Asian Association of Transfusion Medicine

(www.aatmweb.org)

Consensus Document on "Prevention of TTI: Future Directions

Introduction

A seminar on 'Prevention of TTI: Future Directions' was organized by Indian Chapter of AATM on 14th May 2016 at Hotel Le Meridian Gurgaon (Delhi NCR). During this seminar a workshop and round table discussion was held to discuss key aspects related to testing for infectious disease markers as a strategy for prevention of TTI's. Particular emphasis was placed on Nucleic Acid Testing (NAT) and the key focus areas for the discussion were

a) Strategies to reduce window period risk (acute and occult infections)
b) Centralised/Regional models for donation testing vs testing by individual blood banks
c) Algorithms for testing, confirmation of results, release/discard of blood
d) Should NAT be mandated nationally in India
e) Individual Donation NAT (ID-NAT) vs Mini Pool NAT (MP-NAT)

Four working groups were given specific topics from the list above and requested to deliberate on the topic and present the outcomes of the group to the seminar participants. After each presentation sufficient time was allowed for discussion and further contribution from the audience and a consensus position was agreed for each topic.

a) Strategies to reduce window period risk (acute and occult infections)

It was acknowledged that AATM comprises a group of Asian countries with different socio-economic development and variability in health facilities and budgets. Currently all member countries have regulations and policies for testing to prevent TTI, with mandatory testing for HIV infection, Hepatitis B & C infection and syphilis and few countries have some additional testing (e.g. Malaria) that are required by their regulators. Each country has its own uniqueness and challenges in terms of its donor resource and blood utilization.

Each member country thus needs its own individual approach to reduce TTI to near zero risk. Members **strongly recommended** that within a country (e.g, India) a co-ordinated, synchronized approach is required to reduce the TTI amongst its population.

The group concurred that depending on various factors such as financial and human resources, size of blood centre and location there were significant differences in the testing strategies and systems used for TTI screening and these ranged from rapid tests, ELISA, Chemiluminescence (CHLIA) and ID-NAT in some laboratories. Window period (WP) varies with the different test assays leading to a higher WP with rapid testing methodology; WP is further reduced with ELISA methodology especially 4th generation /CLIA; but still leaves a considerable window period i.e. 15 days for HIV, 58.3 days for HCV and 38.3 days for HBV. Implementation of ID-NAT in addition to serology further significantly reduced WP to 4.5 days, 2.2 days and 16.3 days for HIV, HCV & HBV infection respectively.

Incorporation of NAT as a screening tool in blood donors will reduce the window period and will make blood very low risk risk against at least three viral infections namely HIV, HBV & HCV. Also automated and integrated testing methods will improve the work flow and achieve operating efficiency of operator by saving time and multiple steps, simultaneously reducing the human error factor.

The following recommendations were made by the working group and endorsed by the participants:

- **a)** As far as possible blood should be collected from Repeat Non Remunerated Voluntary Blood Donors (RNRVBD).
- **b)** The sensitivity and specificity of kits &/or reagents should be well established prior to its use, to make it possible for incorporation in any testing centre for reducing or elimination of risk from TTI.
- **c)** 4th generation ELISA/ tests should be the preferred serology assay.
- **d)** Nucleic Acid testing (NAT) to be added as a supplementary assay to further reduce TTI transmission, especially in high prevalence settings.

e) Robust Quality Management Systems (QMS) must be in place to ensure quality assured testing.

b) Centralised/Regional models for donation testing vs testing by individual blood banks

The working group concluded that prevalence of large number of small to medium sized blood banks in different members states/countries led to multiple testing centres for TTI by ELISA/ CHLIA. Centres found it difficult to achieve economies of scale, implement full automation and implement more complex assays like ID-NAT. Incorporation of NAT by a small blood centre is neither feasible nor cost effective. Members argued for NAT incorporation for occult blood infection /window period in blood donors. There was agreement that it was always preferable to start NAT as regional centre for a defined geographical areas catering to various local blood centres. This would ensure long term sustainability, cost effectiveness and better utilization of human and capital resources.

The following recommendations were made by the working group and endorsed by the participants:

a) Authorities to consider rationalising to regional/central testing centres for a defined geographical area eg. District/ state/central/national level for more effective and cost efficient approach to test for TTI. Serology and NAT to be done at these centres
b) There could be even further centralisation for NAT testing based upon the geopolitical factors and population.
c) Develop a shared IT system or electronic mail system for speedy delivery of reports from Testing Centre to Blood Banks
d) Regional testing centres will manage external quality assurance system (EQAS)

c) Algorithms for testing, confirmation of results, release/discard of blood

An algorithm is a step-by-step guide to a set of operations to be performed. An algorithm guides laboratories in testing and retesting strategies to confirm tests results, release blood

products and contact donors to counsel. Additional complexity arises in NAT testing where a result may be positive once and then negative on replicate testing. This is due to Poisson distribution where there is discrete frequency distribution which gives the probability of a number of independent events occurring in a fixed time. NAT is performed on donor samples that may have very low viral copies depending on sampling. Users of different assay in India use a consensus algorithm. The algorithm was designed and implemented during the early phases of implementation and queries were raised whether it was still necessary to do the large amount of additional testing on NAT initial reactive, serology negative samples. The group debated whether the algorithm should be modified or whether additional data was required from users prior to making informed changes.

The following recommendations were made by the Working Group and endorsed by the participants:

a) For users that have implemented NAT assay the current/ respective algorithm should be followed universally by all users to generate data nationally for India
b) Data should be analysed at one central location and the vendor should assist in this regard.
c) All the reactive samples should be stored in appropriate conditions and transported to the centre that will perform ELISA and NAT with uniform testing standards.
d) The data generated will help in determining the true NAT yield cases across India.
e) The current/ respective algorithm can be reviewed only when there is statistically significant data from a large number of laboratories.
f) Where NAT implementation is not possible, it was recommended that 4th generation assays be implemented to get the higher sensitivity
g) Where ID-NAT has been implemented, laboratories could consider continuing with 3rd generation serology and ID-NAT combination in order to reduce the costs.

d) Should NAT be Mandated Nationally in India

The working group highlighted the various challenges to low risk blood and preventing TTI's in India.

- There are about 2761 licensed blood banks (37% in the Government sector) and the annual whole blood collection is about 10.8 million blood units.

- Compared to developed countries, India has high prevalence of TTI's in the general population and there has been many TTI transmissions reported every year.
- Blood is collected from mainly first time donors either Replacement Donors & Voluntary Donors (in camps or in blood banks). Ideally, Repeat Non-Remunerated Voluntary Blood Donors (**RNRVBD**) are the safest donors. But this category of blood donors is very negligible in India, and increasing donations in this category seems a remote possibility mainly because of following reasons:
    a) Blood Banking in India is very fragmented & proper standardized counselling across India seems impossible at present.
    b) Developing RNRVBD pool also involves cost requiring skilled manpower for donor selection, counselling, travel etc. The development and retention of RNRVBD pool and collecting blood from this pool also involves cost.
    c) Already there is shortage of blood with first time donors, so RNRVBD is a distant dream at present.

The group concurred that with the frequency of TTI's being higher in first time and family replacement donors, robust testing strategies were required to detect as many positive donors as possible and mitigate against risk of TTI transmission. It was acknowledged that even with the current Government mandated tests there are still a number of positive donations that are not detected resulting in an increasing number of TTI cases mainly due to longer window periods and also quality issues.

It was recognised that NAT testing would reduce TTI transmissions and that this sensitive molecular technology detects viral genes much before the routine serological tests become positive and makes blood near zero risk against viral infections (HIV, HBV & HCV).

The following recommendations were made by the Working Group and endorsed by the participants:

- NAT screening should be mandated nationally for all collected blood units in order to ensure a safer blood supply.
- ID-NAT should be mandated as multiple research studies proved the superiority of ID-NAT over MP-NAT in detecting infections, especially HBV infections which is of high prevalence in India. Many countries have shifted and are shifting from MP-NAT to ID-NAT as they missed many infections with MP-NAT over a period of time (3-4 references from high impact journals).
- Centralized NAT Testing Centres should be created, probably at every district level across India, catering to the needs of that region with **hub-and-spoke model**. Such models are already working successfully since years in **Bengaluru-Karnataka & Delhi**
- For Centralized NAT Testing with hub-and-spoke model, ID-NAT testing format is more feasible & practical as it allows parallel serological & NAT testing of collected blood units.

- MP-NAT seems impractical for Centralized NAT Testing, for which ID-NAT is the only solution.

The working group also recommended that laboratories perform a cost vs benefit analysis that can be utilised to gauge how the benefits derived from implementing ID-NAT will compensate for the initial and ongoing costs of testing. Factors to be considered in the cost model would be prevalence data for the TTI's being tested, number of infections transmitted annually without implementation of ID-NAT, costs of treatment, litigation costs, reputational costs, etc.

The group developed a simple cost vs benefit model (refer Appendix 1) with estimated costs based on certain assumed scenarios. This model can be used by laboratories to perform their own costing vs benefit analysis using actual test kit cost, prevalence data, average litigation and treatment costs that are applicable in their regions.

e) Individual Donation NAT (ID-NAT) vs Mini Pool NAT (MP-NAT)

The working group re-iterated that despite a significant increase in safety of blood transfusion in the past few decades due to recruitment of low-risk donor populations, improved donor selection and sensitive serologic screening assays, the residual risk of infections getting transmitted by blood remains a "threat" especially in high prevalence countries. Nucleic Acid Testing (NAT) has dramatically reduced the residual risk of transmission of viruses like HIV, HBV, and HCV. The advantage of this method is that it detects the infections much earlier than the other screening methods thereby narrowing the window period.

It has been shown in various studies that pooling of samples result in decreased sensitivity of detection as the volume of individual sample gets smaller in a pool. Scientific models estimate that NAT reduces the infectious window period by 35-91% for HIV-1, HCV and HBV with individual donation testing, while only 17-87% with mini-pool i.e. pools of 16 (ref needed, 3-4 no).

The following recommendations/findings were made by the Working Group and endorsed by the participants:

- Various studies published so far have proven that NAT does reduce the Window Period donations and therefore make blood supply safer and that ID-NAT is more sensitive than MP- NAT. This is important for high prevalence countries where reducing sensitivity by pooling could result in a high number of TTI's going undetected.
- There is still concern regarding the costs of implementing ID-NAT and the benefits were not clear for India due to limited studies and publications

- Further multi-centre studies be performed to illustrate the real benefits of ID-NAT vs MP-NAT (these would relate to number of additional TTI's detected by ID-NAT, impact on patients of the undetected TTI's)
- Data collection to be attempted from multiple centres. Retrospective data for TTI incidence data to be collected. In retrospective data subgroup analysis can be done. Following groups may be analysed separately:
    i. 3rd Gen ELISA + NAT
    ii. 4th Gen ELISA + NAT
    iii. Chemiluminescence +NAT
- Assistance be sought from international experts to assist with the design of the study

Appendix 1: Example of Cost vs Benefit Model for India if ID-NAT is Implemented

Cost of ID-NAT implementation in all India Blood Banks

Currently 1 Crore blood donations per year in India.
1 Crore NAT Tests = **Rs. 1000 Cr/ Year** (Rs 1000/- per NAT Test including direct & indirect expenses)

BENEFITS
NAT will prevent 1 infection (HIV, HBV or HCV) per 1000 blood units collected
1 Cr Units = 10,000 TTI detected by NAT
1 Unit will infect 3 patients through blood components (Red Cell, Plasma & Platelets) = 30,000 TTI new cases every year
Each new patient in turn infects 3 persons in society = 90,000 TTI new cases in society / Year
So with mandating NAT, we can **prevent 90,000 new infections every year** in India

QALY / Quality Adjusted Life Years
With current mandate of TTI screening by serological methods only, there is an additional burden of about 90,000 new infections every year in the society. We need to measure the effects as infections avoided and quality-adjusted life-years (QALYs) gained.

Cost of Treatment & Management of every patient of HIV/HBV/HCV is very high

1 HIV Patient needs about Rs 25000/ Year x 50 Years = Rs 12.5 Lac
Other Management cost Rs 5 Lac in a life span (Hospitalization, Investigation etc)
So Total average treatment cost per HIV infection = 12.5 + 5 = **Rs 17.5 Lac**

1 HBV Patient need medicine of Rs. 2000/Month Lifelong, about Rs.25000/ Year x 50 Years = Rs 12.5 Lac
Other Management cost Rs 5 Lac in a life span (Hospitalization, Investigation etc)
20% of patients (11-30%) need Liver Transplant costing 25 Lac each (5 Lac/ HBV infection, distributed over all HBV case)
5% of patients (1-10%) develop Liver Malignancy, treatment costing 30 Lac each (1.5 Lac/ distributed over all HBV case)
So the average treatment cost per HBV infection = 12.5 + 5 + 5 + 1.5 = **Rs 24 Lac**

1 HCV Patient need medicine therapy of Rs. 100,000/cycle, (10% needs 2-3 repeat cycles)
Other Management cost Rs 5 Lac in a life span (Hospitalization, Investigation etc)
20% of patients (16-24%) needs Liver Transplant costing 25 Lac each (5 Lac/ distributed over all HCV case)
5% of patients (1-10%) develop Liver Malignancy, treatment costing 30 Lac each (1.5 Lac/ distributed over all HBV case)

So Total HCV Management cost = 1 + 5 + 5 + 1.5 = **Rs 12.5 Lac**

Majority of our patients cannot afford the treatment and hence they either suffer or die.
NAT yield pattern in India is 10% HIV, 70% HBV, & 20% HCV
So in India out of 90000 new TTI cases, there will be 13500 HIV, 63000 HBV & 13500 HCV new infections/ year

Cost Analysis of newly infected TTI cases per year in the country:

% of TTI cases	HIV-10%	HBV-70%	HCV-20%	Total
New infections per year	9000	63000	18000	90000
Treatment Cost per case (Rs in Lac)	17.5	24	12.5	
Total Treatment Cost (Rs in Lac)	157500	1512000	225000	1894500

So, the cost of treatment of TTI cases per year is **Rs. 18,945 Crore**
In addition, few patients go for litigation (approximately 1%).
TTI litigation cost = Rs 25 Lac on average (compensation + counselor fee)
10% i.e. 9000 cases = **Rs 2250 Crore**

Also, NAT tested plasma/ FFP sent for fractionation can fetch additional Rs 400 per liter
1 Cr blood units, 200 ml FFP/ Unit = 20 Lac Liter FFP = **Rs 80 Crore** additional revenue saving

So by mandating NAT, we can save net **Rs 21,275 Crore** (18945 + 2250 + 80)

COST : Rs. 1,000 Crore
BENEFIT : Rs. 21,275 Crore
SAVING : Rs. 20,275 Crore

So, with the cost of about Rs 1,000 Crore one could potentially save about Rs. 20,000 Crore by mandating NAT for blood screening in India

Additional Benefit: This will boost **Medical Tourism**. Blood safety is the main concern of global patients, when they think of India for medical tourism. The medical tourism will definitely boost health care industry & in turn national economics.
By preventing the spread of serious viral infection in our country, overall health burden will be reduced & quality of life in society will be improved.
Further Cost Utility Analysis (CUA) may be done by the experts in the field.

Limitation: *This is a worst case scenario of treating patients infected by blood transfusions for a prolonged period and infected individuals actually infecting a number of other people. Actual costings done by Blood Banks must take into account that many blood recipients will not be alive 5 to 10 years after receiving a transfusion and treatment periods need to be adjusted*

based on actual data. It is important that calculations are based on actual data and not assumptions. Nevertheless, the savings associated with implementing ID-NAT in high prevalence countries is significant and quite likely outweigh the costs of implementing the test