
Screening For Blood Transfusion Transmissible Viruses In Resource Limited Settings

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Citation

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Abstract

Transmission of viruses such as HIV, HBV and HCV through blood transfusion has been effectively reduced in resourceful countries due to organized central blood transfusion service, which applies stringent donor selection criteria, screening methods involving detection of viral nucleic acids and pathogen inactivation. This very costly but rewarding venture has remained difficult in countries with limited health budget such as Nigeria. There is poor donor mobilization capacity with difficulty in implementing donor selection, use of antibody only testing strategies, which leaves large numbers of early infection undetected and lack of organized central blood transfusion service. Many especially the primary and secondary health care centers are yet to implement screening for these viruses and pathogen inactivation methods are not available. There is need for the new developing Nigerian National Blood Transfusion Service (NNBTS) which is supported by Safe Blood for Africa in South Africa (SBAF) to address this problem at the outset if we are to achieve the risk reduction required especially as many of these viruses are endemic in our environment.

INTRODUCTION

The goal of any transfusion service is to provide adequate and safe blood and blood products that meet the needs of patients in the environment. Blood safety interventions in the developed nations have greatly reduced the overall risk of transfusion-transmitted infections (TTI). Blood donors are questioned about risk factors for several parenterally or sexually transmitted viruses, such as the human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV), Hepatitis G virus (HGV), Epstein Barr Virus (EBV), Cytomegalovirus (CMV), Human T Lymphocytic virus (HTLV - 1 & HTLV - 2) and blood is screened for indicators of infection.¹ Donors are also asked about risk factors for malaria, babesiosis, and Chagas' disease. Blood intended for transfusion to immunosuppressed patients who are at increased risk for cytomegalovirus (CMV) disease is tested for CMV antibody or undergoes leukocyte reduction, since CMV resides in the white cells. These viruses can also be transmitted by tissue transplantation.² Many of these infectious agents may cause lifetime morbidity and/or mortality. Hence it is necessary to understand the organisms which could be transmitted through blood transfusion and the means by which this could be prevented.

There are four main groups of micro-organisms known to cause infections but only three groups of microbes - viruses, bacteria and protozoa - have been reported to be transmitted by blood transfusion. Individuals with fungal infections are usually too sick to be accepted as blood donors. Viruses are most commonly transmitted by transfusion mainly because many donors may be asymptomatic at the time of presentation.

Recently, a new form of infectious agent - the prion - has been identified in the UK, all unexposed individuals receive only plasma and its products imported from the USA since most donors have been exposed to consumption of the contaminated beef that may transmit prions.³

In order to be transmitted by blood transfusion, an infectious agent must be present in the donated blood. This agent must be capable of using the blood stream as a route of entry into the host. The infected donor must be essentially free of any noticeable signs and symptoms of disease, otherwise, they would have been identified during donor screening and the donor would have been excluded or deferred. The agent must exist naturally for a period of time, either free in the plasma or present in a cellular component in the blood stream of an infected donor.

Other factors that may contribute to transmission include the immune status of the patient and the dose of infectious agent transfused.

Risk free blood transfusion is quite expensive but worthwhile, but near risk free has been achieved in resourceful developed countries mainly because of organised central blood transfusion centres that are equipped to deal with such and even emerging and re-emerging infections using various sensitive screening tests and/or pathogen inactivation. The bulk of the donors in this setting are voluntary who have no hesitation in answering truthfully the stringent donor questionnaire that is targeted at screening out donors that are at risk of having asymptomatic TTIs in incubation or window period. The large number of blood units collected daily also allows time in quarantine of donated blood to undergo maximal screening tests and in case of plasma up to 6 months before fractionation at which time a donor would have re-presented and been rescreened. This has gone a long way in reducing TTIs in such countries. In Nigeria however, the blood transfusion service is at its teething stage and is not yet fully equipped to cater for the extensive screening tests obtained elsewhere despite the high burden of such infections. There is also a restriction in answering some of the questions mainly because the bulk of donors are family replacement donors,⁴ and present in company of other family members thus, are likely to withhold information about their personal lifestyle. This leaves the burden of detection of TTIs to laboratory tests only which are mostly the antibody based tests that do not offer near risk free detection limits. Three viruses including HBV, HCV and HIV 1 & II are currently those that are routinely tested for prior to blood donation in Nigeria in conformity with the recommendation by the Nigerian National Blood Transfusion Service (NNBTS) guidelines.⁶ Other viruses such as CMV are only tested for in blood intended for immune-suppressed patients. These viruses are endemic in Nigeria with high prevalence in the blood donor population therefore, blood transfusion may be very efficient in transmitting these infections, especially in places where screening is not practiced.

This review examines the risk of transmitting viral infections by blood transfusion in Nigeria where there is resource constrain in implementing effective measures for risk reduction and contrasts it to what has currently been achieved in resourceful countries. It aims to bring to light the shortcomings of our blood transfusion services which is greatly dependent on hospital based transfusion with support

from the up coming NNBS in order to alert authorities concerned to create appropriate and sustainable strategies that would reduce the risk of viral transmission through blood transfusion to near zero as obtains elsewhere.

The literature was assessed using appropriate terms on the pubmed and google scholar and full articles were obtained from the journals where available.

HEPATIS B VIRUS

Hepatitis B virus (HBV) is the most common cause of serious liver infection in the world and is said to have infected more than two billion people with 350 million people being chronic carriers.⁷ The virus consists of a nucleocapsid and an outer envelope composed mainly of three hepatitis B surface antigens (HBsAg) that play a central role in the diagnosis of HBV infection. The nucleocapsid contains hepatitis B core antigen (HBcAg), a DNA polymerase reverse transcriptase, the viral genome as well as cellular proteins.⁸ The protein encoded by the pre-core [pre-C]/core gene [C] undergoes post-translational modification to yield hepatitis B e antigen (HBeAg), which is a sero- marker for high viral replication and infectivity.⁸

The common modes of transmission of HBV in developing countries are perinatal, early childhood, unsafe injections practices, blood transfusions and sexual contact.⁹ Having been infected, HBV infection runs a clinical course of an incubation period lasting between 4 - 12 weeks, acute illness of 2 weeks – 3 months and eventual recovery for individuals who resolve their infection¹⁰. Many infected adults are without classical symptoms and individuals in whom HBsAg is present in their blood for more than six months are considered to be chronically infected with HBV.¹⁰ Such individuals with chronic infection have a high risk of liver cirrhosis and hepatocellular carcinoma¹¹ but may pass the medical tests required for blood donors and the current serological test of HBsAg may be negative, this has a grave implication on blood safety in countries like Nigeria where only HBsAg tests are used as indicators for infection.

The HBV carrier rate is 10.4% among black Africans and 15% in young volunteer blood donors.¹² That is to say that by age 40, many people would have come in contact with the virus.^{12,13} Nigeria, one of the most populous nations in Africa is considered hyper endemic for HBV infection with prevalence of HBsAg in the adult population including replacement blood donors ranging between 1.2 % and 26%¹⁴⁻²⁰ and 2.4% in voluntary donors.^{21,22}

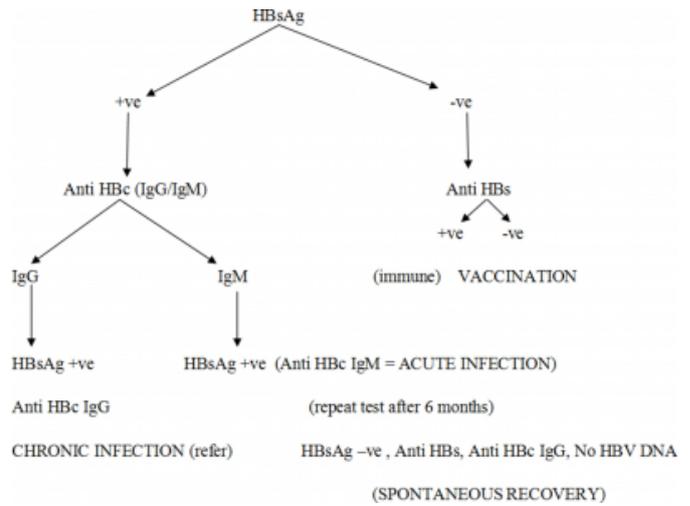
This setting additionally, does not allow for optimal donor selection, or indeed donor testing as obtains in the developed nations where the prevalence is less than 1% of the population.¹² Current testing strategies for Hepatitis in Nigeria, is by HBsAg screening using either Latex method which lives nearly half of the presumably infectious units undetected¹⁴ or in some hospitals, the more sensitive Enzyme Immunosorbent Assay (ELISA) which only gives an additional 2% level of higher detection than Latex agglutination.²³

In the current practice here, blood donors are tested for HBsAg, with permanent deferral of donors with a reactive test. Testing for anti- HBe was used in the USA as a surrogate test for NANB viral hepatitis. After discovery of hepatitis C virus (HCV) and implementation of HCV testing, testing for anti-HBe continued in some countries to detect some HBV infected HBsAg negative donors (though anti-HBe is associated with many false positives).²⁴ Testing for HBsAg is usually performed using EIA, radioimmunoassay or other immunological based assays. Since the inception of HBsAg testing in 1971, the sensitivity has increased by two orders of magnitude²⁵ with the latest, most sensitive HBsAg detection method using Chemiluminescence being widely used in most developed nations.²⁶ Numerous commercial kits are available for HBsAg testing. Positive tests are often confirmed by retesting the sample after incubation with anti-HBs, to see if the HBsAg result can be neutralized. True positives for HBsAg will have the antigen neutralized by the specific antisera. In countries with limited resources rapid and less sensitive immunofiltration methods using latex based, or immunochromatographic methods are used, often without confirmatory or neutralization testing,¹⁰ as what obtains in Nigeria. Testing for anti-HBe, anti- HBs and anti-HBe is usually performed by radioimmunoassay or enzyme based immunoassay. In countries without formal kit licensing requirements, simultaneous presence of anti- HBe strengthens the validity of an HBsAg positive result. Alternatively, the presence of HBV DNA, determined by nucleic acid testing (NAT), is evidence of infection and infectivity. Nucleic acid testing has been able to reduce the window period of other viral infections such as HIV and HCV but has not been shown with testing for HBV DNA especially in countries with low prevalence.²⁶ NAT testing is not available in Nigeria to test its significance in this high prevalence country.

Figure 1 shows the diagnostic work- up for hepatitis B infection.

Figure 1

Figure 1: Diagnostic work – up for HBV infection.



Currently HBsAg –ve donors are accepted for donation and those that are HBsAg positive are deferred for 6 months and retested. There after, if HBsAg is negative and with evidence of Anti -HBs or anti HBc IgG and negative for HBV DNA, they are considered non infectious and therefore eligible for blood donation. Since this test is not available in Nigeria, it may be safer practice to permanently differ any previous HBsAg positive donor or until a time when such verifications can be made. This means that the already poor donor pool will be further restricted with consequent inability to meet blood requirement.

HEPATITIS C VIRUS

Following the introduction of screening for HBsAg there were still reports of transfusion associated hepatitis. This lead to the discovery of transfusion transmitted non-A non-B hepatitis (NANB) which is a generally mild or asymptomatic infection.²⁷⁻²⁹

NANB was eventually discovered to be HCV following DNA characterization from plasma of infected chimpanzees³⁰ and this lead to the first donor screening test for antibody to HCV in 1990, and thereafter, hepatitis incidence fell to near zero level in 1992.³¹

HCV is a flavivirus with long incubation period of 2 to 26 weeks found in plasma of infected persons with the same routes of transmission as HBV. Poverty, high-risk sexual behavior (though being less efficient than transmission of HIV),³² less than 12 years of education, and having been divorced or separated are factors found to increase the risk of infection for unexplained reasons.³³ Other routes of transmission include transfusion with contaminated blood

and blood products before 1990, or needles, and vertical transmission from mother to her fetus/child during the perinatal period.³⁴

It is estimated that about 170 million people are infected worldwide and is said to be five times as widespread as infection with the human immunodeficiency virus type 1 (HIV-1).²⁷ Mild infection may progress to chronic infection in 80% of infected individuals leading to liver cirrhosis, liver failure and/or hepato-cellular carcinoma.^{35,36} HCV-related disease is now the leading indication for liver transplantation though, this does not seem to offer cure and recurrence is universal.³⁷

Factors that increase the risk of progression to cirrhosis include age over 40, consumption of even moderate amounts of alcohol,³⁸ and increased age of acquisition of infection. Patients infected by transfusion are also thought to have more aggressive disease with the risk of progression to cirrhosis related to the degree of liver inflammation and fibrosis seen at the time of a biopsy. Patients with persistently normal ALT have a lower likelihood of progression to cirrhosis.³⁹

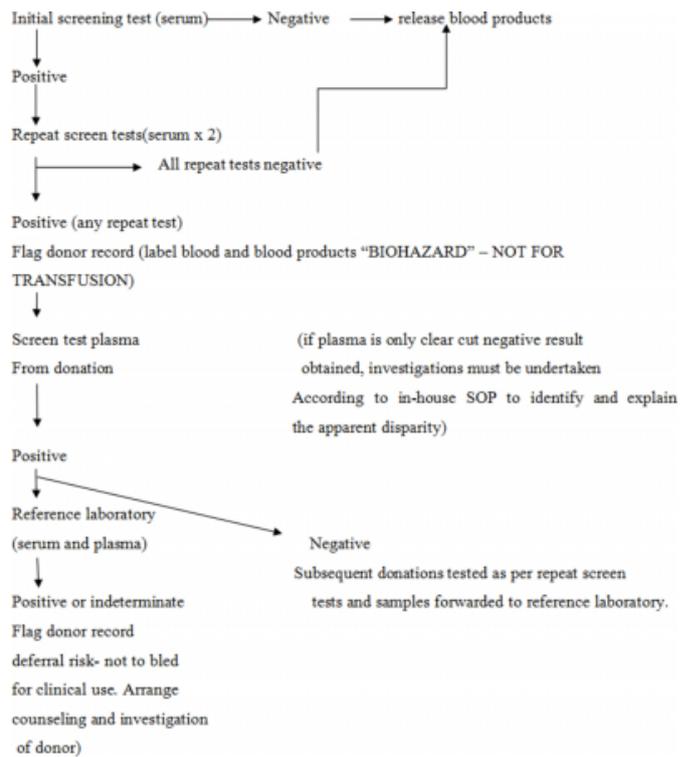
HCV infection is endemic in Nigeria with varying prevalence rate in the different geographical states ranging from 0.5% to 12.3%.^{16,40} Yet, some centers in Nigerian do not practice screening for anti-HCV before blood transfusion.⁴¹ Serological and molecular detection tests for HCV have been used to identify donor exposure. Primary serological assays have continuously been revised and developed with increasing sensitivity and specificity. The current second- and third-generation enzyme immunoassays can detect antibodies within 4 to 10 weeks after infection, false positive results may occur in low risk population such as blood donors and health care workers where recombinant immunoblot assay may be used to confirm results³³ and false negative results can occur in immune compromised individuals^{42,43} who lack the ability to mount an immune response. Such group of patients are primarily too sick to pass as blood donors and are therefore of no consequence to blood transfusion service. Molecular method for detection of HCV RNA (NAT) has become the preferred method of detection of HCV in blood donors in resourceful settings and this could be qualitative or quantitative and thus can also be used in monitoring treatment response in infected patients.

The current practice in most centers that screen for this virus in Nigeria is to test donors for anti-HCV prior to donation and the donor is accepted if this test is negative, in

conformity with the guidelines of NNBTS.⁶ Contrary to this, an action chart has been in use in developed countries since 1991 (figure 2) and the current testing methods have progressed even further to the use of chemiluminescence or nucleic acid testing which has now reduced the risk of transfusion transmitted hepatitis (TTH) to a residual of 1 in 2 million transfusions as compared to the previous 1 in 276,000 with serological testing.⁴⁴ This has translated to prevention of the transmission of 5 HIV infections and 56 HCV infections per year at the costs of more than \$100 million annually, or about \$2 million per infection prevented.⁴⁴ This is an enormous amount that can hardly be accommodated in the Nigerian Health budget. It remains clear then that safety is implied but not practice as far as blood transfusion is concerned in Nigerian context.

Figure 2

Fig. 2 Action chart – anti-HCV testing; adopted from Gunson HH, Dodsworth H. Transfusion transmitted infection. Transfusion medicine, 6(1), 1996.26-36



TRANSFUSION-TRANSMITTED HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Following the devastating history of transfusion hepatitis between 1970s and early 1980s, evolution of HIV as a new disease that can be transmitted by blood transfusion struck with terror for both blood recipients and those responsible for the blood supply.⁴⁵⁻⁴⁷

The HIV is a retrovirus that infects humans and causes gradual but profound loss of cellular immune response due to depletion of the helper- T (CD4+) lymphocytes leading eventually, to the acquired immune deficiency syndrome (AIDS).^{48,49} Once AIDS develops, there is associated onset of opportunistic infections the rate at which is closely related to HIV-I RNA in plasma.⁴⁹ Early infection results in destruction of memory CD4+ T-cells in the gastrointestinal tract with associated inability of the mucosal lymphocytes to control invading organisms.⁴⁹⁻⁵² Associated activation of the immune system during the chronic phase correlates with viral load independent of the rate of depletion of CD4+ T-cells,⁴⁹ there is also related activation of CD38 T –cells on CD4+ T-cells⁵³ and eventually, to development of AIDS associated malignancies such as high grade non- Hodgkin's lymphoma.

Transmission of HIV through blood transfusion is a well established associated risk as evidenced by many patients such as haemophiliacs and others who received blood components prior to the discovery of the virus and subsequently developed the infection.^{45,54} By 1992, 9261 cases of AIDS were attributed to blood transfusion due to lack of defined testing method.⁴⁵ From then on a dramatic and remarkable decrease in the incidence of transfusion-transmitted AIDS followed the discovery of HIV in late 1983 and 1984 by investigative groups led by Luc Montaigne²⁷ and Robert Gallo.⁵⁵

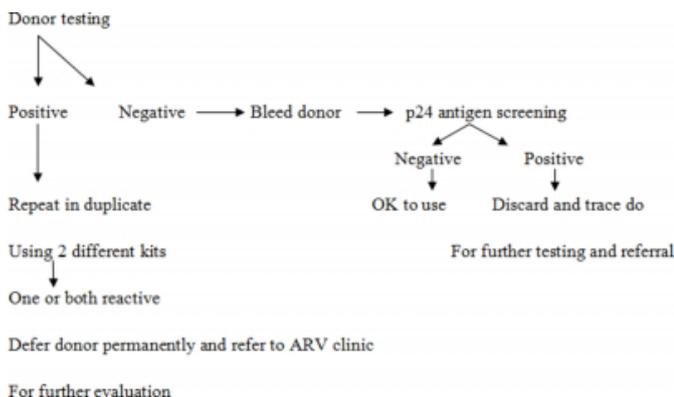
Thereafter, assay for anti-HIV was licensed and used to test all blood products before transfusion and thus, the prevalence was reduced to 49 transfusion-associated cases mainly due to donations made in the window period. As at 1992, transfusion transmitted AIDS accounted for 10% of all cases of AIDS in Africa at which time many countries do not screen, though this risk exist even in countries where all blood products are fully screened.⁵⁶ All blood components can transmit HIV infection and this is due to collection of blood from infectious donors during the “window period” which is said to be about one in every 60,000 or laboratory errors in one out of 2. 6 million donations in the US.⁵⁷ Other risk factors for HIV infection mainly include transmission through hetero- or homosexual contact, with multiple partners, mother to child transmission either during childbirth or through breast milk during lactation, sharing of injections by injection drug users, and a smaller proportion by traditional practices (e.g uvulectomy, circumcision) using unsterilized utensils The risk of infection through blood transfusion is relative to the prevalence among the

population from which the blood donors are derived. This risk is reduced when the bulk of donation comes from voluntary non – remunerated blood donors as seen in the developed countries where additionally, there is low prevalence of this infection and is mainly with HIV I. In Nigeria, there is high burden of infection with both HIV I and II among the general population and is said to be about 5.8% according to the sentinel survey as reported by the Federal Ministry of Health⁵⁸ having a prevalence of 3% in blood donors⁵⁹ with over 90% of the donor population being family replacement donors⁶⁰ The risk of infection with HIV following transfusion with a unit of infected blood approaches 90%⁶¹ and the risk through receipt of a unit that is antibody- negative to HIV-1 approximates to 1 in 360,000 to 1 in 153,000.^{57,62} With the introduction of nucleic acid testing, this risk has further been reduced to 1 in 2 million transfusions⁴⁵ at the cost which may seem to be a prohibit able for the health system of Nigeria.

The current testing strategy in some Nigerian hospitals that are supported by US funding agencies, includes the use of 3 antibody detection kits and p24 antigen testing as depicted in figure 3. A donor that tests antibody negative with a rapid test is accepted for donation further testing is with p24 antigen in mini pools of about 3 to 5 sera for all antibody negative units. The prevalence of p24 antigen positive test in antibody negative blood units in this environment was found to be 3.3% ,⁶³ this translates to a residual risk of transmitting HIV infected blood to about 33,000 units per million compared to a residual risk of one in 1.6 to 2 million units in developed nations.⁶⁴ The current testing strategy adopted since its approval by the FDA is nucleic acid–amplification testing (NAT) which has since replaced other testing methods including HIV-1 p24 antigen in such environments.^{65,66} However, even the p24 antigen testing is not widely practiced in Nigeria and thus the risk of transmitting HIV by blood transfusion is expectedly high, thus blood transfusion should only be used when benefit clearly outweighs the risk. This risk is further increased with repeated blood transfusions to about 10.3% in multiply transfused patients with sickle cell anaemia.⁶⁷

Figure 3

Figure 3:HIV Testing strategy of blood donors in Nigeria



CONCLUSION/RECOMMENDATIONS

While the resourceful developed countries have achieved a remarkable reduction or near zero risk of transmitting viral infections through blood transfusion, resource limited countries like Nigeria are evidently lagging behind. The paramount safety of blood transfusion cannot be overemphasized and thus a lot needs to be done to achieve the level of safety required as a matter of urgency. Government needs to substantiate funding for the growing NNBS to obtain all necessary tools that are required including PCR and NAT testing. Leucodepletion and irradiation should be implemented especially in blood meant for transfusion in immune compromised patients including the neonates. The NNBS should strive to improve other preventive measures such as increasing returning voluntary blood donor pool and pathogen inactivation methods. In the meantime, blood transfusion should only be given when the benefit clearly outweighs the risk.

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