Donation Testing and Donor Notification

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History

- **Until 1980s testing focused on prevention of hemolytic transfusion reactions**
  - **ABO/Rh**
  - **Red cell antibody**

- **Two tests for potentially infectious units**
  - **Syphilis (<1950)**
    - **Blood banks reported positive results to Departments of Health who notified donors**
  - **HBsAg (1970)**
    - **Notifications done by Blood Center, initially driven by research interests**

Current Screening and Confirmatory Tests

- Screening Tests
  - **HIV-1/HIV-2 antibody and NAT**
  - **HTLV-I/II antibody**
  - **Hepatitis B Surface Antigen and NAT**
  - **Hepatitis B Core antibody**
  - **HCV antibody and NAT**
  - **Syphilis antibody**
  - **West Nile Virus NAT**
  - ***T. cruzi* antibodies (Chagas Disease)**
  - **ABO/Rh**
  - **Zika NAT**
  - **Cytomegalovirus (CMV)**
  - **Sickle Cell (HgS)**
  - **Red cell antibody Screen**
  - **Extended red cell antigen typing**

- Confirmatory Tests
  - **HIV-1/HIV-2 Algorithm (only if antibody RR/NAT NR) - Western blot, or IFA, HIV-2 antibody, HIV 1/2 Ab Assay** (unlicensed immunochromato-graphic assay)
  - **HTLV-I/II – Western Blot**
  - **HCV-alternate antibody (only if antibody RR/NAT NR)**
  - **HBsAg Neutralization (only if antibody RR/NAT NR)**
  - **Syphilis (IgG-ABS)**
  - ***T. cruzi* antibodies (Chagas Disease) ESA (Enzyme Strip Assay)**

Required tests **Inventory, special needs*** **Recent changes**

Current Serological Rate Estimates

Test	% RR	% Confirmed
HIV-1/2	0.088	6.3
HCV	0.080	41.8
HBsAg	0.033	50.3
HTLV-1/2	0.041	29.1
HBCore	0.590	N/A
Syphilis	0.141	33.8
Chagas	0.073	9.4
CMV	30-60	N/A

- **Overall rate of units with a reactive screening result is 1%. This has decreased over time because the tests are more specific.**

Data provided by Creative Testing Solutions 2016

Risk of Transfusion Transmitted Infections

Marker	TTD Risk per Unit	Donor Prevalence	Population Prevalence	Window Period (days)
HIV-1/2	1:1,000,000	1:16,000	1:250	22 (6-38)
HIV NAT	1:2.3 million	same	same	11 (7-12)
HBsAg	1:200,000-1:500,000	1:3,700	1:33	51(36-72)
HTLV-I/II	1:500,00 - 1:3 million	1:7,000	N/A	82 (54-192)
HCV	1:105,000	1:3,100	1:75	59 (37-87)
HCV NAT	1:1.8 million	same	same	20 (11-22)
Syphilis	<1:1 million	1:2,300	N/A	N/A

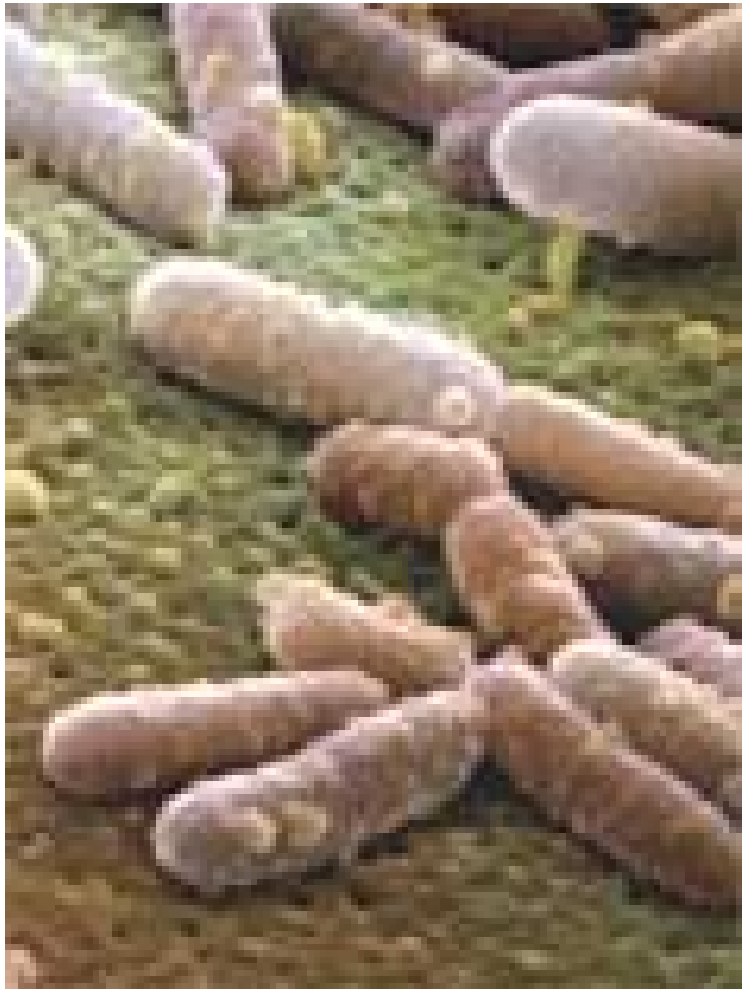
First time donors have marker rates 4-8x repeat donors

Most common causes of death reported to FDA

Complication	FY11 No.	FY11 %	FY12 No.	FY12 %	FY13 No.	FY13 %	FY14 No.	FY14 %	FY15 No.	FY15 %	Total No.	Total %
Anaphylaxis	2	7%	2	5%	-	0%	2	7%	2	5%	8	5%
Contamination	4	13%	3	8%	5	13%	1	3%	5	14%	18	10%
HTR (ABO)	3	10%	3	8%	1	3%	4	13%	2	5%	13	7.5%
HTR (non-ABO)	6	20%	5	13%	5	13%	4	13%	4	11%	24	14%
Hypotensive Reaction	-	0%	-	0%	-	0%	1	3%	1	3%	2	1%
TACO	4	13%	8	21%	13	34%	5	17%	11	30%	41	24%
TRALI*	10	33%	17	45%	14	37%	13	43%	12	32%	66	38%
Other	1**	3%	-	0%	-	0%	-	3%	-	0%	1	.5%

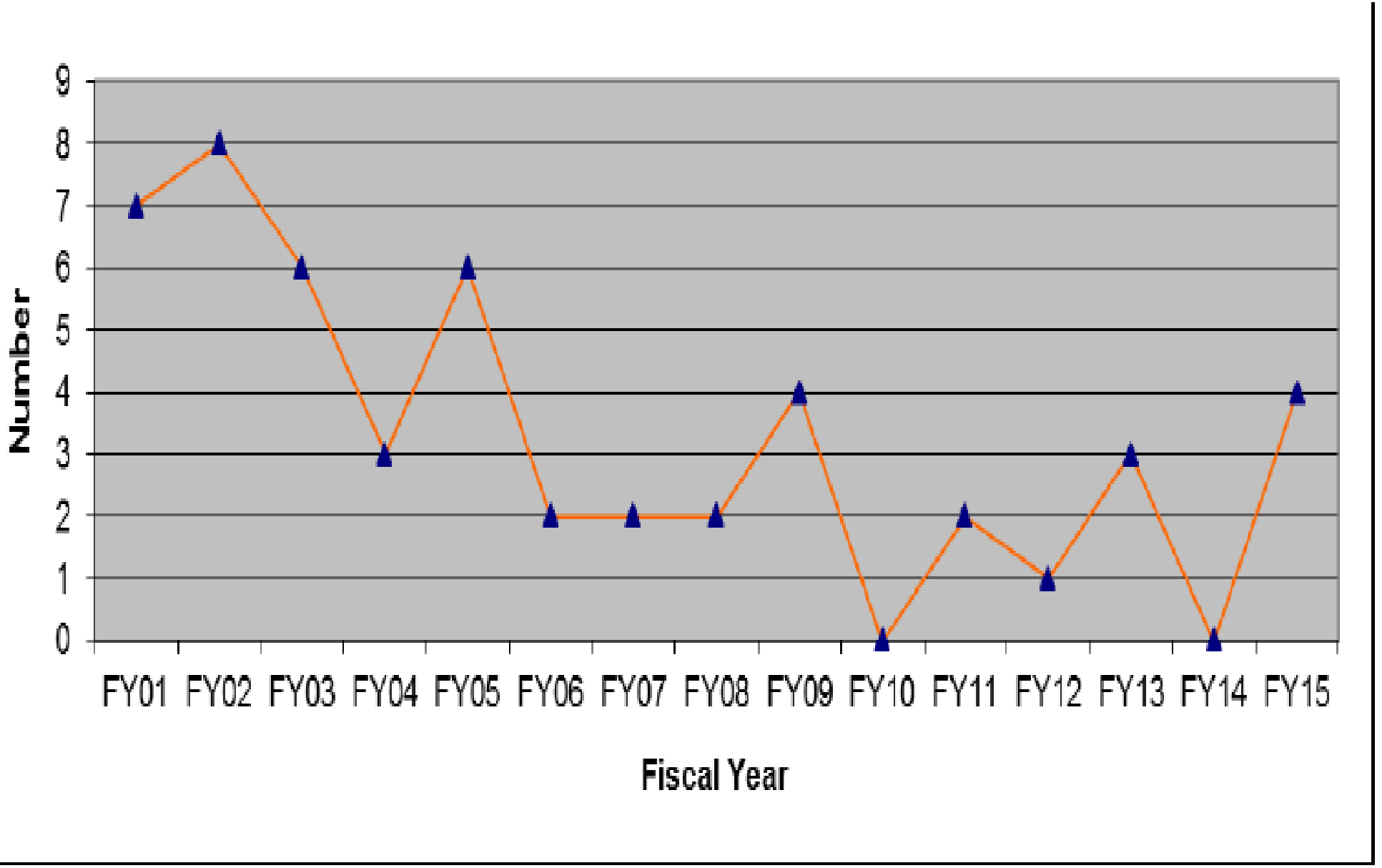
Detection of Bacterial Contamination in Platelets

Bacterial Detection in Single Donor Platelets



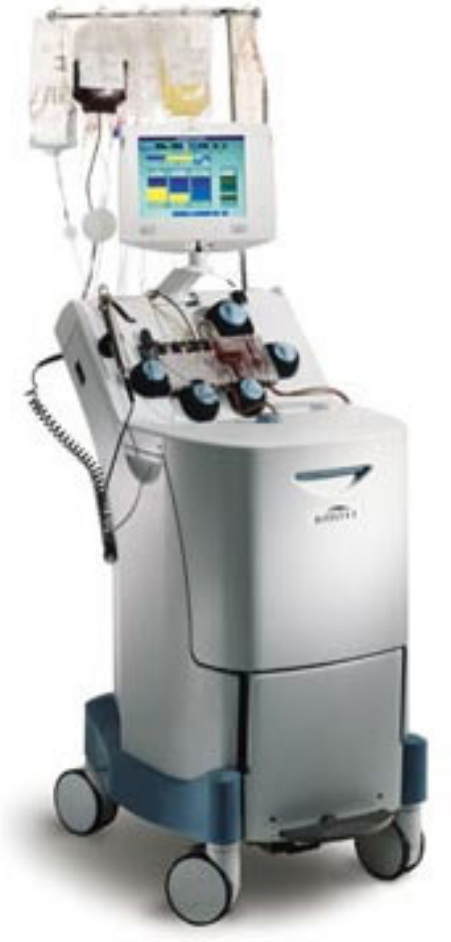
- **Major cause of transfusion related fatalities; typically gram negative organisms**
  - **Clusters of infection/deaths occurred in 2002/2003**
  - **WB plt Contamination = 1:2-4,000**
  - **SDP Contamination = 1:15,000**
  - **Culture positive results – 1:1,500**
  - **Fatalities = ~ 1:40,000 (under reported)**
- **AABB standard - All platelets must be tested for bacterial contamination**
- **FDA Guidance pending on**

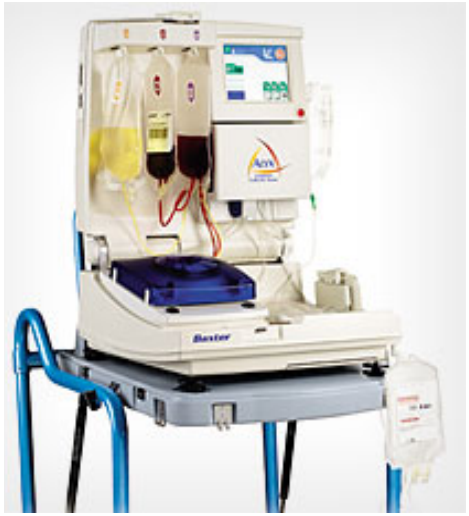
Fatalities from bacteria in transfusion



Sources and Remediation of Bacterial Contamination of Platelets

- **Sources**
  - **Donor skin flora (50-60%)**
  - **Donor bacteremia (40-50%)**
  - **Blood bag or container manufacture damage or defect (rare)**
  - **Blood processing contamination**
- **Remediation**
  - **Improved skin disinfection**
  - **Diversion pouches**
  - **SDPs instead of RDPs (Septic reactions decreased from 1:4818 to 1:15,098 (Ness et al, Transfusion 1999;39:89))**





Detection of Bacterial Contamination in Platelets

- **Use of approved devices for "QC" purposes for SDP – Culture methods**
  - **Culture media (BacT/Alert, CO_2 production)**
  - **Growth *in situ* (Pall BDS; O_2 consumption)**
- **Other methods - Dip-stick, glucose meters, pH, culture plates are no longer allowed.**
- **Point of issue test (Verax and BacTx) available as addition to culture methods**

Detection of Bacterial Contamination in Platelets - Procedure

- Sample platelets into vials containing bacterial culture medium after a 24 h pre-incubation at 22 ^{o}C
- Incubated in the BacT/Alert and check on growth continuously.
- Initial testing in aerobic culture only
- If negative at 16 hrs of incubation release platelets inventory; continue to monitor until expiration.
- If positive, interdict product and send samples for confirmation and species identification.

What we can do now

- **Pathogen Reduction – Apheresis platelets and all plasma components with approved device (Currently Cerus only)**
- **Primary Culture testing – for Apheresis, Pre-Storage Pooled Platelets and Whole blood platelets (single unit)**
  - **Use FDA cleared detection method into at least aerobic bottle or both aerobic and anaerobic**
  - **Use the largest sampling volume permitted in package insert**
  - **Pre-Storage Pooled Platelets and Whole blood platelets (single unit) – no Pathogen Reduction approved for this product as yet.**
  - **Whole blood platelets (single unit) – FDA cleared rapid test may be used (Verax, BacTx)**

What FDA wants in the future (draft guidance)

- **Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion**
  - **March 2016**
  - **Draft Guidance only**
  - **Transfusion Services MAY NOT fully understand expectations**

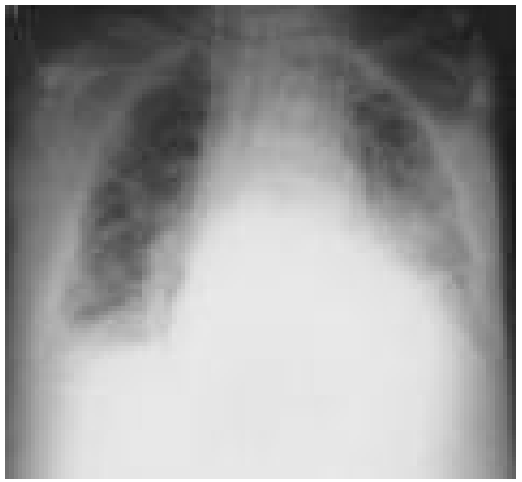
- **Platelets still in inventory of transfusion service on day 4 and day 5**
  - **If Pathogen reduced, no further actions needed**
    - **Not all SDPs may be pathogen reduced**
  - **If not, perform FDA cleared rapid test on day 4 or 5 within 24 hours of transfusion or perform a culture based test on day 4 and release after at least 12 hours (or as noted in package insert**
- **Many questions remain**

TRALI

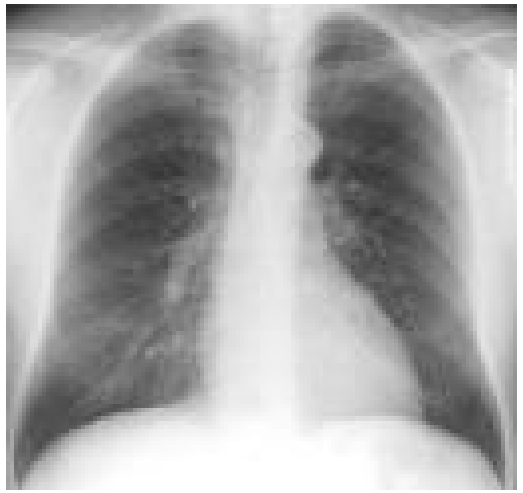
Transfusion Related Acute Lung Injury

TRALI – Clinical Aspects and Causes

- Pulmonary injury (difficulty breathing, fluid in the lungs, fever)
- Associated in time with blood transfusion (onset within 6 hours after transfusion)
- Causes are not clear but TRALI seems to be associated with the presence of antibodies to white blood cells (anti-HLA or anti-leukocyte) in the donated blood that react with the recipient's white cells

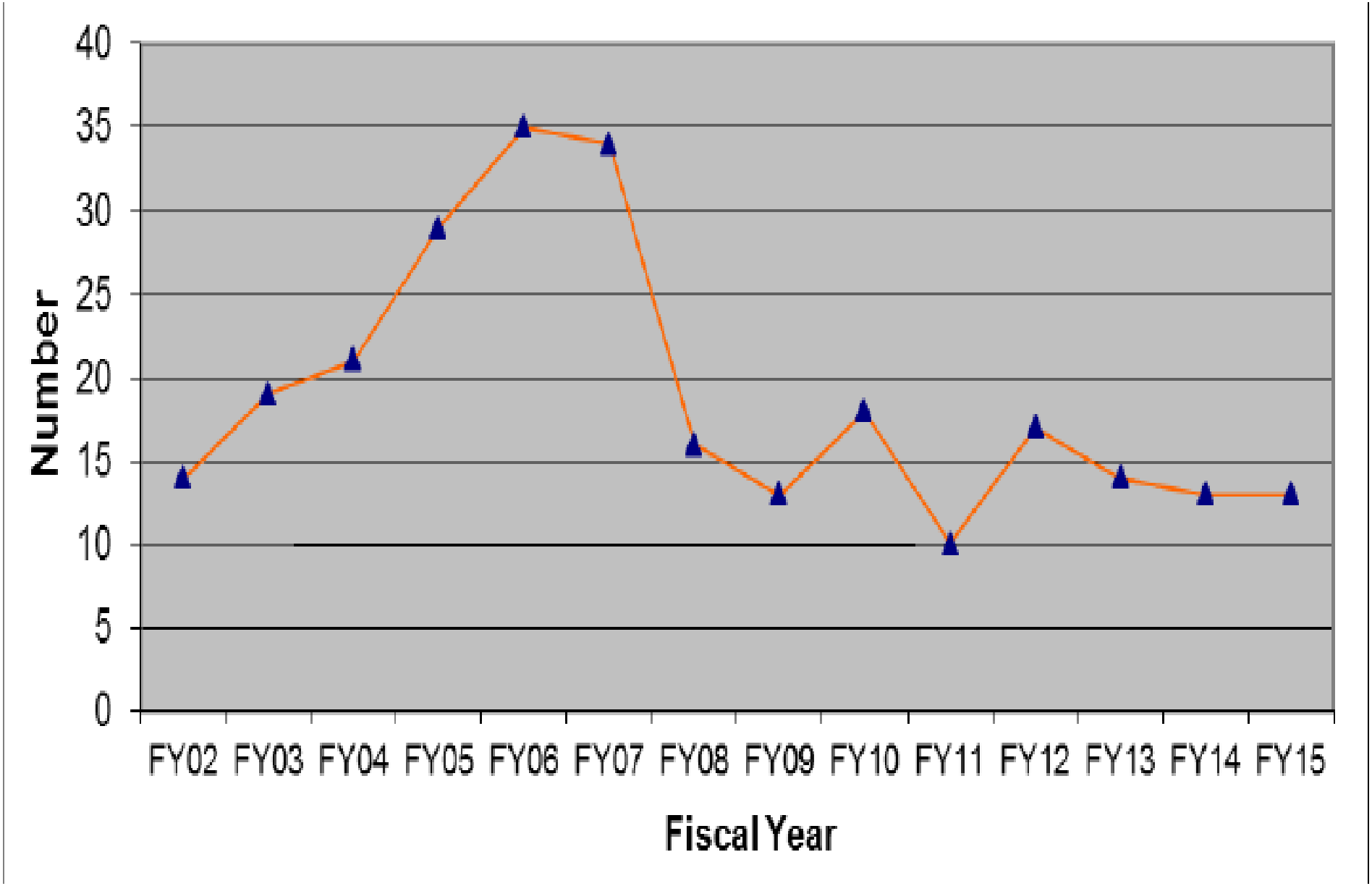


TRALI

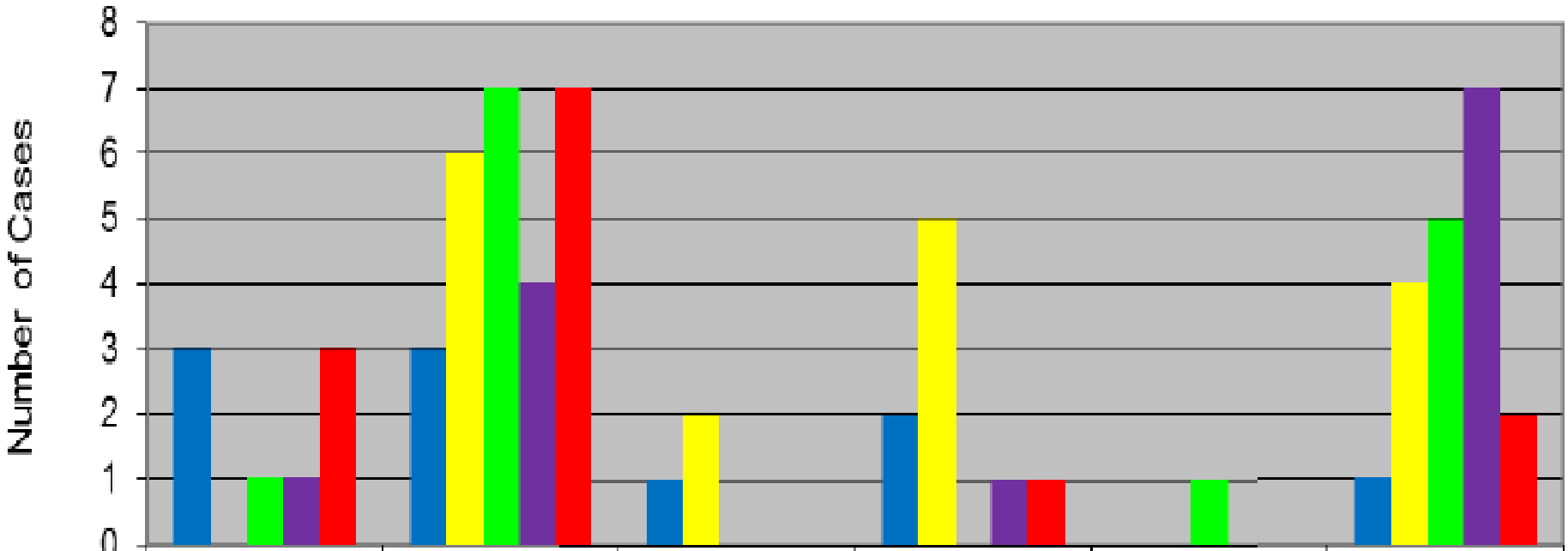


NORMAL

TRALI fatality reports by year



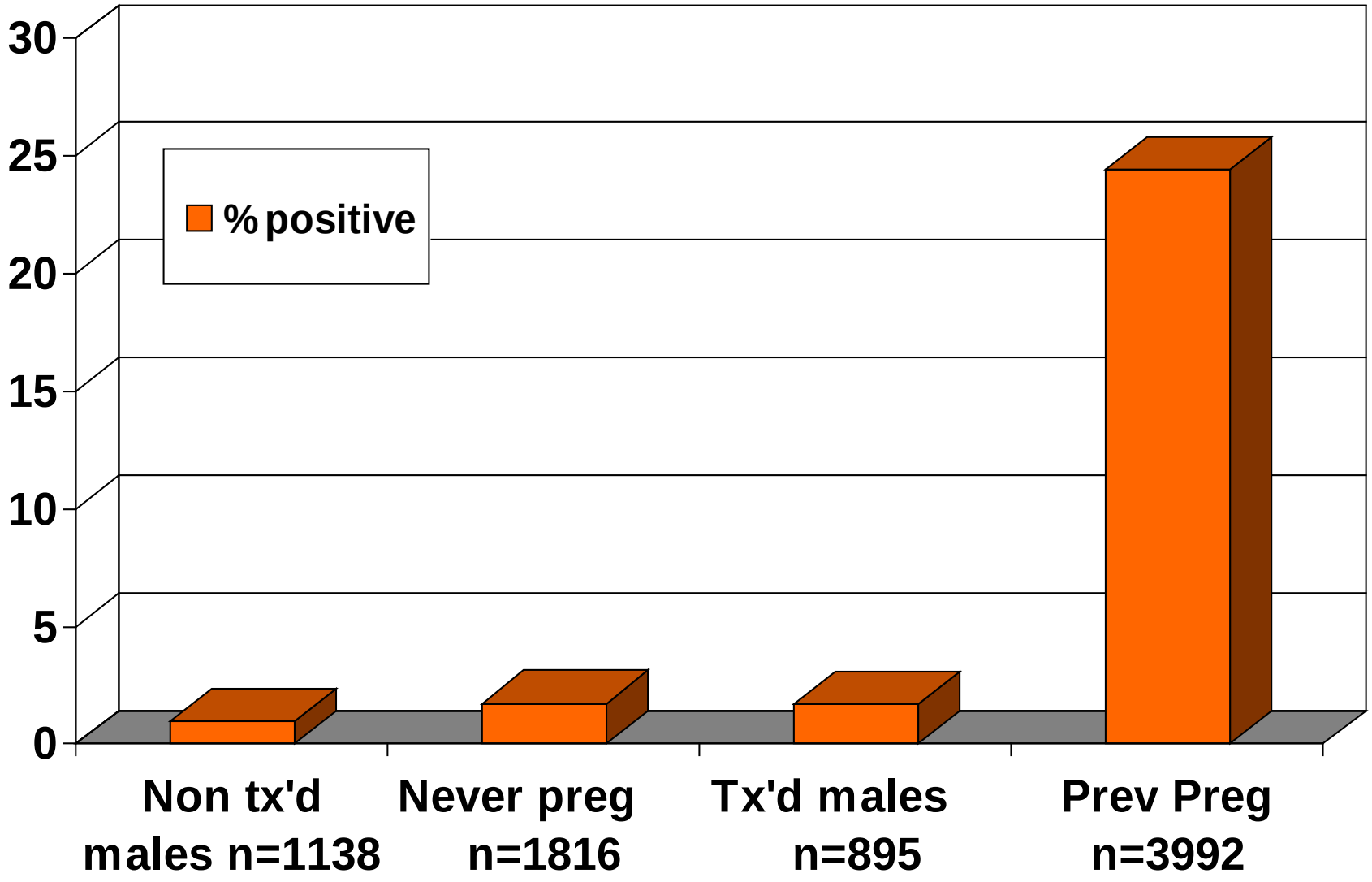
Rate of TRALI by component type



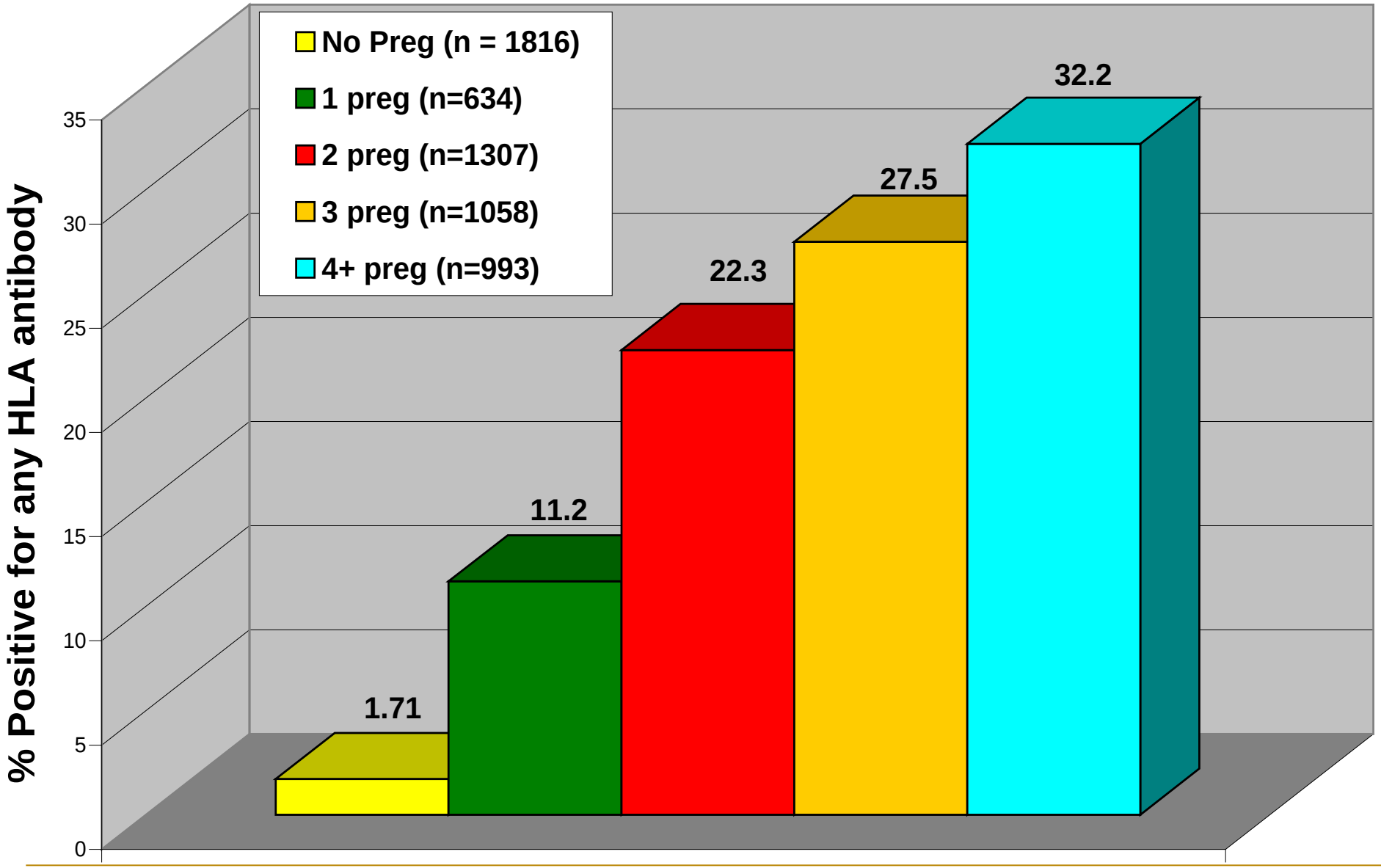
	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY11	3	3	1	2	0	1
FY12	0	6	2	5	0	4
FY13	1	7	0	0	1	5
FY14	1	4	0	1	0	7
FY15	3	7	0	1	0	2

Blood Product

Rate of HLA Alloimmunization in LAPS Donors



Effect of Pregnancy on the Rate of HLA Alloimmunization



TRALI – What to Do About It

- **AABB Standard 5.4.1.3 to reduce the risk of TRALI**

  Plasma, Apheresis platelets and whole blood for allogeneic transfusion shall be from males, females who have not been pregnant, or females who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

*AABB BB/TS Standards 30th Edition

Platelets - Risk Reduction Measures

- Testing all female platelet donors who have had one or more pregnancies for the presence of HLA antibodies
- Defer women with HLA antibodies from future platelet donations. These donors would be permitted to donate DRBCs or whole blood.
- Repeat screening of female donors with a history of an additional pregnancy after their last negative screening test.
- Outcome 13.6% of previously pregnant female platelet donors are positive for HLA antibodies.

Donor Notification and Counseling

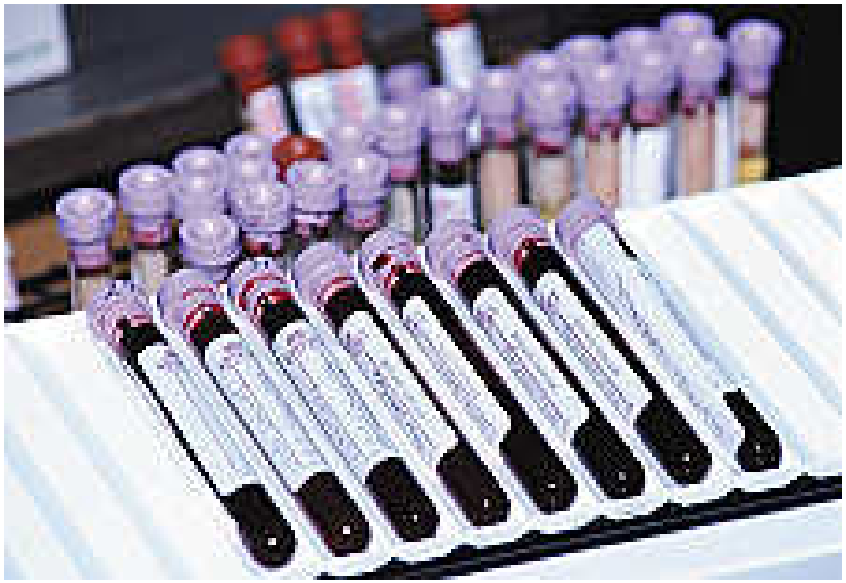
The Impact of HIV Testing

HIV testing brought major shift in notification for donors who confirmed as positive:

- **Extensive counseling**
- **Confidentiality**
- **Social stigma**
- **Donor's right to information**

Current Scene

- **Tests now performed include HIV (antibody and NAT), HTLV, HCV (antibody and NAT), HBV (NAT and/or surface antigen and core antibody), Syphilis, WNV NAT, *T.Cruzi*, Zika NAT.**
- **Due to high false reactive rate in many of these screening tests, most of these donors are not infected or infectious**



Objectives of Donor Notification and Counseling

- **To fulfill ethical and regulatory requirements of disclosure** (FDA Rule - 6/11/2001)
- **To protect the health of the donor**
- **Possibly to protect the health of contacts (sexual partners, pregnancy, needle sharing)**
- **To maintain the safety of the blood supply (communicate that the donor must not donate in the future)**
- **To monitor the effectiveness of donor selection procedures**

Significance of Deferral from Donating Blood

- **Donors who are deferred because of positive test results can be anxious, upset or angry**

- **They attempted to join their peers and help patients and now feel rejected**

- **Generally, they believed that they were healthy, or they would not have donated**

Complexity of Donor Notification

- **Donor notification of test results continues to increase in complexity**
  - **multiple results**
  - **non-specific results**
  - **test interpretation**

Counseling Donors About Indeterminate and False Positive Results

- **Time for seroconversion - retest**
- **Risk review**
- **Offer re-entry:**
  - **complicated**
  - **time consuming**
  - **not always successful**
  - **unavailable**

Other Legal/Ethical Considerations

- **Laws regarding the test (HIV)**
- **Laws regarding donors and information generated about them**
- **Insurance issues**
- **Confidentiality**

Notification Process Difficulties

- **No notification process satisfies the needs of all donors**
  - **expectations of blood center**
  - **understanding of technical material**
  - **response to information about health**

Notification Background

- **Blood donors are, or should be, aware of the standard tests being performed on their blood**
- **By proceeding with the donation, the donor has given up the right not to be tested and be notified of unacceptable test results**
- **Blood Centers need to have processes in place to ensure confidentiality of donor test results**
- **Notification should be timely**
- **The quality of the information given to the donor must be current, reliable and understandable**
- **Notification and counseling must be performed by knowledgeable personnel who are appropriate to the task**

Approaches to Notification

- **Letter and fact sheets**
  - **method of the majority of notifications**
- **Phone Call**
  - **almost never used**
  - **may violate confidentiality**
- **In person**
  - **HIV and HTLV positive results**

Structure of Notification Letters

- **Donor notification letters are composed of discreet segments, each containing an element of the notification message**
  - **standard introduction**
  - **description and meaning of each test result**
  - **recommended medical follow-up**
  - **future donation eligibility**
  - **degree of follow-up by Blood Center**
  - **phone number to call with questions**
  - **standard closing**

Contacting HIV+ Donors

May be NAT+ and/or antibody +

(NAT-/Confirmed Ab Positive - donor most likely on HAART)

- **Non-specific letter - finding of significance to donor's health**
- **Stronger worded letter - still non-specific**
- **Telephone call to donor - no specific information given**
- **Test results given by certified mail; addressee only. Counseling still offered**

HIV Positive Counseling

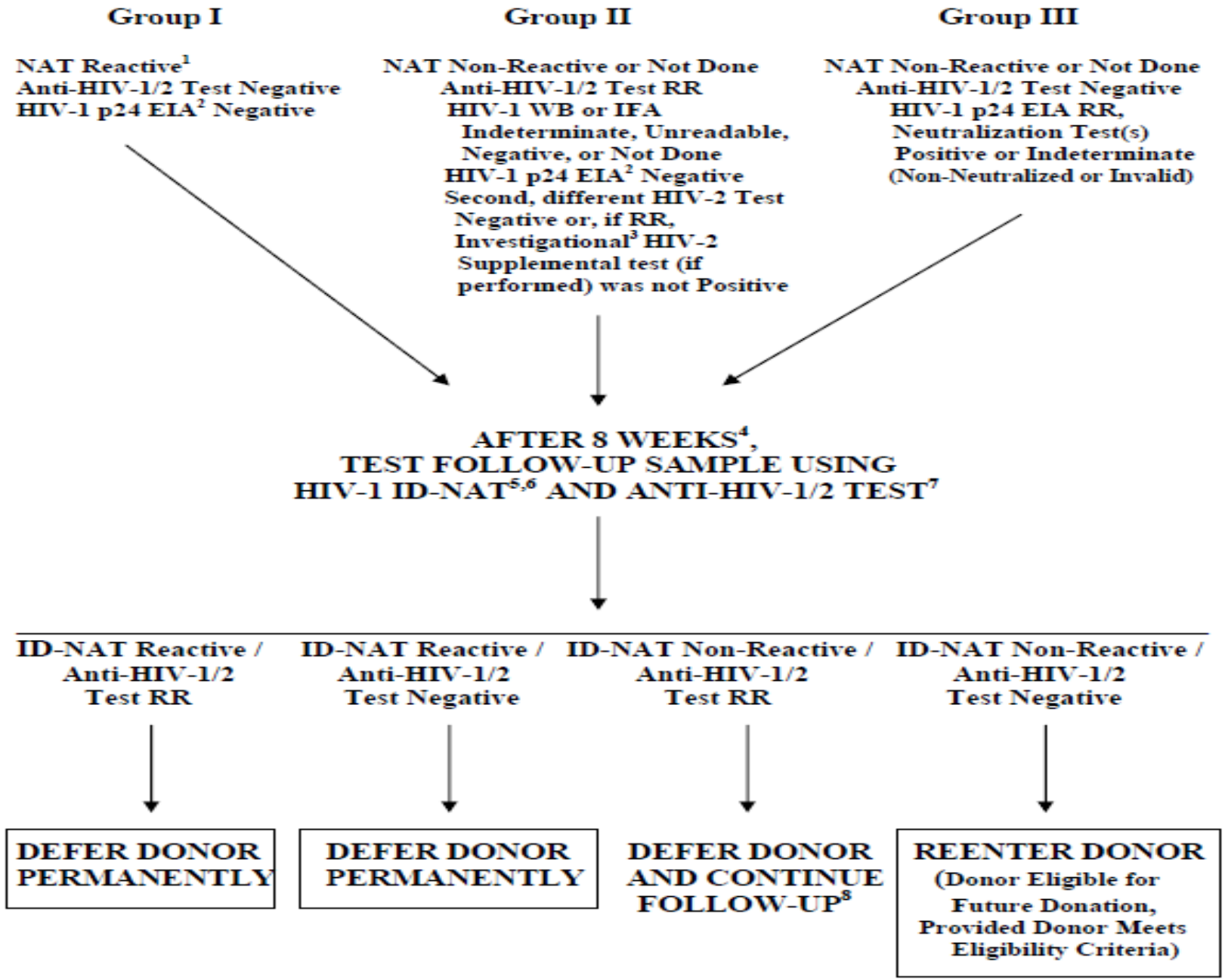
- **Crisis Intervention**
  - **Allow for expression of feelings**
- **Risk assessment**
- **Education**
  - **Explanation of test**
  - **Meaning to health**
  - **Risk reduction**
- **Assess understanding**
- **Referral for follow-up**
- **Written information**
- **Retest and second appointment**

HIV ELISA RR/IFA Confirmation Non-Specific Test Results

- **NAT +/Confirmation Ab Negative or Indeterminate - Possible recent infection.**

- **NAT-/Confirmation Ab Negative or Indeterminate - In the absence of recent risk, no infection, no follow-up.**
- **Reentry possible.**

HIV-1/2 Re-entry Algorithm (Issued May 2010)



Footnotes

1. Reactive on a Discriminatory NAT for HIV-1 or on a Single Virus NAT for HIV-1.
2. May not have been performed, depending upon the conditions of the specific NAT approval.
3. Performance of an investigational HIV-2 supplemental test (if available) is optional. If a supplemental test is licensed in the future it should be performed and it must not have been positive for the donor to be eligible for reentry.
4. HIV-1 ID-NAT and/or an anti-HIV-1/2 test, if performed during the 8 week waiting period, must be negative for the donor to be eligible for reentry.
5. If the original donor sample was reactive on both of the Discriminatory NAT tests for HIV-1 and HCV, we recommend that you test a follow-up sample using HCV ID-NAT and an anti-HCV test also, as in the HCV Reentry Algorithm (see Figure 6).
6. If the original donor sample was reactive on the NAT for HIV-1 (Group I donors), we recommend that you use the same ID-NAT (i.e., the Discriminatory NAT for HIV-1 or the Single Virus NAT for HIV-1) that was run on the original donor sample. If the original NAT is no longer available (e.g., an investigational NAT), we recommend that you use a NAT that has the same sensitivity claims as the original NAT or greater sensitivity claims (e.g., a NAT labeled in the Intended Use as sensitive for HIV-1 including Group O, if available).
7. If the original donor sample was RR on the anti-HIV-1/2 test (Group II donors) we recommend that you use that same test to test this follow-up sample. If the original donor sample was negative on the anti-HIV-1/2 test (Group I donors or Group III donors) or if the original test is no longer available, we recommend that you use an anti-HIV-1/2 test that is labeled in the Intended Use as sensitive for HIV-1 including Group O.
8. At your option you may further test the donor's sample using HIV-1 WB or IFA. If WB or IFA is negative, unreadable, or indeterminate, you may reconsider the donor for reentry by conducting follow-up testing after one or more additional waiting period of 8 weeks. If WB or IFA is positive, we recommend that you defer the donor permanently. 34

HTLV I/II Positive Counseling

- **Not HIV, not related to AIDS**
- **Minimal chance of developing disease**
- **Risk assessment**
- **Significance to health**
- **Transmission routes - risk reduction**
- **Physician follow-up**
- **Written information**
- **Retest and second appointment**

HTLV RR

- **Confirmation Negative -** Donor deferred after second occasion only. No supplemental testing done. No follow-up.
- **Confirmation Positive -** Donor deferred. Counseling as necessary**.**

Donors with Positive Results for Hepatitis

- **HBcAb only**
  - **Donor deferred and notified after second occurrence only**
  - **Donor may have been exposed to HBV**
  - **No follow-up indicated**
  - **Reentry possible**

Anti-HBc 2 Hit Re-entry Algorithm

APPENDIX

REQUALIFICATION PROCESS FOR DONORS DEFERRED BECAUSE OF REPEATEDLY REACTIVE TEST RESULTS FOR ANTI-HBc

Donors previously deferred solely because of repeatedly reactive (RR) anti-HBc test on more than one occasion

↓

After a minimum of 8 weeks[1] following the last repeatedly reactive anti-HBc test result, test a follow-up sample using FDA-licensed HBsAg and anti-HBc tests, and HBV NAT[2]

↓

HBsAg RR[3] or Anti-HBc RR or HBV NAT Reactive	All tests negative
↓	↓
Defer donor indefinitely	Reenter donor (Donor eligible for future donations, provided donor meets eligibility criteria)

[1] If, for donor notification purposes or for medical reasons, you wish to perform follow-up testing on a donor who is deferred because of repeatedly reactive anti-HBc test results before the end of the 8-week waiting period and the blood sample tests HBsAg RR or anti-HBc RR or HBV NAT reactive, the donor should be indefinitely deferred. If, however, the sample tests negative on all three of these tests, the donor should be retested after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test result using licensed HBsAg and anti-HBc tests, and HBV NAT. If, at that time, the sample tests negative on all three of these tests (HBsAg, anti-HBc, and HBV NAT), the donor may be eligible to donate.

[2] The sensitivity of the HBV NAT used should be $\leq$ 2 IU/mL, at 95% detection rate.

[3] Regardless of the neutralization test result.

Donors with Positive Results for Hepatitis

- **HBsAg**
  - **Confirmation negative and anti HBc NR, probable false reactive screening result; no follow-up. Donor deferred for 8 weeks.**
  - **Next donation - If HBsAg and anti HBc are negative on next donation, donor is re-entered, unit may be used. If anti HBc is reactive on any subsequent donation donor is permanently deferred. If HBsAg is RR/NN, donor is deferred for another 8 weeks.**
  - **Confirmation positive, donor is HBV carrier**
    - **Potential transmission to contacts**
    - **Potential for liver disease**
    - **See physician**

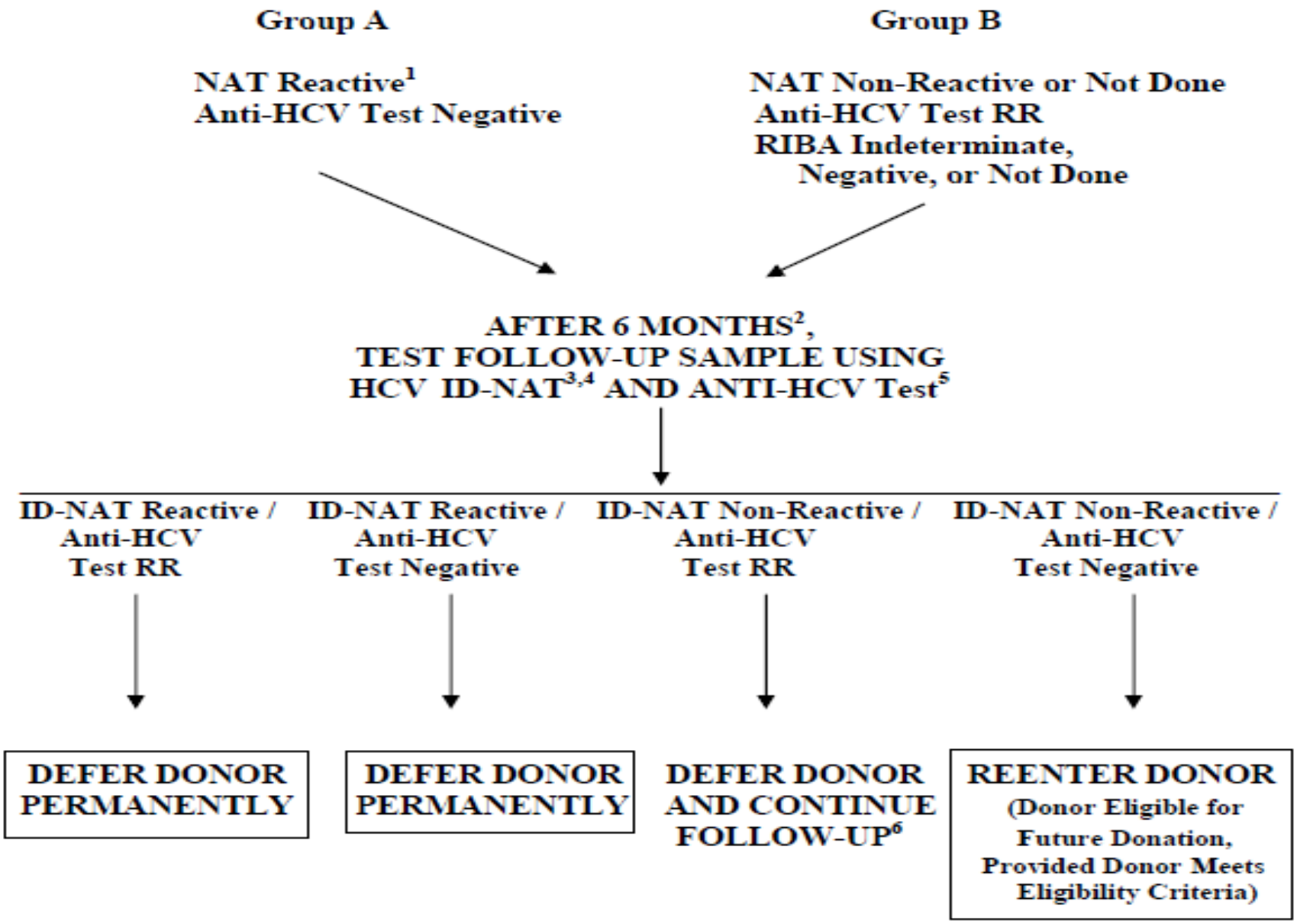
Donors with Positive Results for Hepatitis

- **HBV NAT is a DNA test (HIV and HCV are RNA).**
- **Done in Triplex format**
- **If reactive for HBV NAT only (HBsAg and anti HBc are non-reactive) donor may be tested for reentry after 8 weeks.**
- **Reentry testing must include ID HBV NAT, HBsAg and anti-HBc tests and all must be non-reactive.**

Donors with Positive Results for Hepatitis

- **HCV NAT+/antibody NR - Possible window period infection, follow-up**
- **HCV antibody RR - four possibilities**
  1. **NAT+/RIBA not required - infected, see MD**
  2. **NAT-/RIBA+ - Resolved infection. No follow-up**
  3. **NAT-/ RIBA Indeterminate - either resolved infection or false reactive antibody test, No follow-up**
  4. **NAT-/RIBA - false reactive antibody. No follow-up.**

HCV Re-entry Algorithm (Issued May 2010)



Footnotes

1 Reactive on a Discriminatory NAT for HCV or on a Single Virus NAT for HCV.

2 HCV ID-NAT and/or an anti-HCV test, if performed prior to 6 months, must be negative for the donor to be eligible for reentry.

3 If the original donor sample was reactive on both of the Discriminatory NAT tests for HIV-1 and HCV, test a follow-up sample using HIV-1 ID-NAT and an anti-HIV-1/2 test also, as in the HIV-1 Reentry Algorithm (see Figure 5).

4 If the original donor sample was reactive on the NAT for HCV (Group A donors), we recommend that you use the same ID-NAT (i.e., the Discriminatory NAT for HCV or the Single Virus NAT for HCV) that was run on the original donor sample. If the original NAT is no longer available (e.g., an investigational NAT) we recommend you use a NAT that has the same sensitivity claims as the original NAT or greater sensitivity claims.

5 If the original donor sample was RR on the anti-HCV test (Group B donors) we recommend that you use the same test or a later, more sensitive version (i.e., HCV antibody version 3.0 or later) to test this follow-up sample.

6 At your option you may further test the donor's sample using HCV RIBA. If RIBA is negative or indeterminate, you may reconsider the donor for reentry by conducting follow-up testing after one or more additional waiting period of 6 months. If RIBA is positive, we recommend that you defer the donor permanently.

Donors with Reactive Results for Syphilis

- **Olympus PK-TP treponemal test positive (~MHA-TP, Ab persists after infection)**
- **Confirmation (FTA or Syph G; RPR for counseling purposes).**
  - **Conf. negative (20%), no infection, no deferral**
  - **Conf. positive, RPR negative, past infection**
  - **Conf. positive, RPR positive, current infection depending on titer of RPR.**
  - **Re-entry after 1 year w/doctor's note and a negative screening test.**

Indate Product Retrieval,Lookback and Recipient Notification

What is it?

- **Indate Product Retrieval -** tracing products from donors who have subsequently tested positive on screening test for an infectious disease marker or CJD/vCJD risk
- **Lookback -** The process of tracing recipients of products from some of these donors
- Previously acceptable units may have transmitted disease if the donors were in the window period of infectivity or if there were no tests available at the time of donation

Test Result Product Retrieval and Lookback

Positive Test	Indate product Retrieval	Lookback Trace Length
HIV Ab	All products except pooled plasma	5 years
HIV NAT	All products in prior 1 year except pooled plasma	1 year
HBsAg	All products except pooled plasma	6 months
HTLV	All products except any kind of plasma	5 years (no plasma products)
HBc (Core)	All products except most recovered plasma	none
HCV Ab	All products except pooled plasma	As far back as electronic records available
HCV NAT	All products in prior 1 year except pooled plasma	1 year
T. Cruzi	None	All
WNV	All in prior 120 days	None
Zika	All in prior 120 days	None

CJD/vCJD Product Retrieval and Lookback

Deferral Category	Indate Product Retrieval		Lookback	
	Blood Components	**Plasma Derivatives**	**Blood Components**	**Plasma Derivatives**
Donors dx with CJD	All products	Unpooled products only	ALL	None
Donors dx with nvCJD	same	All Pooled and unpooled products	ALL	ALL
↑ risk for CJD (1)	same	Unpooled products only	ALL	None
Has only 1 blood relative with CJD (2)	same	Unpooled products only	None	None
Lived in UK >3 mo. (3) Transfusion in UK 5+ yrs in France/Europe Military bases in Europe	same	Unpooled products only	None	None
Received bovine derived injectable products from BSE countries (4)	same	Unpooled products only	None	None
Donors <55 years with CJD	same	Unpooled products, refer to FDA for further action (5)	ALL	ALL

Notes on CJD/vCJD Product Retrieval and Lookback

- **All CJD or nvCJD deferrals are permanent (indefinite) If a donor is not familiar with the term Creutzfeldt - Jakob disease it may be taken as a negative response.**
- **(1) Donors at increased risk for CJD include those who have:**
  - **received a dura mater transplant**
  - **received human pituitary hormones (now includes gonadotropins as well as growth hormones). If donor is not sure about human pituitary hormone treatment ask if they received the treatment by needle. If they did not, the donor is acceptable.**
  - **have 2 or more blood relatives with CJD.**
- **(2) Donor with only 1 blood relative with CJD – product retrieval only no recipient tracing or notification**
- **(3) Cumulative 3 months between 1980 and 1996. Includes travel to England, Northern Ireland, Scotland, Wales , the Isle of Man and the Channel Islands. Product retrieval only no recipient tracing or notification**

Notes on CJD/vCJD Product Retrieval and Lookback (cont'd)

- **(4) Obtaining bovine derived injectable products from BSE countries is difficult to do. If the donor doesn't know or is not sure, they are to be indefinitely deferred. Product retrieval only no recipient tracing or notification**
- **(5) FDA will evaluate on a case by case basis to determine if quarantine and withdrawal is indicated.**
- **All in-date product management notifications should be made within 1 week of the donor's deferral for any of the above reasons. Lookback extends back as far as electronic records are available. Recipient notification for Lookback is at the discretion of the care providers.**

Issues in Recipient Notification

- **Must be tailored for the type of Lookback**
  - **Probability of Infection**
  - **Risk of secondary transmission**
- **Concept of window period or timing of new test introduction**
- **Recipient testing and follow-up**

Summary

- **Blood donor and recipient management are highly regulated activities**
- **The goal is to achieve a safe and adequate blood supply**

Thank you!

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