BN. Molecular therapeutics. Methotrexate and its mechanism of action. Arthritis Rheum 1996; 39(12):1951–1960
6. Li P, Zheng Y, Chen X. Drugs for Autoimmune Inflammatory Diseases: From Small Molecule Compounds to Anti-TNF Biologics. *Front Pharmacol* 2017; 8:460
7. Weiner GJ. Rituximab: mechanism of action. *Semin Hematol* 2010; 47(2):115–123
8. Darvin P, Toor SM, Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med* 2018; 50(12):165
9. Bascones-Martinez A, Mattila R, Gomez-Font R, Meurman JH. Immunomodulatory drugs: oral and systemic adverse effects. *Med Oral Patol Oral Cir Bucal*. 2014;19(1):e24-e31. Published 2014 Jan 1. doi:10.4317/medoral.19087
10. Luke J. Cancer Research Institute. 2023. Immunomodulators: Checkpoint Inhibitors, Cytokines, Agonists, and Adjuvants https://www.cancerresearch.org/treatment-types/immunomodulators
11. Martin-Mola E, Balsa A. Infectious complications of biologic agents. *Rheum Dis Clin North Am* 2009; 35(1):183–199. [PubMed] [Google Scholar]
12. Fromentin R, DaFonseca S, Costiniuk CT, El-Far M, Procopio FA, Hecht FM, et al. PD-1 blockade potentiates HIV latency reversal ex vivo in CD4(+) T cells from ART-suppressed individuals. *Nat Commun* 2019; 10(1):814. [PMC free article] [PubMed] [Google Scholar].
13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. *Department of Health and Human Services*. October 17, 2017. [Google Scholar].
14. Fink DL, Hedley L, Miller RF. Systematic review of the efficacy and safety of biological therapy for inflammatory conditions in HIV-infected individuals. *Int J STD AIDS* 2017; 28(2):110–119. [PubMed] [Google Scholar].
15. Peluso MJ, Chen J, Munter S, Reed A, Teraoka J, Eshun-Wilson I, Henrich TJ, Chin-Hong PV. Outcomes of immunomodulatory and biologic therapy in people living with HIV. *AIDS*. 2020 Jul 1;34(8):1171-1179
16. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006; 54(8):2368–2376
17. Arumugham VB, Rayi A. Intravenous Immunoglobulin (IVIG) [Updated 2023 Jul 3]
18. Justiz Vaillant AA, Jamal Z, Patel P, Ramphul K. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Aug 28, 2023. Immunoglobulin
19. Wood CC, McNamara JG, Schwarz DF, Merrill WW, Shapiro ED. Prevention of recurrent pneumonococcal bacteremia with intravenous gammaglobulin in a child with AIDS-related complex.*Pediatr Infect Dis J* 1987; 6:564-6.
20. Schaad UB, Gianella-Borradori A, Perret B, Imbach P, Morell A.Intravenous immune globulin in symptomatic paediatric human immunodeficiency virus infection. *Eur J Pediatr* 1988; 147:300-3
21. Mofenson LM, Bethel J, Moye J et al. Effect of intravenous immunoglobulin (IVIG) on CD4+ lymphocyte decline in HIVinfected children in a clinical trial of IVIG infection prophylaxis. *J Acq Immune Def Syndr* 1993; 6:1103-13
22. Saint-Marc T, Touraine JL, Berra N. Beneficial effects of intravenous immunoglobulins in AIDS. *Lancet* 1992 (Letter); 340:1347
23. Yap PL, Todd AAM, Williams PE, Hague RA, Mok J, Burns SM, et al. Use of intravenous immunoglobulin in acquired

immune deficiency syndrome. *Cancer* 1991; 68:1440-50
24. Wagner N, Bialek R, Radinger H, Brackmann HH, Becker M. Intravenous immunoglobulin in HIV-I infected haemophilic patients. *Arch Dis Child*. 1992;67(10):1267-1271
25. Gor, D., Singh, V., Gupta, V., & Levitt, M. (2022). A Persistent Parvovirus Infection Causing Anemia in an HIV Patient Requiring Intravenous Immunoglobulin Maintenance Therapy. *Cureus*, 14(4), e24627. https://doi.org/10.7759/cureus.24627
26. Levy J, Youvan T. Effectiveness and safety of passive hyperimmune therapy (PHT) in HIV disease: 12-month study analysis. Proceedings of the IX International Conference on AIDS, (Abstr.) Berlin, 1993
27. Cummins LM, Weinhold KJ, Matthews TJ et al. Preparation and characterization of an intravenous solution of IgG from human immunodeficiency virus-seropositive donors. *Blood* 1991;77:1111-7
28. Osther K, Wiik A, Black F et al. PASSHIV-l treatment of patients with HIV infection. A preliminary report of a phase 1 trial of hyperimmune porcine immunoglobulin to HIV-1. *AIDS* 1992; 6:1457-64
29. Hague RA, Yap PL, Mok JYQ et al. Intravenous immunoglobulin in HIV infection: evidence for the efficacy of treatment. *Arch Dis Child* 1989; 64:1146-50
30. Sliva J, Pantzartzi CN, Votava M. Inosine Pranobex: A Key Player in the Game Against a Wide Range of Viral Infections and Non-Infectious Diseases. *Adv Ther*. 2019;36(8):1878-1905. doi:10.1007/s12325-019-00995-6
31. Beran J, Šalapová E, Špajdel M; Isoprinosine Study (EWO ISO-2014/1) Team. Inosine pranobex is safe and effective for the treatment of subjects with confirmed acute respiratory viral infections: analysis and subgroup analysis from a Phase 4, randomised, placebo-controlled, double-blind study. *BMC Infect Dis*. 2016;16(1):648. Published 2016 Nov 7 doi:10.1186/s12879-016-1965-5
32. Tsang PH, Sei Y, Bekesi JG. . Isoprinosine-induced modulation of T-helper-cell subsets and antigen-presenting monocytes (Leu M3+Ia+) resulted in improvement of T- and B-lymphocyte functions, in vitro in ARC and AIDS patients. *Clin Immunol Immunopathol* 1987; 45:166–76
33. De Simone C, Famularo G, Tzantzoglou S, Moretti S, Jirillo E. Inosine pranobex in the treatment of HIV infection: A review. International *Journal of Immunopharmacology*.1991;Vol. 13(1):19-27
34. "Pneumocystis pneumonia | Fungal Diseases CDC". www.cdc.gov. 2020-07-27. Retrieved 2020-08-10.
35. Choi JS, Kwak SH, Kim MC, Seol CH, Kim SR, Park BH, et al. Clinical impact of pneumothorax in patients with Pneumocystis jirovecii pneumonia and respiratory failure in an HIV-negative cohort. *BMC Pulm Med* 22, 7 (2022). https://doi.org/10.1186/s12890-021-01812-z
36. Summah H., Zhu Y.-G., Falagas M.E., Vouloumanou E.K., Qu J.-M. Use of real-time polymerase chain reaction for the diagnosis of Pneumocystis pneumonia in immuncompromised patients: A meta-analysis. *J. Chin. Med*. 2013;126:1965–1973
37. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med*. 1996 May 1. 124(9):792-802.
38. Hughes W, Leoung G, Kramer F, Bozzette S A, Safrin S, Frame P, Clumeck N, Masur H, Lancaster D, Chan C, Lavelle J, Rosenstock J, Falloon J, Feinberg J, LaFon S, Rogers M, Sattler F. Comparison of atovaquone (566c80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. *N Engl J Med.* 1993;328:1521–1527
39. Castro JG, Morrison-Bryant M. Management of Pneumocystis Jirovecii pneumonia in HIV infected patients: current options, challenges and future directions. *HIV AIDS (Auckl).* 2010;2:123-134. doi:10.2147/hiv.s7720
40. Briel M, Boscacci R, Furrer H, Bucher HC. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection: a meta-analysis of randomised controlled trials. *BMC Infect Dis*. 2005;5:101. Published 2005 Nov 7. doi:10.1186/1471-2334-5-101
41. Roux A, Canet E, Valade S, et al. Pneumocystis jirovecii pneumonia in patients with or without AIDS, France.

Emerg Infect Dis. 2014;20(9):1490-1497. doi:10.3201/eid2009.131668

42. Almaghrabi RS, Alfuraih S, Alohaly R, Mohammed S, Alrajhi AA, Omrani AS. Pneumocystis jiroveci Pneumonia in HIV-Positive and HIV-Negative Patients: A Single-Center Retrospective Study. *Tanaffos*. 2019;18(3):238-243
43. Fekadu G, Turi E, Kasu T, et al. Impact of HIV status and predictors of successful treatment outcomes among tuberculosis patients: A six-year retrospective cohort study. *Ann Med Surg (Lond)*. 2020;60:531-541. Published 2020 Nov 15. doi:10.1016/j.amsu.2020.11.032
44. MN Vogel, P Weissgerber, B Goeppert, J Hetzel, M Vatlach, CD Claussen. Accuracy of serum LDH elevation for the diagnosis of Pneumocystis jiroveci pneumonia. *Swiss Med Wkly*. 2011;141:w13184