ISSN: 2573-9565

Review Article

Journal of Clinical Review & Case Reports

The Challenge of Transfusion of Patients Infected with HIV/AIDS

Dr. Carlos A. Gonzalez[1, 2]* Silvana Gonzalez[3] and Jeremías Gonzalez[4]

[1]*Servicio de Hemoterapia, Hospital Muñiz, Buenos Aires, Argentina*

[2]*Dirección de Posgrado, Medical School, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina*

[3]*Medical School, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina*

[4]*Cangallo School, Buenos Aires, Argentina*

***Corresponding author**
Carlos A Gonzalez, Servicio de Hemoterapia, Hospital Muñiz, Buenos Aires, Argentina, Dirección de Posgrado, Medical School, Pontificia Universidad Católica Argentina, Buenos Aires, Argentina, Uspallata 2272, Buenos Aires, Argentina, Tel: +54 11 43057893; Fax: +54 11 43057893; E-mail: carlosgonzalez@buenosaires.gob.ar

Submitted: 20 Jan 2019; **Accepted**: 28 Jan 2019; **Published**: 11 Feb 2019

Abstract
The transfusional support of human immunodeficiency virus-infected patients is a challenge both for the clinical physician and for the blood services, either because of the immunohematological problems or the microbiological/thrombotic risk associated.

The immunohematological risk caused by positive crossmatch is resolved by autologous adsorption; if the patient was recently transfused, the adsorption will be homologous.

The thrombotic risk (due to hypercoagulable state) is resolved by pretransfusion heparin administration and leukoreduction only in autoimmune hemolytic anemia cases; and the presumed microbiological risk is similar to HIV-negative patients.

Keywords: Blood Transfusion – HIV/AIDS Patients - Autoantibodies – Antiglobulin Test

Introduction
Infectious diseases are one of the most important public health problems of the world, reaching even 25% of annual cause of death. In developing countries, it represents the first cause of death [1].

Among infectious diseases, the Human Immunodeficiency Virus (HIV) still is one of the major public health problems in the world; more than 35 million deaths are attributed to this virus. In the world, 36, 7 million individuals are estimated to be HIV-infected [2].

Most of HIV-infected patients present some degree of anemia during the natural history of the disease [3]. The etiology of the anemia is frequently multifactorial and many times is refractory to conventional treatment of anemia (iron, erythropoietin, folate and vitamin B12), being the red blood cells (RBC) transfusion the main treatment for symptomatic anemia in these patients.

The transfusional support of HIV-infected patients is a challenge both for the clinical physician and for the blood services, either because of the immunohematological problems or the microbiological/thrombotic risk associated.

The Hospital Muñiz is an institution specialized in infectious diseases. It is a medical center of reference of the more complex cases. This publication tries to display the experience of this hospital and the more frequently detected problems proposing a basic resolution scheme.

Immunohematological Risk
The HIV attacks the immune system and deteriorates the systems of defense against infections and certain types of cancer and the patient acquires a progressive immunodeficiency because the HIV destroys the immune cells. The most advanced stage of HIV infection is the Acquired Immunodeficiency Syndrome (AIDS) which, according to the person, can take between 2 and 15 years to manifest. The patients with AIDS can have certain types of cancer and infections or present other clinical manifestations of importance that might reach a high degree of lethality.

The immunohematological consequences of the direct and indirect action of HIV in the immune system of the patient or the associated infections are so diverse and heterogenous that the consequences are from clinical insignificance to life risking (Figure 1). To its adequate understanding, the alloimmune risks will be discussed first, then the ones concerning erythrocytes and serum.

Immune Response to Blood Group Antigens
One of the first consequences of the action of HIV on the immune system is the decrease of the alloimmune response to the exposition of “non-self” erythrocytes [4]. The general hospital population presents an incidence of irregular antibodies of 8-10% versus the HIV-infected of 0 – 2, 6% [5,6].

This situation is to be expected, since it expressions the inability to recognize and present blood group antigens by the antigen-presenting cells (APC) and the decrease of lymphocytes T CD4+ type 2, a subpopulation that's essential to this process [7].

In animal models, viral infections or viral-like inflammation can potentiate the alloimmunization, whereas Gramm negative bacterial infection or sepsis suppress or diminish alloimmune response [5].

On the other hand, the levels of antibodies of ABO system, anti-A and anti-B are usually normal, a situation that's compatible with the fact that the immune response that produces this anti-carbohydrates and anti-glycolipids antibodies is T independent (Figure 2).

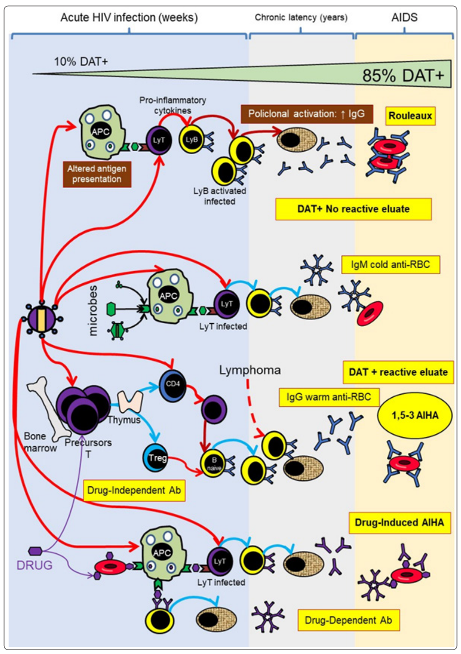

Figure 1: HIV effect and microbes of immunohematological importance
Ly: Lymphocyte
APC: Antigen present cell
DAT: Direct antiglobulin test

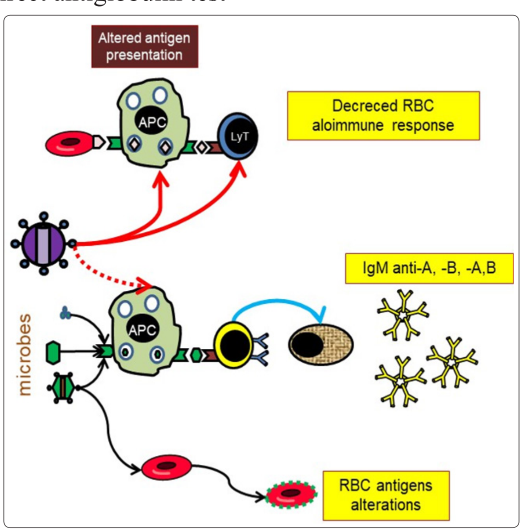

Figure 2: HIV effect on alloimmune response to blood group antigens and effect of other germs over molecules carrying antigens in RBC membrane

Erythrocytes Problems

The natural history of infections with hematogenous dissemination of microorganisms tends to count with the participation of RBC as receptors (Table 1), as "target" of their direct action or their products/enzymes. In fact, HIV can interact with glycolipid and glycoproteic structures of the erythrocyte membrane, although its clinical significance is still uncertain [8].

Table 1: Blood group antigens receptors to microbes

Agent	Receptor	Clinical manifestations
M. Pneumoniae	I	Pneumonia
P. vivax/ P.knowlesi	DARC (Fy6)	Malaria
P. Falciparum	A / B, GPA (MN), GPB (SsU), GPC (Ge), Banda3 (Di), CR1, CD36, ICAM-1, XK, Ok^a	Malaria
HIV	H, P, Lu^b, Ok^a	AIDS
H pilori	Le^b H	Pyloric ulcer
E. Coli	DAF (CROM); GPA (M); GLOB1 (P)	Urinary infection
Echovirus / Coxsackie	DAF (CROM)	Diarrhea, meningitis, pneumonia
M. Tuberculosis	CR1 (Knops)	Tuberculosis
M Leprae		Leprosy
H influenzae	AnWj	Severe infection
Parvovirus B19	Glob1 (P)	RBC aplasia, Fifth disease
Poliovirus	CD44 (IN)	Poliomyelitis
Pseudomona aer	B, P1, Pk,	Sepsis
Giardia	A	Parasitism
Streptococus suis	GLOB1 (P)	Sepsis

Alteration in Blood Group Antigens

From the microbe-erythrocyte interaction, arise alterations in the structures of the cell membrane surface, these alterations very rarely modify in a clinically significant way the half-life of RBC.

The most affected structures tend to be the proteins or carbohydrates of blood group antigens and can potentiate, depress or acquire "de novo" blood group antigens (Table 2).

The blood group antigens are products of the expression of one or more inherited genes (genotype), this phenomenon (modification of phenotype) are usually passengers and remit spontaneously or by the action of medical treatment.

In some cases, the erythrocyte membrane can be modified by microbial enzymes (Neuraminidase, β-Galactosidase, Deacetylase) that can diminish the expression of blood group antigens. In the case of A and B antigens of ABO system, not always this diminution of expression may be detected by conventional agglutination test.

Table 2: Blood group antigens affected by microbes

Action on antigens	Infectious agent or most important clinical manifestations	Target
Depression	HIV/AIDS	CR1 / Knops
	Sepsis	A, B, H, I, K, M, N
	Epstein Barr Virus	Le
Potentiation	Sepsis	T, Tk, Th y Tn
Acquired	Sepsis	B_{adq}
	E. Faecium	K_{adq}, Jkb_{adq}
	Micrococcus	Jk^{b}_{adq}

In other cases and by a similar mechanism to the previously described (modification of membrane by bacterial enzymes) it may have the opposite effect that is to potentiate blood group antigens that are not generally detected by conventional test. These antigens are T, Tk, Th and Tn and responsible for the polyagglutination phenomenon. This problem is in general detected by "minor crossmatch"; resulting positive in saline medium at room temperature (patient's erythrocytes vs donor's plasma). Although in the case of "natural" antibodies not complement-activator IgM and non-reactive in anti-globulin medium, they usually do not have clinical significance and may be ignored.

More rarely, the detection of unexpected antigens is usually the result of the direct action of microbial enzymes or the adsorption of bacterial products in the surface of erythrocytes. In these cases, they often produce discrepancies in ABO typing or other blood group systems (Figure 2).

Positive Direct Antiglobulin Test and Non-Reactive Eluate

Since the beginnings of the HIV/AIDS pandemic the high incidence of positive Direct Antiglobulin Test (DAT) and non-reactive eluate was described in HIV-infected individuals, without clinical-laboratorial evidence of immune hemolysis, This incidence at the beginning of the infection is usually 10% increasing progressively as the disease advances reaching 85% in the final stage of infection (AIDS) [3,9].

The most probable cause of DAT positive is polyclonal hypergammaglobulinemia (resolved with serum dosage of immunoglobulins); another cause may be the presence of circulating immune complexes and IgG autoantibodies.

The differential diagnoses are ABO incompatibility, erythrocytes covered by IgA/IgM and anti-drug antibodies (Table 3) [10].

Table 3: Positive DAT differential diagnosis in HIV/AIDS

Differential diagnosis	Antecedent		Resolution
Postransfusional ABO incompatibility	Transfusion last 3 months	RBC	Mixed field. Elution vs A / B RBC and IAT
		Platelet, plasma, hemoderivates	Elution vs RBC A / B and IAT
	Clinical signs of hemolysis	Acute anemia, shock, hemoglobinemia, hemoglobinuria, jaundice, renal insufficiency, thrombosis, disseminated intravascular coagulation	Medical treatment
	Laboratory indirect parameters	LDH, haptoglobin, reticulocytes, bilirubin	
RBC coated by C3d /IgA or IgM			DAT with anti-C3d, -IgA, -IgM
Drug-induced antibodies	Recent drug administration and clinical/laboratorial parameters of hemolysis		Drug dependent-antibodies detection in serum/ eluate

Auto Agglutination

Frequently, the HIV-infected patients have cold antibodies (mostly without clinical significance) during the disease [11]. Rarely, these cold antibodies (IgM) may be sufficiently potent to produce spontaneous agglutination of the blood sample that can cause discrepancies with ABO and Rh typing [12].

The resolution is to try that the cold antibody does not interfere with the RBC typing. So, initially let the sample incubates at 37ºC for 60 minutes and then washes RBC with physiological solution at 37ºC [13,14].

If the control (albumin at 6%) invalidates the typing by spontaneous agglutination, we must use a conservative elution of RBC (heat, chloroquine, etc.) or treatment with reducing agents (2-ME, DTT). Finally, and if the cold autoantibody is very potent (very rare), must use genotype typing with nucleic acid amplification techniques.

Serum Problems

The main functions of the immune system are to recognize microbes and control/destroy the pathogenic ones; destroy tumoral cells and protect fetal and normal cells. Integrating the immune response to bacteria (T independent) the "natural" antibodies of blood group (ABO, H, Le) mostly IgM, IgG2/IgG4 of low affinity are generated and if they do not fix complement they are usually clinically not significant (apart of ABO antibodies).

The previous exposure to pathogens carrying sequences of peptides similar to blood group antigens (T dependent) could explain the relationship between infection and detection of irregular antibodies [15] (Table 4).

Table 4: Blood group antibodies related to infections

	Infection
Anti-M	*Proteus mirabilis*
Anti-P_1	Hydatidosis, liver flukes
Anti-K	*E. coli, Campylobacter jejuni, M. tuberculosis, E. faecalis*
Anti-Jk^b	*Micrococcus; Proteus Mirabilis*
Anti-P	*E. Coli, measles, mumps, chickenpox, adenovirus, Cytomegalovirus, Epstein Barr Virus, syphilis, Haemophilus influenzae, M. pneumoniae*
Anti-Pr	Viral infections
Anti-I	*M. pneumoniae*
Anti-i	*Epstein-Barr, Virus HIV*
Anti-Rx	viral Infection

As mentioned previously, there is a strong relationship between infections and development of anti-RBC autoantibodies (with or without hemolysis); the prevalence in HIV-infected patients is higher [16].

There are several proposed mechanisms, not mutually exclusive, that explain these findings [17]:

a) Molecular mimicry [18]. The structural similarity between HIV and RBC structures could induce the production of autoantibodies associated with the development of autoimmune hemolytic anemia (AIHA).
b) Escape to thymic deletion of auto reactive clones [17].
c) Disfunction T-B which decrease of Tregs lymphocytes and increase of Th2; it may even generate polyclonal B-cell activation [19].
d) Predisposition to develop drug-induced antibodies [20]. This mechanism may be the consequence of a rearrangement of the homeostasis of the immune system, which leads to exacerbate functions and express pre-existing autoreactive elements. When the immune system is exposed to polymerization (which is often in our institution), patients may develop anti-drug antibodies (via primary RBC-microbe-drug interaction).

The antibodies produced can be cold (IgM) or warm (IgG).

Cold Autoantibodies

The pathological cold autoantibodies are defined by presenting a positive DAT by anti-C3d (negative for anti-IgG), title at 4º C > 64 and evidence of clinical hemolysis. Any cold antibody that does not meet these characteristics is generally considered non-pathological.

The clinically significant antibodies are detected by pre-heated 37°C the samples; in cases of very potent antibodies (with high thermal range), must use the cold autologous adsorption supernatant.

Warm Autoantibodies

Different publications have documented that patients infected with HIV/AIDS have AIHA incidence of 3%; being their risk 28 times higher than the controls even in those patients treated with antiretroviral therapy, the prevalence may be the same or higher [21,22].

The clinical presentation of AIHA associated with HIV varies from a mild form, moderate to fulminant hemolysis (infrequent) [23].

Most of the well-documented cases of drug-induced AIHA in patients infected with HIV/AIDS are diagnosed in our Hospital and it certainly reflects a higher level of suspicion compared to other institutions [20].

The diagnosis of AIHA in patients infected with HIV/AIDS follows the same clinical-laboratory steps of the non-infected [24]. That is, clinical evidence (acute anemia, shock, hemoglobinemia, jaundice, renal insufficiency, coagulopathy) and indirect parameters of hemolysis (increase of LDH and indirect bilirubin, decrease of haptoglobin).

Clearly the finding of positive DAT + in patients infected with HIV/AIDS (in the absence of clinical and laboratory signs of hemolysis) is not sufficient evidence for the diagnosis of AHAI.

Synthesis: The HIV infected patients may develop clinically significant alloantibodies (less frequently that HIV-negative); autoantibodies (more frequently that HIV-negative) and Drug-Induced antibodies (more frequently that HIV-negative).

Selection of Blood to be transfused

The indication of transfusing patients infected with HIV/AIDS does not differ substantially compared with HIV-negative [25]. However, the main immunohematological problem is the positivity of pretransfusional crossmatch test (Figure 3) [10,26]. Prior to any attempt at resolution, always consider the patient's antecedents (transfusion, pregnancy, drugs, etc.) since they can guide to the possible causes of the positive crossmatch, positive DAT and positive Indirect Antiglobulin Test (IAT).

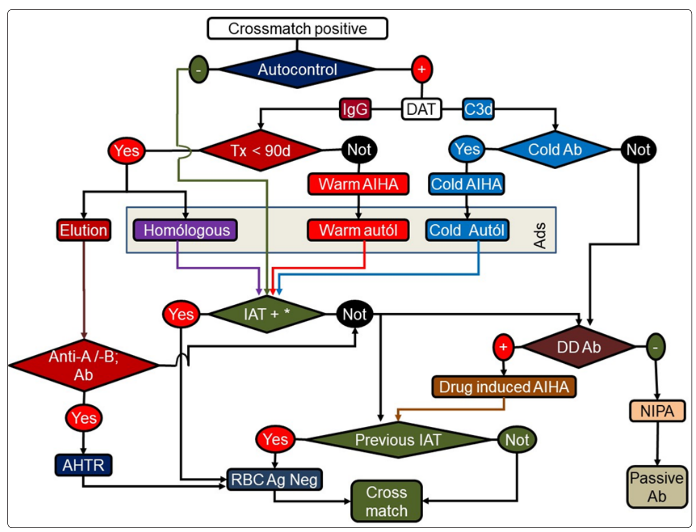

Figure 3: Basic resolution scheme of positive crossmatch

Ads: Adsorption
Autol: Autologous
Ab: antibody
* Clinically significant
DD: Drug Dependent
NIPA: No immune protein adsorption
AIHA: autoimmune hemolytic anemia
IAT: indirect antiglobulin test

Tx: transfusion
RBC: red blood cells
Ag: antigen
AHTR: Acute hemolytic transfusión reaction

If the patient was transfused in less than 3 months, may suspect postransfusional hemolytic reaction by performing eluate and homologous adsorption to detect clinically significant antibodies/ perform crossmatch. If there is not an antecedent of recent transfusion, the best choice is autologous adsorption to detect clinically significant antibodies and to perform cross-match. Another important antecedent is the previous detection of clinically significant antibodies. In such case, select antigen negative RBC (even if they are not actually detected). If the patient had a recent administration of drugs associated with positive DAT/AIHA (α-Methyl Dopa, Cefotetan, Ceftriaxone, Piperacillin, diclofenac, etc.), the problem is solved by performing drug- dependent antibody detection tests in serum/eluate [20].

Transfusional Risk

Patients infected with HIV/AIDS are up to 4 times more likely to present thrombosis compared to the general population due to their hypercoagulable state/ pre-disseminated intravascular coagulation (DIC) and, since transfusion is a potentially thrombogenic factor, thromboprophylaxis has been suggested [27,28].

Initially retrospective studies suggested that RBC transfusion to HIV-infected patients may re-activate endogenous Cytomegalovirus, Herpes Virus 8 and HIV, therefore proposing universal leukoreduction, subsequently three prospective multicentric controlled trials did not prove beneficial effect of universal leukoreduction in patient's HIV-infected, being the clinical indication to leukoreduction the same as for HIV-negative patients [29-34].

Regarding the universal irradiation of blood components to transfuse to HIV-infected patients, there is only one case of postransfusional GVHD [35]. This is probably because postransfusional microchimerism in HIV-infected patients is rarely detected, so the universal irradiation of blood components is not recommended. The indications to irradiation are the same as for HIV-negative patients [36,37].

In summary, the immunohematological risk in HIV positive patients detected by positive crossmatch is solved by adsorption techniques; the thrombotic risk (due to hypercoagulable state) is solved by pretransfusional heparin administration and leukoreduction only in cases of AIHA; and the presumed microbiological risk is similar to HIV-negative patients (Table 5).

Table 5: Transfusional risk in HIV positive patients

Risk	Cause	Resolution
Immunohematological	Positive crossmatch	Adsorption techniques
Thrombotic	Hypercoagulability	Heparin / leukoreduction only in AIHA
Microbiological	CMV, HH8, HTLV	Leukoreduction and universal irradiation without proven benefit
	Reactivation of endogenous virus	

Conclusion

The world incidence of HIV infection/AIDS is relevant; therefore, it is important to recognize the transfusional risks and problems that can be produced and how they can be solved. This publication aims to contribute to its resolution.

Acknowledgment

I express my gratitude to my medical guide Prof. Dr. Enrique Rewald (1926-2016+), a brilliant mind that Argentina did not know how to value. Special thanks to Ana Maria Ahumada FUHESA for support.

References

1. https://www.who.int/es/news-room/fact-sheets/detail/the-top-10-causes-of-death
2. https://www.who.int/es/news-room/fact-sheets/detail/hiv-aids
3. Zon LI, Arkin C, Groopman JE (1987) Hematologic manifestations of the human immune deficiency virus (HIV). Br J Haematol 66: 251-256.
4. Boctor FN, Ali NM, Mohandas K, Uehlinger J (2003) Absence of D-alloimmunization in AIDS patients receiving D-mismatched RBCs. Transfusion 43: 173-176.
5. Hendrickson JE, Tormey CA (2016) Understanding red blood cell alloimmunization triggers. Hematology 1: 446-451.
6. Körmöczi GF, Mayr WR (2014) Responder individuality in red blood cell alloimmunization. Transfus Med Hemother 41: 446-451.
7. Parker DC (1993) T Cell-dependent B cell activation. Annu Rev Immunol 11: 331.
8. Cooling L (2015) Blood Groups in Infection and Host Susceptibility. Clin Microbiol Rev 28: 801-870.
9. Lai M, d'Onofrio G, Visconti E, Tamburrini E, Cauda R, et al. (2006) Aetiological factors related to a positive direct antiglobulin test result in human immunodeficiency virus-infected patients. Vos Sanguinis 90: 325-330.
10. González CA (2010) Prueba Cruzada Positiva. Rev Arg Transfusion 36: 147-153.
11. González CA (1997) Semiología Inmunohematológica en la Infección por el VIH-1. Revista Argentina de Infectología X: 11-20.
12. Endoh T, Kobayashi D, Tsuji N, Tanabe H, Koshida S, et al. (2006) Optimal prewarming conditions for Rh antibody testing. Transfusion 46: 1521-1525.
13. Judd WJ (2006) How I manage cold agglutinins. Transfusion 46: 324-326.
14. Berentsen S (2018) How I manage patients with cold agglutinin disease. Br J Haematol 181: 320-330.
15. Hudson KE, Lin E, Hendrickson JE, Lukacher AE, Zimring JC, et al. (2010) Regulation of primary alloantibody response through antecedent exposure to a microbial T-cell epitope. Blood 115: 3989-3996.
16. Christen U (2018) Pathogen infection and autoimmune disease. Clinical and experimental immunology 195: 10-14.
17. Barcellini W (2015) New Insights in the pathogenesis of autoimmune hemolytic anemia. Transfus Med Hemother 42: 287-293.
18. Tsiakalos A, Routsias JG, Kordossis T, Moutsopoulos HM, Tzioufas AG, et al. (2011) Fine epitope specificity of anti-erythropoietin antibodies reveals molecular mimicry with HIV-1 p17 protein: a pathogenetic mechanism for HIV-1-related anemia. J Infect Dis 204: 902-911.
19. Okoye AA, Picker LJ (2013) CD4 (+) T-cell depletion in HIV

infection: mechanisms of immunological failure. Immunol Rev 254: 54-64.
20. González CA, Guzmán L, Nocetti G (2003) Drug-dependent antibodies with immune hemolytic anemia in AIDS patients Immunohematology 19: 10-15.
21. Olayemi E, Awodu OA, Bazuaye GN (2008) Autoimmune hemolytic anemia in HIV-infected patients: a hospital based study. Annals of African Medicine 7: 72-76.
22. Yen YF, Lan YC, Huang CT, Jen IA, Chen M, et al. (2017) Human Immunodeficiency Virus Infection Increases the Risk of Incident Autoimmune Hemolytic Anemia: A Population-Based Cohort Study in Taiwan. J Infect Dis 216: 1000-1007.
23. Gonzalez CA (1998) Successful treatment of AIHA with IVIG in a patient with AIDS. Transplant Proc 30: 4151-4152.
24. González CA (2000) Diagnóstico inmunohematológico de anemia hemolítica autoinmune. Revista Argentina de Transfusión XXVI: 21-40.
25. Van den Berg K, James van Hasselt, Evan Bloch, Robert Crookes, James Kelley, et al. (2012) A review of the use of blood and blood products in HIV-infected patients. South Afr J HIV Med 13: 87-104.
26. Chiaroni J, Gouvitsos J, Dettori I, Ferrera V (2009) How we evaluate panagglutinating sera Transfusion 49: 1540-1545.
27. Crum-Cianflone NF, Weekes J, Bavaro M (2008) Thromboses among HIV-infected patients during the highly active antiretroviral therapy era. AIDS Patient Care STDS 22: 771-778.
28. Kato GJ, Taylor JG (2010) Pleiotropic effects of intravascular haemolysis on vascular homeostasis. Br J Haematol 148: 690-701.
29. Lumadue JA, Shirey RS, Kickler TS, Ness PM (1996) Leukocyte reduction of red cells when transfusing patients with autoimmune hemolytic anemia: a strategy to decrease the incidence of confounding transfusion reactions. Immunohematology 12: 84-86.
30. Busch MP, Lee TH, Heitman J (1992) Allogeneic leukocytes but not therapeutic blood elements induce reactivation and dissemination of latent human immunodeficiency virus type 1 infection: implications for transfusion support of infected patients. Blood 80: 2128-2135.
31. Preiksaitis JK (2000) the cytomegalovirus-"safe" blood product: is leukoreduction equivalent to antibody screening? Transfus Med Rev 14: 112-136.
32. Collier AC, Kalish LA, Busch MP, Gernsheimer T, Assmann SF, et al. (2001) Leukocyte-reduced red blood cell transfusions in patients with anemia and human immunodeficiency virus infection: the Viral Activation Transfusion Study: a randomized controlled trial. JAMA 285: 1592-1601.
33. Drew WL (2003) Absence of activation of CMV by blood transfusion to HIV-infected, CMV-seropositive patients. Transfusion 43: 1351-1357.
34. Asmuth DM (2003) Absence of HBV and HCV, HTLV-I and -II, and human herpes virus-8 activation after allogeneic RBC transfusion in patients with advanced HIV-1 infection. Transfusion 43: 451-458.
35. Klein C (1996) Moderate and transient transfusion-associated cutaneous graft-versus-host disease in a child infected by human immunodeficiency virus. Am J Med 101: 445-446.
36. Kruskall MS (2001) Survival of transfused donor white blood cells in HIV-infected recipients. Blood 98: 272-279.
37. HW Reesink, S Panzer, CA Gonzalez, Lena N, Muntaabski P, et al. (2010) Haemovigilance for the optimal use of blood products in the hospital. Vox sanguinis 99: 278-293.