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Review Article

Transfusion Medicine Section

Nucleic Acid Amplification Testing (NAT): An Innovative Diagnostic Approach for Enhancing Blood Safety

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ABSTRACT

Though, blood transfusions have not been ever associated with zero risk, many patients need transfusions and the risk reduction through improvement in infectious disease screening is the need of the hour. Many centers have implemented Nucleic Acid Amplification Testing (NAT) for the purpose of blood safety, it is yet to be mandatory regulatory requirement in India. This review aims to provide an overview of the need for implementation of NAT as an innovative approach in blood banks for reducing the window period and identifying the true sero-prevalence and incidence of Transfusion Transmitted Infections (TTIs) (HBV, HIV and HCV). NAT is highly sensitive way to reduce the window period of HIV to 2.93 days, HBV to 10.34 days and HCV to 1.34 days and definitely improves the transfusion safety. For evidence based implementation of pooled or ID NAT large sample size studies based in India are needed. Cost effective adoption of NAT by single center testing in a referral laboratory would help reduce the disease burden in a society where early diagnosis and management would lead to overall health benefit to both donors and patients.

Keywords: Epidemiology, NAT yield, Transfusion transmitted infections, Window period

INTRODUCTION

A large number of blood transfusions are carried out every day to save innumerable lives. Though, safe blood transfusions carry an inherent risk of transmission of infective diseases. Blood safety procedures and testing of blood and blood products, reduces this risk considerably, however, with the current technology in use, the risk remains. Risk of TTIs is a serious problem in patients receiving chronic transfusions and undergoing invasive procedures with exposure of circulatory system. However, the advent of TTIs has been instrumental in the revolutionary changes and developments in both testing of blood units as well as transfusion protocols to improve blood safety. In India as per the regulatory requirement of the Drug and Cosmetics act of 1940, (1st Amendment rules 1992) it is mandatory to test each donated unit of blood for markers of HIVI and II, HBV, HCV, malaria and syphilis [1]. The chronicity and potentially fatal nature of these TTIs could pose a considerable burden on the health status and economics in a country like India . The need to enhance the blood safety by introducing better methods for testing of blood units cannot be over emphasized. For a safe blood service in India, comprehensive laboratory tests are the need of the hour along with a switch over to 100% voluntary donations. Even after being seronegative the blood transfusions are still at risk of transmitting infections. To reduce the residual risk, sensitive screening tests are needed and as a result NAT has been implemented in different parts of the world starting from Europe. The possibility of detecting window period infections has increased and residual risk of TTIs has been reduced. Currently, in India all the blood donations are screened for various infectious markers using ELISA or rapid methods. The NAT tests of high sensitivity rely on amplification of intended regions of viral nucleic acid for detection. The propose of this review is to provide better understanding of the role of NAT in reduction of the risk of acquiring TTIs as compared to conventional methods currently in use by detection of HBV, HCV and HIV infections earlier than the serological screening methods amongst blood donors and reduction of the window period.

DATA COLLECTION

Electronic databases up to July 2016 were searched by using the key words: need of NAT, TTIs, viral screening methods of blood donors, prevalence of hepatitis B and C and HIV, window period of HIV, HBV, HCV etc. Some of the articles were also hand searched using Google. A total 47 research papers were identified including full length original articles , review articles and abstracts. Out of 47 articles, only 37 were selected as references keeping the purpose of the present manuscript.

RESULTS

The Need of NAT for Screening of Blood Units

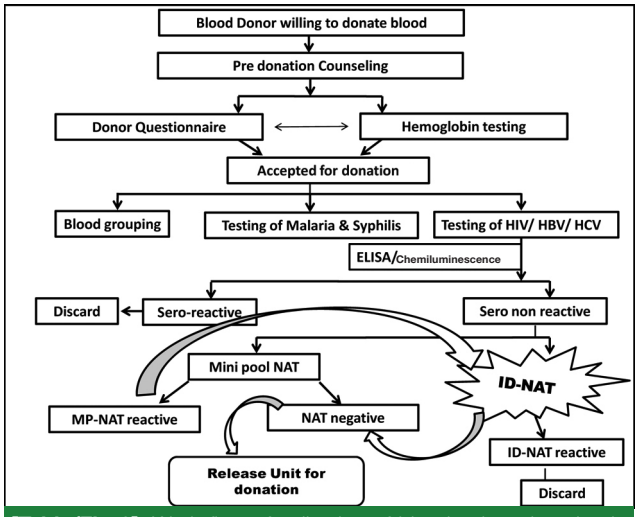
NAT testing is not yet mandatory for screening blood units in India but has been started in a few centers in India to

enhance blood safety [2]. However, the debate has already started and need felt as many private blood banks and hospitals and state Governments of few states have started implementing NAT for blood safety. In India, the scenario is slowly shifting with blood banks gradually introducing NAT to provide safe blood. In a multicentric study from eight blood banks 8 NAT positive cases in 12,224 samples were detected [3]. High combined NAT yield of 0.034% in 23,779 donors, as compared to other developed countries, has been reported in a study from Jaipur [4]. Out of a total of 18,354 donors tested by ELSIA and ID NAT in a study from North India, 7 were found to be NAT-positive for HBV and HCV [5]. The studies with high yield of NAT suggest higher prevalence of TTIs in India and thus the need for NAT in blood banks for screening the donations. In central India, no large study has been done to test or detect window period infections missed by serology. However, two pilot studies warranted the need to establish the NAT as a technology for mandatory screening of donor units as a routine to prevent TTIs [6, 7]. Though, blood transfusion is being used as supportive therapy to save millions of lives all across the globe each year, it is utmost critical that the transfused blood is safe enough to prevent the spread of blood borne infectious diseases. The threat of TTIs were not observed until 1940s when hepatitis B, hepatitis C, HIV, malaria and syphilis were recognized as major diseases transmitted through blood [8]. The laws for mandatory screening of blood units have been formulated for blood borne infections in different countries on the basis of prevalence and surveillance data of donor populations. The prevalence of potentially transmissible agents and the pathogenic potential of the agent along with political, social or ethical considerations play a vital role in deciding the policy of screening for any country.

The problem of blood borne infections poses a major threat still in developing countries, to safe blood transfusion due to less number of voluntary donations, non-uniformity of screening policy, use of less sensitive assays for viral screening and high prevalence of the viral diseases like Hepatitis B and C and HIV. In India according to Drugs and Cosmetic act, it is mandatory to screen the blood units for serological markers of HIV, HBV, HCV, syphilis and malaria. The current mandatory screening strategy in the country does not address the problem of critical window period case detection. The period of time from infection to the time of detection of the infection by any given blood screening assay is called window period and with test results and algorithms of pooled and ID NAT window phase transmission risk models have been developed [9]. [Table/Fig-1] shows, the comparison of window period infections (in days) when units are screened by ELISA and NAT. The blood unit is collected from a screened donor who is accepted for donation through selection process and the sample thus collected is tested [Table/Fig-2].

S. No.	Infectious Marker	ELISA Screening Window Period	NAT Screening Window Period
1.	HIV	21 days	2.93 days
2.	HBV	38 days	10.34 days
3.	HCV	60 days	1.34 days

[Table/Fig-1]: Comparison of window periods of the TTIs by serology and NAT.



[Table/Fig-2]: Work flow of collection of blood unit and testing in the banks.

Epidemiology

Blood transfusion has never been associated with zero risk and there is 1% chance of complications associated with it which includes TTIs [10]. The routes of infections included through blood transfusion are similar in the three important infections of viral origin, HBV, HCV and HIV. Therefore, it would be advisable to screen for these viruses with best available methods in all blood donors for blood safety. With no cure at present, preventive strategies could save thousands of lives who are yet to be exposed to the HIV virus. HIV 1 is the dominant type of the two HIV infections, HIV 1 and HIV 2. The routes of transmission of HIV 1 and 2 are similar. In India National AIDS Control Program (NACP) has been established under Department of AIDS, Ministry of Health and Family Welfare, Government of India. Ministry of Health and Family Welfare has released a report on HIV Estimations 2012: According to the report, HIV prevalence rate in the country is 0.27%. The overall adult HIV prevalence has declined from 0.41% in 2001 to 0.27% in 2011 and in blood donors is 0.32% [11,12]. With about 2.5-3.0 million cases of HIV-1, India has become the country with second highest HIV population in the world. HIV-2 cases have been reported mainly from West and South India both amongst the general and blood donor populations [13].

The prevalence rate of transmission of hepatitis B virus (HBV) infection determines the risk of transmission. The risk is approximately 1:60,000 where the prevalence is low and

in countries like India where HBV infection is endemic, the transmission rate is much higher. In India, nearly 4% of the population , about 40 million people have been estimated to be chronic HBV carriers, making HBV an infection of intermediate endemicity [14], many of them asymptomatic (high endemicity >8%, intermediate 2%–8%, low <2%) [15]. Amongst the voluntary blood donors the frequency of hepatitis C virus (HCV) infection has been reported to be 1%–2%, as evaluated by anti-HCV antibody positivity, and 0.87% in the general community [16].

Impact of NAT as a Technique for Enhancing Blood Safety

The purpose of introduction of NAT in blood banks is for providing additional layer of blood safety. In the developed countries it was introduced in the late 1990s and early 2000s. Currently, approximately 33 and 27 countries in the world have implemented NAT for HIV and HBV respectively [17]. NAT is highly sensitive and specific for viral nucleic acids and is based on amplification of targeted regions of RNA and DNA and thus is the technique of choice. By early detection than serology, the window period of HIV, HBV and HCV infections narrows and in addition with NAT, the issues of donor notification and counseling are resolved well as false reactive donations are identified. In Germany at the time NAT was introduced for the first time for HCV was first introduced in 1997, it was used as Minipool NAT [MP-NAT] performed on pooled samples of 96 blood donations [18]. Later, NAT also got available as ID-NAT for testing each donation individually. The data available from many studies has shown ID NAT to be more sensitive on comparison to pools of 16 or 8 or 4 samples [19]. However, the issue of higher cost in the developing world accounts for the limitation of ID NAT. The utility of NAT as a technique for successful reduction of risk of TTIs has been shown by a study from United States. A reduction by 53% in the prevalence of HCV from 1999 to 2008 among first time donors was reported. Over a period of 10 years, out of the 66 million donations screened 32 HIV and 244 HCV NAT yield donations were identified. When compared with 1999, the prevalence of HCV decreased by 53% in 2008 among first time donors [20]. It was observed that a measurable contribution to blood safety with decreased residual risk of HBV infection was made by the introduction of combined policy of HBV vaccination and HBV NAT in the United States [21]. Similarly, the risks of HCV and HIV have been reduced by 95% and 10% respectively by NAT in the United Kingdom [22]. In the initial year of implementation of NAT, June 2009 by the American Red Cross, the impact of screening by the automated triplex NAT for HIV, HCV and HBV result analysis on blood safety by detection of sero-negative donations was little [23]. HBV yield rate of 1:1056 for blood donations has been observed in China in a pilot study of 18 months, comparing ID NAT with enzyme immunoassays [24]. NAT yield of 1:3100 has been documented where screening 15,655 first time donors were screened and 5 window period HCV donations were identified [25]. In countries like India, hemovigilance has recently received attention and it is being now considered that NAT screening may prove to be more beneficial looking at the burden of the TTI and the endemicity of Hepatitis B and C with high sero-prevalence of transfusion transmissible infectious agents. The studies done so far have also indicated the need to introduce NAT on a wider basis to enhance blood safety in India [3-7]. A summary of various international studies reporting the implementation of NAT as add on test for blood safety has been given in [Table/Fig-3].

S. No.	Authors/ Year/ Reference	Study Summary
1.	Hourfar MK et al., 2008, [18] Germany	Initial study where blood donations from 1997 to 2005 were included and a total of 31,524,571 samples were screened by minipool NAT. 23 HCV, 7 HIV-1, and 43 HBV NAT-only-positive donations were detected. The study concluded that with pooled NAT the risk of transfusion transmitted HIV 1, HBV and HCV has reduced and individual donation testing would have a marginal effect on interception of window period donations.
2.	Zou S et al., 2010, [20] United States	This was a study in United States over a period of 10 years . Out of 66 million units screened with 32 HIV (1:2 million) and 244 HCV (1:270,000) NAT yield donations were identified. There was a remarkable decrease in HCV prevalence by 53% from 1999 to 2008.
3.	Soldan K et al., 2005, [22] United Kingdom	This study included blood donations in United Kingdom during 1996 to 2003 when NAT was introduced. The estimated frequency of infectious donations entering the blood supply during 1996-2003 was 1.66, 0.80 and 0.14 per million for HBV, HCV and HIV respectively. NAT has reduced the risk of HCV by 95% and that of HIV by 10%. Thus, improvements in donation testing lead to lowering the risk of transfusion-transmitted HBV, HCV and HIV infection in the UK.
4.	Dong J et al., 2013, [24] China	A study of 18 months (Between 1st August, 2010 and 31st December, 2011) on a total of 178,447 donations at a Chinese blood centre was done where initial screening was for HBsAg, anti-HIV and anti-HCV using two different EIA for each marker and then all samples were screened using multiplex ID NAT assay for the detection of hepatitis B virus (HBV) DNA, Hepatitis C Virus (HCV) RNA and Human Immunodeficiency Virus-1 (HIV-1) RNA. While no NAT yield cases were found for HIV-1 or HCV 169 HBV NAT yield cases (0.095%) were detected. HBV yield rate of 1:1056 in the blood donor population was found. The study advocated the implementation of NAT to provide a significant increase in blood safety relative to serological screening alone for blood donations.

[Table/Fig-3]: A summary of various Indian studies reporting the implementation of NAT as add on test for blood safety.

Implementation of NAT in India

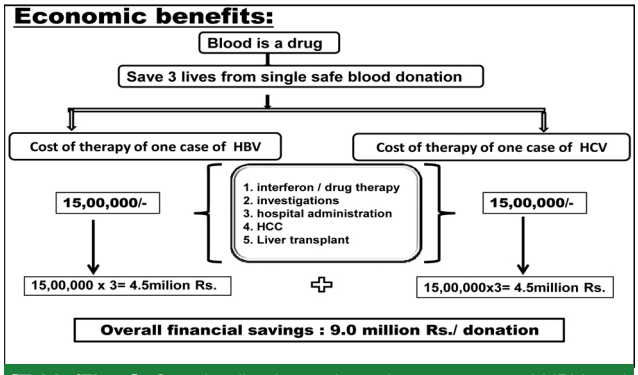
On reviewing the research articles, it was found that NAT Technology is a highly sensitive and advanced methodology for screening blood units which turn out to be seronegative and has also reduced the window period considerably. However, as NAT is an add-on assay for screening, certain facts need to be considered for the best impact as concluded by a recent study by Naidu et al., [26]. Although, the strategy of testing non-reactive donations by NAT has been implied, the sero-reactive donations when tested by NAT may also turn out to be false reactive. NAT alone if applied for screening blood units will not be feasible in the situation where viral load is low and undetectable and antibody can still be detected by ELISA. Thus, the strategy of using NAT as an additional test is applied resulting in higher cost. However, NAT is recommended for occult hepatitis an extremely important fact for India. Non-seroconverting or delayed seroconverting disease is missed by ELISA alone and can be picked up by NAT. The study suggested that in the current scenario implementation of NAT would be challenging and should be preferred only when blood has been collected from safe voluntary non – remunerated blood donors with-protocol based pre-donation donor counseling and selection. Quality management systems should be in place and hemovigilance and initial testing of blood units is done as per regulatory standards [26]. A study from Kenya advocates that implementing the costly NAT is unlikely to add a significant safety benefit and a national testing policy of adding 4th generation ELISA and donor selection algorithm has been effective. Substantial reduction in the risk of transfusion transmitted HIV infection can be attained by adopting WHO blood safety strategies [27]. A recent study from Punjab showed that implementation on NAT helped in preventing 129 patients (blood components included) from getting infected through blood transfusion as out of 32,978 samples, 43 (one for HIV 1 , 27 for HBV and 13 for HCV) sero nonreactive samples were detected positive by ID NAT. The overall NAT yield was 1 in 753 samples. The universal application of NAT in blood banks for blood safety is needed for not only matching the international standards but also reducing the burden of the diseases in the society by large, the study concluded [28]. In another study from North India, on testing 35,722 seronegative donations, NAT screening detected a total of 156 samples positive (108 HBV, 46 HCV and 2 HIV) which reduced to 93 cases (57 HBV, 34 HCV and none HIV) when additional testing with Electro chemiluminescence immunoassay was included further. The NAT yield rate for HBV, HCV and HIV was 1:627, 1:1051 and 1:17,861 respectively indicating the benefits of adding better technology for blood screening in terms of sensitivity. If compared with Japan, the data from studies from India suggested that the NAT yield for all three viruses could be 29 times higher and study supported implementation of NAT as a blood safety measure in blood banks [29]. Makroo et al.,

S. No.	Authors/ Year/ Reference	Study Summary
1.	Makroo et al., 2008, [3]	This study was undertaken as a multicentric study including 8 blood centers from India . Of the 12,224 samples tested, 209 (1.71%) were seroreactive. One hundred thirty three samples (1.09%) were reactive by Ultrio assay, 84 samples were seroreactive but NAT non reactive. There were eight NAT yield cases: 1 HIV, 1 HIV-HCV co-infection, and 6 HBV. It was estimated that NAT testing could interdict 3272 infectious donations in a year.
2.	Jain R et al., 2012, [4]	This study from Rajasthan had a combined NAT yield (NAT reactive/seronegative) for HIV, HCV, and HBV of 0.034% (1 in 2972 donations) . Out of the total donations initially tested with enhanced chemiluminescence immunoassay (ECi), 50% which were negative on ECi were randomly selected and subjected to NAT testing for HBV, HCV, and HIV ad 8 turned out to be reactive on NAT testing and all were positive for HBV DNA . The study asserted that cost alone should not be a reason not to implement NAT for blood safety in a country like India where window period infections in significant numbers could be detected in view of high prevalence of TTIs and risk of transmission through transfusion.
3.	Chatterjee K et al., 2010, [5]	In this study conducted in north India (AIIMS , New Delhi) , 18,354 donors were tested by both ID-NAT and fourth generation enzyme-linked immunosorbent assay (ELISA), 7 were found to be NAT-positive but ELISA-negative (NAT yield) for HBV and HCV. The prevalence of NAT yield cases among routine donors was 1 in 2622 donations tested (0.038%). The blood component preparation of 7 NAT positive units could have affected 21 patients which could have been infected with HBV and HCV viruses. Use of NAT would ensure safer blood transfusions, the study concluded.
4.	Kumar R et al., 2015, [28]	A recent study from Punjab showed that implementation on NAT helped in preventing 129 patients (blood components included) from getting infected through blood transfusion as out of 32,978 samples, 43 (one for HIV 1, 27 for HBV and 13 for HCV) sero nonreactive samples were detected positive by ID NAT. The overall NAT yield was 1 in 753 samples. The universal application of NAT in blood banks for blood safety is needed for not only matching the international standards but also reducing the burden of the diseases in the society by enlarge, the study concluded.
5.	Chandra T et al., 2016, [29]	In another study from North India, on testing 35,722 seronegative donations, NAT screening detected a total of 156 samples positive (108 HBV, 46 HCV and 2 HIV) which reduced to 93 cases (57 HBV, 34 HCV and none HIV) when additional testing with Electro chemiluminescence immunoassay was included further. The NAT yield rate in this study donor population for HBV was 1:627; HCV was 1:1051 and HIV at 1:17,861.
6.	Kabita C et al., 2016, [30]	A retrospective analysis of 5 years of NAT implementation from AIIMS , New Delhi , concluded that NAT is an important interdictory step in prevention of transfusion transmitted infections and it could help interdict 228 probable TTI to 684 patients as there was 100% component preparation.

[Table/Fig-4]: A summary of various Indian studies reporting the implementation of NAT as add on test for blood safety.

also noted high yields of HIV-1 and HCV (515 times, 21.5 times respectively) in Indian multicentric study as compared to the US and Canada. The same study observed 89 times higher NAT yield for HIV -1 and 26.5 times higher NAT yield as compared to Italy [3]. A retrospective analysis of 5 years of NAT implementation from AIIMS, New Delhi, concluded that NAT is an important interdictory step in prevention of transfusion transmitted infections and it could help interdict 228 probable TTIs to 684 patients as there was 100% component preparation. Though, the study cautioned that there is possibility of false positive reactivity with NAT and this should be kept in mind [30]. A summary of various Indian studies reporting the implementation of NAT as add on test for blood safety and the need for its implementation has been given in [Table/Fig-4].

The conflict between pooled versus ID NAT needs also be resolved through large studies based in India so that the conclusions be evidenced based and help in implementation of NAT in blood banks. For cost effectively adopting NAT, single center testing in a referral center and dissemination of test information by use of software based information technology is a strategy worth considering in a resource constrained country like India. The cost of implementation of NAT as a quality and safety measure is much lower than the cost of treating infected patients after receiving blood from window period donations. The cost of disease burden and treatment of HBV and HCV is very high and can't be overlooked in view of millions of carriers already in the country and the lack of facilities and resources of treatment including Hepatocellular Carcinoma (HCC) or liver transplantation [Table/Fig-5].



[Table/Fig-5]: Cost implications of treating one case of HBV and HCV due to TTI and economic benefits of implementation of NAT.

CONCLUSION

The lack of uniformity in the blood transfusion services and transfusion protocols in a diverse country like India makes blood safety challenging. The voluntary blood donation programme and the focus on improving blood services all across the country are the initiatives which have contributed immensely. NAT as a technique if used for blood unit screening will have high impact in enhancing blood safety. NAT unravels the cases missed by currently mandatory serological testing and in addition NAT can detect window period infections in blood donor population. The donor notification and prevention of TTIs will finally be reducing the burden of the disease, chronic effects and economic burden of treatment of such cases. Introducing treatment at the early stages of the disease, preventing chronic complications like hepatocellular carcinoma in HBV and HCV and increasing longevity and quality of life in HIV patients will have overall health benefit for both donors and recipient of blood and blood products. For developing a national screening strategy, studies with large sample size comparing pooled and ID NAT for screening of blood units as compared to currently employed strategies are need of the hour.

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