Multicenter efficacy study of HBV, HCV and HIV blood screening scenarios

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Blood Systems Research Institute
Study objectives

• Classify HIV, HCV, and HBV infections into various phases of infection and analyze these data by geographic region
  – South Africa, Egypt, Mediterranean, Central Europe, North Europe, Eastern Europe, SE Asia, Pacific

• Compare the efficacy of different possible NAT and serology screening scenarios in first time, lapsed, and repeat donors for HIV, HCV, and HBV infection
  – Calculate modelled residual risk based on observed ID NAT (Ultrio, Novartis Diagnostics) and serology yield in each region
  – Calculate efficacy as the percentage of transmission risk that is removed by a given testing strategy

• Compare the cost effectiveness of these scenarios
Foundations for a robust transmission risk and efficacy analysis of screening scenarios

- Cost effectiveness
- Screening efficacy
- Transmission risk (based on local epi)
- Agent infectivity in each stage of infection
- Analytical sensitivity of assay
- Standardization of screening markers

Screening costs for infections or QALYs prevented

% of risk avoided
Calculate transmitted infections per million donations

50%, 63%, 95%
LOD in copies/ml

NAT and serology assays

In copies per ID$_{50}$ from animal experiments

Calculate transmitted infections per million donations
Participating institutions

• South Africa
  – South African National Blood Service
  – Western Province Blood Transfusion Service (HIV/HBV)
• Egypt
  – National Blood Transfusion Service, Cairo
  – Shabrawishi Hospital, Dokki, Egypt
• Mediterranean
  – Banc de Sang I Teixits, Barcelona
  – Regional Blood Transfusion Center, Valencia
  – St Anna Hospital, Turin, Italy
  – University of Turin, Turin, Italy
  – Red Cross Blood Center, Madrid (HBV only)
• Central Europe*
  – Blood Transfusion Service SRC Berne, Switzerland
  – Blood Transfusion Center of Slovenia

Etablissement Français Sanguine in discussion
Participating institutions

- **North Europe**
  - Irish Blood Transfusion Service
  - Multiple blood banks in Denmark
  - Finnish Red Cross Blood Service

- **Eastern Europe**
  - Institute of Haematology and Transfusion Medicine, Poland
  - Warsaw Blood Center

- **Southeast Asia**
  - Hong Kong Red Cross
  - Health Systems Agency, Singapore
  - National Blood Centre, Malaysia

- **Pacific**
  - New Zealand Blood Service

  - These participating users constitute the majority of world-wide Novartis/GenProbe ID NAT users

*Australian Red Cross Blood Service to be included*
Input data obtained from each participant

- Number of donations tested:
  - classified by donor status: first time, repeat (<12 month interval), and lapsed
  - variable timeframes reported (1 to 5 years)
- Test yield data:
  - NAT only, serology only, and concordant NAT/serology classified by donor status
- More detailed data on positive donations
  - Pre-seroconversion or pre-NAT conversion interdonation interval
  - Confirmatory NAT and serology, additional index donation and follow-up testing data as available
Data validation and standardization

• Numerous Email, phone, and in-person exchanges between participating sites and central investigators

• Use of standardized definitions for phases of infection - applied by on-site investigators and reviewed/adjudicated by central personnel
  – HIV: WP (RNA only), concordant (RNA plus serology), elite controller (antibody only)
  – HCV: WP (RNA only), concordant (RNA plus serology), resolved infection (antibody only) or occult infection if RNA demonstrated by additional sensitive testing
  – HBV: more complex due to additional phases (e.g.: early recovery phase, chronic OBI) and due to difficulty in accurate classification (e.g. acute vaccine breakthrough)
Modelling residual risk for RBCs

• Use the statistical risk day equivalent model (Weusten et al, Transfusion 2011;51:203-15) to calculate residual risk in repeat donors with ID NAT in place
  – Can also calculate for MP NAT at various pool sizes
• Calculate risk in first time donors by using the ratio of ID NAT yield rate in first time to repeat donors as a conversion factor
• For lapsed donors, can either do the primary calculation (if intervals are available) or can use a calculated NAT yield conversion factor
• This model does not directly calculate incidence in person-years; instead uses the number of sero and NAT conversions in repeat donations and the harmonic mean of the pre-seroconversion inter-donation intervals

\[ \text{Risk} = \frac{r_{days}}{t_{between}} \frac{D_{conv}}{D_{total}}. \]
Probability of infectivity during the window period

The graph shows two curves:
- **Probability of non-detection**
- **Probability of infection**

The area under the curve gives the overall risk in days ("Window phase risk days equivalents").

The product of the two curves represents the overall risk.
Infectivity in blood

Kleinman SH, Lelie N, Busch MP. Transfusion 2009:49:2454-89

Kleinman S et al Vox Sang 96, Suppl1, ISBT abstract
Komiya K et al. Transfusion 2008;48:286-9
Hijikata J. Virol 1993 67:1953
Alter H et al. J. Viral Hep 1995, 2:121;
Katayama K et al. Intervirology 2004;47:57-64
Random viral load distribution in window period and in elite controllers
(South Africa, SANBS, 3 year)

Copies/ml bDNA 3.0 assay

Viral load determined by probit analysis on replicate assays against DDL HIV-1 subtype C standard calibrated in bDNA copies

Vermeulen M et al. personal communication, SANBS, 3 years
Distribution of HIV-RNA load (copies/mL) in WP, concordant HIVAb+/RNA+ and in elite controllers.

Quantified by probit analysis against HIV subtype C standard.

**SANBS**
- WP NAT yield
- p24Ag pos WP
- p24Ag neg WP
- Cut off p24Ag assay

**REDS HIVAb+/RNA+**
- Cut off bDNA assay
- Cut off Ultrio assay
- 50% LOD TMA MP16 assay
- ~4% MP16 RNA neg
- ~1% SANBS Elite controllers

**Distribution**
- WP Ag-
- WP Ag+
- Concordant
- Elite controller
Modeling distribution of Infectivity titers (ID$_{50}$/20 mL) in WP, concordant HIV-Ab+/RNA+ and in elite controllers.
Modeling distribution of infectivity titers (ID$_{50}$/20 mL) in WP, concordant HIV-Ab+/RNA+ and in elite controllers.
Clinical data: HIV transmission by anti-HIV+ components

(Busch et al. JID 1996, 174,26-33)

118/132 recipients (89%; 95%CI: 83%-94%) of anti-HIV + donations acquired infection

Median viral load higher in transmitters (p=0.01).

Effect of storage on infectivity of RBC: 93% <25 days vs 50% >25 days
HIV data
HIV prevalence and WP NAT yield in first time donations

<table>
<thead>
<tr>
<th>Region</th>
<th>Donations tested</th>
<th>Total number of HIV infections</th>
<th>Prev per million donations</th>
<th>Number of WP NAT yield cases</th>
<th>WP NAT yield rate per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA</td>
<td>477,000</td>
<td>4956</td>
<td>10,381</td>
<td>53</td>
<td>111.2</td>
</tr>
<tr>
<td>SE Asia</td>
<td>325,000</td>
<td>112</td>
<td>345</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Medit</td>
<td>238,000</td>
<td>53</td>
<td>223</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Egypt</td>
<td>120,000</td>
<td>17</td>
<td>142</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>East Europe</td>
<td>90,000</td>
<td>3</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cen Europe</td>
<td>97,000</td>
<td>3</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nordic</td>
<td>108,000</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NZ</td>
<td>43,000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
HIV prevalence and WP NAT yield in first time donations

prevailing per million

SA | East Europe | Medit | Egypt | Cen Europe | Nordic | NZ

WP NAT yield per million

prevailing per million donations | WP NAT yield rate per million
### Total HIV infections detected and WP NAT yield in repeat (<1 year interval) donations

<table>
<thead>
<tr>
<th>Region</th>
<th>Donations tested</th>
<th>Total number of HIV infections</th>
<th>Prev per million donations</th>
<th>Number of WP NAT yield cases</th>
<th>WP NAT yield rate per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA</td>
<td>3,513,000</td>
<td>901</td>
<td>256</td>
<td>100</td>
<td>28.5</td>
</tr>
<tr>
<td>SE Asia</td>
<td>501,000</td>
<td>19</td>
<td>38</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>Medit</td>
<td>1,134,000</td>
<td>29</td>
<td>26</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Egypt</td>
<td>12,000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>East Europe</td>
<td>205,000</td>
<td>5</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cen Europe</td>
<td>392,000</td>
<td>4</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nordic</td>
<td>1,114,000</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>NZ</td>
<td>321,000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Total HIV infections detected and WP NAT yield in repeat (<1 year interval) donations
Risk from different categories of donors

• Previous published data indicates that NAT yield rates are higher in FT than repeat donors (Stramer, Glynn, Kleinman et al. N Engl J Med 2004; 42:1037-45)
  – HIV: 4.1 fold (95%CI: 1.0-17.0)
  – HIV (p24 ag neg): 2.7 fold (95%CI: 0.5-12.7)
  – HCV: 3.1 fold (95% CI: 2.0 -5.0)

• Previous analysis of SANBS data indicated that lapsed donors may have a risk profile more like FT than repeat donors; hence they might be expected to have a higher NAT yield rate than repeat donors

• We used the multicenter HIV dataset to evaluate the issue of relative risk in first time, lapsed, and repeat donors
HIV transmission risk in lapsed and repeat donations using the Weusten model

<table>
<thead>
<tr>
<th></th>
<th>HIV positive donations (detected by RNA, serology, or both)</th>
<th>Transmission risk per million at ID$_{50}$ of 3.16 virions</th>
<th>Risk ratio: lapsed/repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lapsed*</td>
<td>repeat</td>
<td>lapsed</td>
</tr>
<tr>
<td>SANBS</td>
<td>836</td>
<td>823</td>
<td>6.52</td>
</tr>
<tr>
<td>Western Cape</td>
<td>43</td>
<td>78</td>
<td>2.93</td>
</tr>
<tr>
<td>Barcelona</td>
<td>26</td>
<td>16</td>
<td>0.36</td>
</tr>
<tr>
<td>Valencia</td>
<td>11</td>
<td>10</td>
<td>0.21</td>
</tr>
<tr>
<td>Malaysia</td>
<td>42</td>
<td>9</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not able to calculate due to missing data
HIV WP donations in first time, lapsed, and repeat donors

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of cases</th>
<th>Rate per million donations</th>
<th>NAT yield ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FT</td>
<td>Lapsed</td>
<td>Repeat</td>
</tr>
<tr>
<td>SANBS</td>
<td>52</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>W. Cape</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Barcelona</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Valencia</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
Lapsed / Repeat Ratio comparison:
All HIV seroconverters versus WP cases

<table>
<thead>
<tr>
<th>Region</th>
<th>Risk ratio from all seroconverters</th>
<th>NAT yield ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANBS</td>
<td>0.97</td>
<td>1.33</td>
</tr>
<tr>
<td>W. Cape</td>
<td>0.92</td>
<td>0</td>
</tr>
<tr>
<td>Barcelona</td>
<td>0.58</td>
<td>2.10</td>
</tr>
<tr>
<td>Valencia</td>
<td>0.47</td>
<td>0</td>
</tr>
</tbody>
</table>
HIV transmission risk in lapsed and repeat donations using the Weusten model

HIV WP yield rate in first time, lapsed, and repeat donors

Transmission risk per million at ID$_{50}$ of 3.16 virions

Rate per million donations
WP infections as a percentage of all detected infections in 3 selected regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of WP infections</th>
<th>% of detected infections that were WP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First time</td>
<td>Lapsed</td>
</tr>
<tr>
<td>SA</td>
<td>170</td>
<td>1.07%</td>
</tr>
<tr>
<td>SE Asia</td>
<td>5</td>
<td>0.89%</td>
</tr>
<tr>
<td>Med</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

* Elite controllers were identified only in SA. These were 0.67% of all infections (45 cases)
WP infections as a percentage of all detected infections in 3 selected regions

* Elite controllers were identified only in SA. These were 0.67% of all infections (45 cases)
HIV test efficacy analysis in SANBS
Efficacy of HIV screening assays in repeat or lapsed donations

HIV Ag/Ab combo assay efficacy

Anti-HIV assay efficacy

MP-NAT yield

Concordant anti-HIV and HIV-RNA yield

ID-NAT yield

Concordant anti-HIV and HIV-RNA yield

Overall risk of infectious donations over time
Proportion of WP and elite controllers in first, lapsed and repeat donors at SANBS

<table>
<thead>
<tr>
<th>category</th>
<th>first (n=4828)</th>
<th>lapsed (n=836)</th>
<th>repeat (n=823)</th>
<th>all (n=6487)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-RNA+ WP</td>
<td>1,1%</td>
<td>2,0%</td>
<td>11,5%</td>
<td>2,5%</td>
</tr>
<tr>
<td>RNA+, HIVAb+ concordant</td>
<td>98,1%</td>
<td>97,6%</td>
<td>88,3%</td>
<td>96,8%</td>
</tr>
<tr>
<td>HIV-RNA- elite controller</td>
<td>0,81%</td>
<td>0,36%</td>
<td>0,12%</td>
<td>0,66%</td>
</tr>
</tbody>
</table>

Vermeulen M et al. manuscript, in preparation
Sensitivity of HIV-RNA and anti-HIV assays in detecting HIV infected donors

Vermeulen M et al. manuscript, in preparation
Efficacy of HIV screening scenarios (based on risk analysis SANBS, 5 years)

Vermeulen M et al. manuscript, in preparation

Risk analysis based on Weusten J et al, Transfusion 2011;51:203-15
Efficacy of different HIV testing scenarios*

<table>
<thead>
<tr>
<th>testing scenario</th>
<th>first (n=4828)</th>
<th>lapsed (n=836)</th>
<th>repeat (n=823)</th>
<th>all (n=6487)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID-NAT and anti-HIV</td>
<td>99,84%</td>
<td>99,69%</td>
<td>98,27%</td>
<td>99,62%</td>
</tr>
<tr>
<td>ID-NAT alone</td>
<td>99,75%</td>
<td>99,67%</td>
<td>98,27%</td>
<td>99,58%</td>
</tr>
<tr>
<td>MP8 NAT and anti-HIV</td>
<td>99,69%</td>
<td>99,42%</td>
<td>96,76%</td>
<td>99,28%</td>
</tr>
<tr>
<td>MP16 NAT and anti-HIV</td>
<td>99,65%</td>
<td>99,34%</td>
<td>96,29%</td>
<td>99,18%</td>
</tr>
<tr>
<td>HIV-Ag and anti-HIV</td>
<td>99,13%</td>
<td>98,74%</td>
<td>91,23%</td>
<td>98,07%</td>
</tr>
<tr>
<td>anti-HIV</td>
<td>98,76%</td>
<td>97,66%</td>
<td>86,93%</td>
<td>97,10%</td>
</tr>
</tbody>
</table>

* Based on HIV transmission risk avoided (SANBS, 5 year)

Vermeulen M et al. manuscript, in preparation

Risk analysis based on Weusten J et al, Transfusion 2011;51:203-15

<table>
<thead>
<tr>
<th></th>
<th>WP ID_{50}</th>
<th>Elite controller ID_{50}</th>
<th>Proportion elite controllers infectious</th>
<th>50% ULTRIO LOD</th>
<th>95% ULTRIO Plus LOD</th>
<th>p24 Ag 50% LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3,16 virions</td>
<td>316</td>
<td>5%</td>
<td>2.7 cps/ml</td>
<td>18.4 cps/ml</td>
<td>10,000 cps/ml</td>
</tr>
</tbody>
</table>
Efficacy of HIV screening scenarios in repeat donors

Vermeulen M et al, personal communication

Risk analysis based on Weusten J et al, Transfusion 2011;51:203-15
HCV data
HCV prevalence and WP NAT yield in first time donations

<table>
<thead>
<tr>
<th>Region</th>
<th>Donations tested</th>
<th>Total number of HCV infections</th>
<th>Prev per million donations</th>
<th>Number of WP NAT yield cases</th>
<th>WP NAT yield rate per million</th>
<th>% “resolved”</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA</td>
<td>316,000</td>
<td>166</td>
<td>526</td>
<td>2</td>
<td>6</td>
<td>11%</td>
</tr>
<tr>
<td>SE Asia</td>
<td>325,000</td>
<td>492</td>
<td>1515</td>
<td>1</td>
<td>3</td>
<td>13%</td>
</tr>
<tr>
<td>Medit</td>
<td>238,000</td>
<td>411</td>
<td>1726</td>
<td>1</td>
<td>4</td>
<td>28%</td>
</tr>
<tr>
<td>Egypt</td>
<td>120,000</td>
<td>3431</td>
<td>28,649</td>
<td>16</td>
<td>134</td>
<td>27%</td>
</tr>
<tr>
<td>East Eur</td>
<td>90,000</td>
<td>45</td>
<td>2976</td>
<td>0</td>
<td>0</td>
<td>14%</td>
</tr>
<tr>
<td>Cen Eur</td>
<td>97,000</td>
<td>23</td>
<td>465</td>
<td>0</td>
<td>0</td>
<td>42%</td>
</tr>
<tr>
<td>Nordic</td>
<td>108,000</td>
<td>267</td>
<td>213</td>
<td>0</td>
<td>0</td>
<td>44%</td>
</tr>
<tr>
<td>NZ</td>
<td>43,000</td>
<td>28</td>
<td>649</td>
<td>0</td>
<td>0</td>
<td>32%</td>
</tr>
</tbody>
</table>
HCV prevalence and WP NAT yield in first time donations

Prevalence per million

WP NAT yield per million

SA SE Asia Medit Egypt East Europe Cen Europe Nordic NZ

Prev per million donations WP NAT yield rate per million
<table>
<thead>
<tr>
<th>Region</th>
<th>Donations tested</th>
<th>Total number of HCV infections</th>
<th>Prev per million donations</th>
<th>Number of WP NAT yield cases</th>
<th>WP NAT yield rate per million</th>
<th>% “resolved”</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA</td>
<td>2,303,000</td>
<td>13</td>
<td>5.6</td>
<td>2</td>
<td>0.9</td>
<td>23%</td>
</tr>
<tr>
<td>SE Asia</td>
<td>501,000</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>2.1</td>
<td>20%</td>
</tr>
<tr>
<td>Medit</td>
<td>1,230,000</td>
<td>9</td>
<td>7.3</td>
<td>2</td>
<td>1.6</td>
<td>22%</td>
</tr>
<tr>
<td>Egypt</td>
<td>12,000</td>
<td>1</td>
<td>79.1</td>
<td>1</td>
<td>79.1</td>
<td>0</td>
</tr>
<tr>
<td>East Eur</td>
<td>205,000</td>
<td>3</td>
<td>14.6</td>
<td>2</td>
<td>9.8</td>
<td>0</td>
</tr>
<tr>
<td>Cen Eur</td>
<td>392,000</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>Nordic</td>
<td>1,114,000</td>
<td>6</td>
<td>5.4</td>
<td>2</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>NZ</td>
<td>321,000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Total HCV infections detected and WP NAT yield in repeat (<1 year interval) donations
HCV viral load distribution in window period and at viral set point (Egypt)

Copies/ml

Window period

40% combo ELISA reactive

Anti-HCV+, RNA+ set point

sample number
Efficacy of different HCV screening scenarios (Analysis on 3431 infections in 119,756 Egyptian first time donors)

Based on risk avoided according to WP ratio model (Busch MP et al. Transfusion 2005;45:254-264) and transmission risk model (Weusten J et al, Transfusion 2011;51:203-15).

<table>
<thead>
<tr>
<th>testing scenario</th>
<th>efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID-NAT and anti-HCV</td>
<td>99,99%</td>
</tr>
<tr>
<td>MP8 NAT and anti-HCV</td>
<td>99,98%</td>
</tr>
<tr>
<td>MP16 NAT and anti-HCV</td>
<td>99,97%</td>
</tr>
<tr>
<td>combo ELISA</td>
<td>99,71%</td>
</tr>
<tr>
<td>anti-HCV</td>
<td>99,52%</td>
</tr>
<tr>
<td>ID-NAT alone</td>
<td>99,95%</td>
</tr>
</tbody>
</table>

Assuming 1.2% of anti-HCV+/RNA- donations are low viremic with 100-fold reduced infectivity.
Further work and analysis plans

• Complete risk and efficacy analyses per region and on WW data
• Further modelling of risks from HIV elite controllers and occult HCV
• Complete the data validation and classification of HBV infections*
• Model HBV risks in multiple stages of infection
• In the context of introduction of pathogen reduction for platelets and transfusable plasma, analyze if it would be possible to eliminate serologic testing for repeat and lapsed donors
  – Run model at 20 ml (RBCs) and 200 ml (FFPs) infused
  – Run ‘ID-NAT only model’ for repeat (<12 mo) as well as lapsed + repeat donors
• Determine cost effectiveness of different test strategies

*For example, IgM anti-HBc Malaysia, anti-HBc in HBsAg+/DNA- in Egypt, Hong Kong etc.
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