HIV data from a multicenter efficacy study of HIV, HCV, and HBV blood screening scenarios

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Blood Systems Research Institute with funding from Novartis Vaccines and Diagnostics
Disclosures for: Dr. Steven Kleinman

WFH requires the following disclosures be made at each presentation:

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td></td>
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<tr>
<td>Director, Officer, Employee</td>
<td></td>
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<tr>
<td>Shareholder</td>
<td></td>
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<td>Honoraria</td>
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<tr>
<td>Advisory Committee</td>
<td></td>
</tr>
<tr>
<td>Consultant</td>
<td>Novartis Diagnostics; Cerus</td>
</tr>
</tbody>
</table>
Study objectives

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

• 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
Participating institutions

• South Africa
  – South African National Blood Service
  – Western Province Blood Transfusion Service (HIV/HBV)

• Mediterranean Europe
  – 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/ Northern Europe
  – Blood Transfusion Service SRC Berne, Switzerland
  – Blood Transfusion Center of Slovenia
  – Irish Blood Transfusion Service
  – Multiple blood banks in Denmark
  – Finnish Red Cross Blood Service
  – Institute of Haematology and Transfusion Medicine and Warsaw Blood Center, Poland
Participating institutions

• Southeast Asia
  – Hong Kong Red Cross
  – Health Systems Agency, Singapore
  – National Blood Centre, Malaysia

• Oceania (Southwest Pacific)
  – New Zealand Blood Service
  – Australian Red Cross Blood Service

• Egypt
  – National Blood Transfusion Service, Cairo
  – Shabrawishi Hospital, Dokki, Egypt

– These participating users constitute the majority of world-wide Novartis/GenProbe ID NAT users
Foundations for a robust transmission risk and efficacy analysis of screening scenarios

- Screening costs for infections or QALYs prevented
- In copies per ID₅₀ from animal experiments
- Cost effectiveness
- % of risk avoided
- Calculate transmitted infections per million donations
- Transmission risk (based on local epi)
- Agent infectivity in each stage of infection
- Analytical sensitivity of assay
- Standardization of screening markers
- Screening efficacy
- 50%, 63%, 95% LOD in copies/ml
- NAT and serology assays
Evolution of HIV viremia and antibody during early infection

Peak viremia: $10^6$-$10^8$ gEq/mL

- Ramp-up viremia
  - DT = 21.5 hrs
- p24 Ag EIA
- HIV MP-NAT
- HIV ID-NAT

- HIV RNA (plasma)
- HIV p24 Ag

- First generation
- Second generation
- Third generation

Virals set-point: $10^2$-$10^5$ gEq/mL

Closing the WP through improved screening tests
Input data obtained from each participant

• Number of donations tested:
  – classified by donor status: first time, repeat (≤ 365 day interdonation interval), and lapsed (> 365 day interval)
  – 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)
## HIV prevalence and WP NAT yield in FT donations

<table>
<thead>
<tr>
<th>Region</th>
<th>Donations tested</th>
<th>Total number of HIV infections</th>
<th>HIV prevalence 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>South Africa</td>
<td>477,394</td>
<td>4956</td>
<td>10,381</td>
<td>53</td>
<td>111.0</td>
</tr>
<tr>
<td>SE Asia</td>
<td>324,665</td>
<td>112</td>
<td>345</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Med Europe</td>
<td>238,021</td>
<td>53</td>
<td>223</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cen/Nor Eur</td>
<td>294,367</td>
<td>7</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oceania</td>
<td>152,961</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All but SA</td>
<td>1,010,014</td>
<td>173</td>
<td>171</td>
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<td>1.0</td>
</tr>
<tr>
<td>All</td>
<td>1,487,408</td>
<td>5129</td>
<td>3,448</td>
<td>54</td>
<td>36.3</td>
</tr>
</tbody>
</table>
HIV prevalence and WP NAT yield per million in first time donations
HIV prevalence and WP NAT yield in lapsed donations

<table>
<thead>
<tr>
<th>Region</th>
<th>Donations tested</th>
<th>Total number of HIV infections</th>
<th>HIV prevalence 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>South Africa</td>
<td>458,302</td>
<td>879</td>
<td>1,918</td>
<td>17</td>
<td>37.1</td>
</tr>
<tr>
<td>SE Asia</td>
<td>225,815</td>
<td>50</td>
<td>221</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td>Med Europe</td>
<td>517,521</td>
<td>41</td>
<td>79</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Cen/Nor Eur</td>
<td>612,815</td>
<td>9</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oceania</td>
<td>106,717</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>All but SA</td>
<td>1,462,868</td>
<td>100</td>
<td>68</td>
<td>3</td>
<td>2.1</td>
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<tr>
<td>All</td>
<td>1,921,170</td>
<td>979</td>
<td>510</td>
<td>20</td>
<td>10.4</td>
</tr>
</tbody>
</table>
HIV prevalence and WP NAT yield per million in lapsed donations
HIV prevalence and WP NAT yield in repeat donations

<table>
<thead>
<tr>
<th>Region</th>
<th>Donations tested</th>
<th>Total number of HIV infections</th>
<th>HIV prevalence 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>South Africa</td>
<td>3,513,477</td>
<td>901</td>
<td>256</td>
<td>100</td>
<td>28.5</td>
</tr>
<tr>
<td>SE Asia</td>
<td>500,901</td>
<td>21</td>
<td>44</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>Med Europe</td>
<td>1,135,033</td>
<td>29</td>
<td>26</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Cen/Nor Eur</td>
<td>1,710,500</td>
<td>13</td>
<td>8</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Oceania</td>
<td>1,282,802</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All but SA</td>
<td>4,629,236</td>
<td>65</td>
<td>14</td>
<td>8</td>
<td>1.7</td>
</tr>
<tr>
<td>All</td>
<td>8,142,713</td>
<td>966</td>
<td>119</td>
<td>108</td>
<td>13.3</td>
</tr>
</tbody>
</table>
HIV prevalence and WP NAT yield per million in repeat donations

![Bar chart showing HIV prevalence and WP NAT yield per million in repeat donations across different regions.](image)
HIV prevalence per million in different donation categories

- South Africa
- SE Asia
- Med Europe
- Cen/Nor Eur
- Oceania
- All but SA
- All

Categories:
- First Time
- Lapsed
- Repeat
- Combined L/R
Modelling residual risk for RBCs

• We used the statistical risk day equivalent model (Weusten et al, Transfusion 2011;51:203-15) to calculate residual risk with ID NAT testing in place
  – This requires data on interdonation interval for infected donors
  – These data are available for lapsed and repeat donors but not for first time donors
  – The calculation uses the number of seroconversions and NAT conversions and the harmonic mean of the pre-seroconversion inter-donation intervals; incidence in person-years is not needed

• We made similar calculations for MP NAT at pool sizes of 8 and 16

• Residual risk in first time donors cannot be directly calculated in this model; data from repeat donors must be used with or without a conversion factor determined by the ratio of ID NAT yield in first time versus repeat donors
Probability of infectivity during the window period

Probability of non-detection

Probability of infection

Area under the curve gives the overall risk in days ("Window phase risk days equivalents")

Product of the two
Validating a model assumption: linear viral load distribution in window period donors

(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
- Cut off viral load assay
- 50% Cut off Ultrio assay

NAT-yield

Serology yield

- Elite controllers

Vermeulen M et al. personal communication, SANBS, 3 years
Risk from different categories of donors

• Previous published data indicates that MP NAT yield rates in the US (pools of 16 and 24) were higher in FT than non-FT 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 might have a risk profile more like FT than repeat donors; hence they might pose a greater risk than repeat donors

• We used this international HIV dataset to evaluate the issue of relative risk in lapsed and repeat donors
HIV transmission risk in lapsed, repeat, and L/R combined donations using the Weusten model

<table>
<thead>
<tr>
<th>Region</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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lapsed</td>
<td>Repeat</td>
</tr>
<tr>
<td>South Africa</td>
<td>879</td>
<td>901</td>
</tr>
<tr>
<td>SE Asia</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>Med Europe</td>
<td>41</td>
<td>29</td>
</tr>
<tr>
<td>Cen/Nor Eur</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Oceania</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All but SA</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>All</td>
<td>979</td>
<td>966</td>
</tr>
</tbody>
</table>
HIV transmission risk per million in different donation categories
(Weusten model at ID50 of 3.16 virions and using ID NAT)
Risk from different categories of donors

• The data indicate that HIV residual risk from lapsed and repeat donations are equivalent

• Previous published data indicates that MP NAT yield rates in the US (pools of 16 and 24) were higher in FT than non-FT donors (Stramer, Glynn, Kleinman et al. N Engl J Med 2004; 42:1037-45)

• We used our international HIV dataset to evaluate the issue of relative risk in FT versus L/R combined donors
## HIV WP donations in FT and combined L/R 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>L/R combined</td>
<td>FT</td>
</tr>
<tr>
<td>South Africa</td>
<td>53</td>
<td>117</td>
<td>111.0</td>
</tr>
<tr>
<td>SE Asia</td>
<td>1</td>
<td>4</td>
<td>3.1</td>
</tr>
<tr>
<td>Med Europe</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Cen/Nor Eur</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Oceania</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>All but SA</td>
<td>1</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td>All</td>
<td>54</td>
<td>128</td>
<td>36.3</td>
</tr>
</tbody>
</table>
HIV WP NAT yield rate per million in different donation categories

- First Time
- Lapsed
- Repeat
- Combined L/R
Assumptions for risk and efficacy analysis of HIV screening scenarios

• $\text{ID}_{50}$ in WP is 3.16 (1-10) virions
• $\text{ID}_{50}$ in elite controllers 316 (100-1000)virions
  – From experimental SIV data
• Ultrio 50% and 95% LOD 2.7 and 18.4 cps/ml
• 20 ml plasma in RBC unit
• Observed HIV-RNA, HIV Ag and anti-HIV detection rates
• ID, MP8 and MP16 residual risk according to Weusten et al (Transfusion 2011;51:203)
WP infections as a percentage of all detected HIV infections

<table>
<thead>
<tr>
<th>Region</th>
<th>% of detected infections that were WP</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First time</td>
<td>Lapsed</td>
<td>Repeat</td>
<td>L/R combined</td>
<td>All</td>
</tr>
<tr>
<td>South Africa</td>
<td>1.1</td>
<td>1.9</td>
<td>11.1</td>
<td>6.6</td>
<td>2.5</td>
</tr>
<tr>
<td>SE Asia</td>
<td>0.9</td>
<td>2.0</td>
<td>14.3</td>
<td>5.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Med Europe</td>
<td>0</td>
<td>4.9</td>
<td>10.3</td>
<td>7.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Cen/Nor Eur</td>
<td>0</td>
<td>0</td>
<td>7.7</td>
<td>4.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Oceania</td>
<td>0</td>
<td>0</td>
<td>50.0</td>
<td>50.0</td>
<td>33.3</td>
</tr>
<tr>
<td>All but SA</td>
<td>0.6</td>
<td>3.0</td>
<td>12.3</td>
<td>6.7</td>
<td>3.6</td>
</tr>
<tr>
<td>All</td>
<td>1.1</td>
<td>2.0</td>
<td>11.2</td>
<td>6.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>
WP infections as a percentage of all detected HIV infections in different donation categories
Sensitivity of HIV-RNA and anti-HIV assays in detecting HIV infected donors

- HIV-RNA and anti-HIV
  - First (n=4828): 99.2%
  - Lapsed (n=836): 99.6%
  - Repeat (n=823): 99.9%
  - All (n=6487): 99.3%

- HIV-RNA
  - First (n=4828): 98.9%
  - Lapsed (n=836): 98.0%
  - Repeat (n=823): 92.8%
  - All (n=6487): 98.4%

- HIV-Ag and anti-HIV
  - First (n=4828): 98.0%
  - Lapsed (n=836): 98.0%
  - Repeat (n=823): 88.5%
  - All (n=6487): 97.5%

- Anti-HIV
  - First (n=4828): 98.9%
  - Lapsed (n=836): 98.0%
  - Repeat (n=823): 88.5%
  - All (n=6487): 97.5%
RBC transmission risk per million for different test scenarios (SANBS, 5 year)

assumptions: ID$_{50}$ in WP 3.16 and in elite controllers 316 virions

<table>
<thead>
<tr>
<th>Test strategy</th>
<th>Risk per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID-NAT + HIVAb</td>
<td>25</td>
</tr>
<tr>
<td>ID-NAT alone</td>
<td>27</td>
</tr>
<tr>
<td>MP8 NAT + HIVAb</td>
<td>47</td>
</tr>
<tr>
<td>MP16 NAT + HIVAb</td>
<td>54</td>
</tr>
<tr>
<td>HIV-Ag + HIVAb</td>
<td>104</td>
</tr>
<tr>
<td>HIVAb</td>
<td>146</td>
</tr>
</tbody>
</table>

(first) (lapsed) (repeat) (all)
Efficacy of HIV screening scenarios (based on risk analysis SANBS, 5 years)

![Efficacy of HIV screening scenarios graph](image-url)
Efficacy of HIV screening scenarios in repeat donors (based on risk analysis SANBS, 5 years)

Test strategy

<table>
<thead>
<tr>
<th>Test strategy</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID-NAT + HIVAb</td>
<td>97.6%</td>
</tr>
<tr>
<td>ID-NAT alone</td>
<td>97.6%</td>
</tr>
<tr>
<td>MP8 NAT + HIVAb</td>
<td>95.6%</td>
</tr>
<tr>
<td>MP16 NAT + HIVAb</td>
<td>94.9%</td>
</tr>
<tr>
<td>HIV-Ag + HIVAb</td>
<td>90.6%</td>
</tr>
<tr>
<td>HIVAb</td>
<td>86.4%</td>
</tr>
</tbody>
</table>

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

• Complete efficacy analyses in each region
• In the context of introduction of pathogen reduction for platelets and transfusable plasma, analyze the consequence of eliminating serologic testing for repeat and lapsed donors
• Determine cost effectiveness of different test strategies
International ID NAT User Group

- Marion Vermeulen, Ravi Reddy, South African National Blood Service, Johannesburg, South Africa
- Arthur Bird, Russell Cable, Western Province Blood Transfusion Service, Cape Town, South Africa
- Heidi Goubran, Faten Moftah, National Blood Transfusion Service, Cairo, Egypt
- Magdy El Ekiaby, Shabrawishi Hospital, Dokki, Egypt
- Sylvia Sauleda, Banc de Sang I Teixits, Barcelona, Spain
- Roberto Roig, Manolo Alvarez, Valencia Regional Blood Tx Center, Valencia, Spain
- Paola Ghiazza, St Anna Hospital, Turin, Italy
- Paola Manzini, University of Turin, Turin, Italy
- Rocio Gonzalez, Emma Castro, Red Cross Blood Center, Madrid, Spain
- Christoph Niederhauser, Martin Stolz, Blood Transfusion Service SRC Berne, Berne, Switzerland
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- Joan O’Riorden, Irish Blood Transfusion Service
- Sussanne Wessberg, Sussane Elkblom, Mervi Lankinen, Finnish Red Cross Blood Service, Helsinki, Finland,
- Christian Erikstrup, Aarhus University Hospital and Henrik Ullum, Copenhagen, Denmark
- Ewa Brojer, Piotr Grabarczyk, Institute of Haematology and Transfusion Medicine, Warsaw, Poland
- Jolanta Gdowska, Dariusz Piotrowski, Warsaw Blood Center, Warsaw, Poland
- Kit Che Lin, Tsoi Wai Chiu, Hong Kong Red Cross
- Diane Teo, Sally Lam, Sze Sze Chua, Health Systems Agency, Singapore
- Abdul Hamid Bon, Sally Lam Tsuey Peng, National Blood Centre, Malaysia
- Peter Flanagan, New Zealand Blood Service, Auckland, New Zealand
- Stewart Brown, Australian Red Cross