True and false NAT reactive, a donor deferral and re-entry problem?

Dr. Joan O’Riordan
Irish Blood Transfusion Service
IPFA/PEI 21st International Workshop, Rome
Nucleic Acid Amplification Testing (NAT) Ireland

IBTS: Serology Prism including anti-HBc

- Nov 99 - HCV NAT SNBTS MP-96
- Sep 02 - HIV and HCV multiplex NAT SNBTS
- 2004 - Duplex HIV-1/HCV MP-8
- April 09 - ID-NAT HIV-1/HCV/HBV

- > 2,300 000 screened donations for HCV RNA*
- > 1,800 000 screened donations for HIV-1 RNA*
- No HCV RNA, or HIV RNA, yield cases
- 753,109 HBV DNA: 2 yield cases

* NHSBT/PHE Infection Surveillance Report Feb 2014
<table>
<thead>
<tr>
<th>Assay</th>
<th>Total tested</th>
<th>Initial Reactive</th>
<th>Repeat Reactive</th>
<th>Confirmed reactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrio Tigris</td>
<td>417,118</td>
<td>279 (0.067%)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>UPlus Tigris</td>
<td>320,288</td>
<td>136 (0.04%)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>UEelite Panther</td>
<td>42,166</td>
<td>18 (0.04%)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

6 HCV
11 HBV
2 HIV
5 HCV
7 HBV
1 HBV
# ID-NAT
## April 2009-Dec 2013

<table>
<thead>
<tr>
<th>Total tested</th>
<th>Initial Reactive</th>
<th>Repeat Reactive</th>
<th>Confirmed reactive</th>
<th>Sample only donor n= 6131</th>
<th>First time donations n= 65 634</th>
<th>Repeat donations n=671 688</th>
</tr>
</thead>
<tbody>
<tr>
<td>743,453</td>
<td>417</td>
<td>31</td>
<td>31</td>
<td>19</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 HIV-1</td>
<td>7 HCV</td>
<td>1 HIV-1</td>
<td>1 HIV-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11 HCV</td>
<td>12 HBV</td>
<td>2 HCV</td>
<td>2 HCV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 HBV</td>
<td></td>
<td>5 HBV</td>
<td>1 HBV</td>
</tr>
<tr>
<td></td>
<td>0.056%</td>
<td>0.004%</td>
<td>0.004%</td>
<td>0.3%</td>
<td>0.01%</td>
<td>0.0006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.34)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 2 HBsAg carriers Ultrio Neg
<table>
<thead>
<tr>
<th>April 2009- Dec 2013</th>
<th>Total Tested (%)</th>
<th>Anti-HBc RR(%)</th>
<th>Anti-HBs Positive (%)</th>
<th>% HBc Ab positive (past hepatitis B infection)* / Total tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOND</td>
<td>6,131(0.8)</td>
<td>220(3.6)</td>
<td>196 (89)</td>
<td>3.2</td>
</tr>
<tr>
<td>Donations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First time</td>
<td>65,634(8.8)</td>
<td>112(0.17)</td>
<td>44 (39.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Repeat</td>
<td>671,688(90.4)</td>
<td>214(0.03)</td>
<td>27 (12.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total</td>
<td>743,453</td>
<td>546(.07)</td>
<td>267</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* anti-HBs pos
Guidance for Industry

Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (HFM-40), Suite 200N, 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
FIGURE 3. Testing, Product Disposition, Donor Management, and Lookback for an Individual Donor Sample that is Reactive on a Multiplex NAT (ID-NAT) after Negative Antibody Screening Tests

Individual Donor Sample Reactive on a Multiplex HIV-1/HCV ID-NAT

TEST USING DISCRIMINATORY HIV-1 AND HCV NATs.

Reactive for HIV-1 and/or HCV

QUARANTINE AND DESTROY OR RE-LABEL UNIT.
DEFER¹ AND NOTIFY DONOR.
PERFORM LOOKBACK² FOR HIV-1 AND/OR HCV, AS APPROPRIATE.

Non-Reactive for both HIV-1 and HCV ("Non-Discriminated Reactive")

QUARANTINE AND DESTROY OR RE-LABEL UNIT.
DEFER³ AND NOTIFY DONOR.⁴
PERFORM LOOKBACK² FOR HIV-1 AND HCV.
Issue Summary
Blood Products Advisory Committee
Gaithersburg, Maryland
July 21, 2005

Topic I: FDA’s Current Considerations on the Management of Whole Blood and Source Plasma Donors and Units when a Donor Tests Positive for Hepatitis B Virus (HBV) DNA by a Nucleic Acid Test (NAT)
Algorithm for ID-NAT Initial Reactives

ID-NAT Initial Reactive
(Serology +/-)

Repeat ID-NAT x 2

Discriminatory assays for HIV-1, HCV & HBV

Negative on repeat NAT and
Discriminatory assays x 3 and serology

Follow up Donor 8/52

Repeat NAT x 2, Discriminatory x 3, and Serology

All Negative
Re-instate Donor 6 months after IR donation

Donation discarded
Donor deferred
Plasma bag retrieved if available,
417 ID-NAT IRs

31 RR, dHXV(+)
- All confirmed

7 NRR, dHXV (+) (1.7% FP)
- All non-confirmed

3 anti-HBcore

376 NRR, dHXV(-) Serology neg

337 (90%) re-attended & screened neg

330 (98%) Re-instated

311 Eligible to donate

209 (67%) Donated and screened neg

39 donors did not return

32 tested by TaqScreen 1 positive
HBV IR (+), RR(-), dHXV(-) serology neg donor

- The Ultrio IR sample from 1 donor who did not attend for follow-up in 2009:
  
  Positive on Roche TaqScreen MPX in ID and by in-house PCR for HBV DNA (SNBTS)

  Partial fragment (316 base pairs) of S gene amplified by nested PCR

  Follow-up 1 year later anti-HBcore pos only
A phylogenetic tree based on a partial fragment of the S (Surface) gene (316bp) of HBV. IBTS HBV isolate (Sample 000459) is in the red box and is clustering with representative HBV Genotype C isolates.
Anti-HBc RR (n=546) and ID-NAT IRs

<table>
<thead>
<tr>
<th></th>
<th>Ultrio</th>
<th>Ultrio P</th>
<th>Ultrio P</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-HBc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-HBs IU/L</td>
<td>&lt; 10</td>
<td>117</td>
<td>44</td>
</tr>
<tr>
<td>ID-NAT</td>
<td>IR,NRR</td>
<td>IR,NRR</td>
<td>IR,1/2 R</td>
</tr>
<tr>
<td>ID-Reps</td>
<td>1/20 pos</td>
<td>3/10 pos</td>
<td></td>
</tr>
<tr>
<td>dHBV</td>
<td>neg</td>
<td>neg</td>
<td>3/10 pos</td>
</tr>
<tr>
<td>Cobas TaqScreen (ID)</td>
<td>neg x3</td>
<td>neg</td>
<td>neg x 2</td>
</tr>
<tr>
<td>MPX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott Real-Time</td>
<td>neg x3</td>
<td>1/2 pos</td>
<td>2/2 pos</td>
</tr>
<tr>
<td>HBV PCR</td>
<td></td>
<td>&lt; 10 IU/ml</td>
<td>&lt; 10 IU/ml</td>
</tr>
<tr>
<td>Donor type</td>
<td>SOND</td>
<td>SOND</td>
<td>lapsed</td>
</tr>
</tbody>
</table>

OBI Ultrio: 1/417,118 Vs 2/320,288 Ultrio Plus p=0.418
Summary 417 ID-NAT IRs

- 31/417 (7.4%) RR and confirmed positive
- 7/417 (1.7%) dHXV(+) false positive
- 3/417 (0.4%) NRR anti-HBc+ OBI
- 1/417 (0.2%) NRR probable HBV WP
- 368/369 (99.7%) of NRR, nondiscriminated serology negatives were false reactive

HBV Residual Risk: 1:2 500 000*
- Incremental risk if NRR x 2 were released: 1:24 000 000
- Incremental risk if NRR x 3 were released: 1:37 000 000

Weusten et al, Transfusion 2011;51:203-215
Acknowledgments

Dr Louise Pomeroy  Joe Donnellan
Dr Michael Thomas  Padraig Williams, Virology

Fiona Boland, NAT

Dr B Crowley, Microbiologist, St James’s Hospital, Dublin
SNBTS- Tony Jordan, Dr Fiona Davidson