

BLOOD PRODUCTS ADVISORY COMMITTEE
69th Meeting - June 14-15, 2001
Gaithersburg, MD

TOPIC: **Reentry for Donors Deferred Because of HIV or HCV NAT or Serological Test Results**

ISSUE: Each year, an estimated 14,000 donors are deferred from donating blood for an indefinite period because of a repeatedly reactive EIA result and a negative or indeterminate supplemental test for antibodies to HIV or HCV. In addition to these indefinite serological deferrals, the implementation of minipool NAT for HIV RNA and HCV RNA has resulted in deferrals of several hundred donors due to potentially false positive NAT test results each year.

In anticipation of licensure of the first minipool NAT method, FDA is developing guidance for industry on implementation of NAT testing. This guidance will address all aspects of donor testing, donor management, and product management and will include algorithms for testing discussed at the March, 2001 Blood Products Advisory Committee meeting, and algorithms for donor reentry to be discussed at the June meeting.

FDA is proposing two new reentry algorithms based on the combined use of NAT and serologic testing for consideration by the Committee and for public comment: one for donors deferred because of HIV test results, and a second for donors deferred because of HCV test results. The proposed algorithms would allow for the possibility of reentering donors who have a positive NAT for HIV RNA or HCV RNA and/or a repeatedly reactive EIA with a negative or indeterminate supplemental test for anti-HIV or -HCV on the initial sample. Reentry (that is, eligibility to donate again) would be permitted, following an appropriate time period, if negative NAT and negative EIA test results are obtained on a follow-up sample.

BACKGROUND:

At the March, 2001 meeting of the Blood Products Advisory Committee, FDA proposed uniform algorithms for management of Whole Blood and Source Plasma donations tested by minipool NAT. The focus of the FDA proposal was the actions that should be taken in the event of discrepant testing results, such as when the Master Pool is reactive and one or more subpools are reactive, but individual donations are non-reactive, or when the Master Pool is reactive but all subpools are non-reactive.

The data presented in the March BPAC session showed that in each discrepant case it was the Master Pool that was falsely positive, due to contamination either during specimen handling or during the assay run, and that false negatives on individual donations have not been seen in the studies performed using various NAT methods under IND. In response to FDA questions, the Committee vote in each case was that the NAT result on individual donations should be considered the definitive test result, and that units could be released in each case. This outcome makes the uniform NAT testing algorithms (**ATTACHMENT 1**) relatively simple. These algorithms recommend the release of all units when all subpools or all individual donations are negative on the NAT test.

These NAT testing algorithms also include recommendations for donor deferral based on individual donation NAT-positive test results. Some of these donors, as well as those deferred on the basis of the results of serological testing for HIV and HCV antibodies that is being performed concurrently with the NAT minipool testing, may be uninfected and could be made eligible to donate blood or plasma again. However, most donors deferred because of serological HIV test results remain deferred because very few blood establishments are even attempting to reenter donors due to the complexity of the current HIV reentry algorithm and concerns about inappropriately reentering a donor because the correct tests were not performed. In addition, many donors deferred because of serological HCV test results also remain deferred because the use of the recently licensed RIBA 3.0 supplemental test as part of the previously published FDA reentry algorithm has not been widely implemented.

The goal of this BPAC session is to outline suitable criteria for reentry of donors deferred because of HIV or HCV NAT or serological test results.

PROPOSAL for HIV REENTRY:

Options for HIV reentry are summarized in **ATTACHMENT 2**. Donors are placed into three groups based on the screening test results. FDA's current thinking is to propose that "Group 2" donors (donors who are seronegative but have NAT positive results that are unconfirmed) may be considered for reentry. Additionally, FDA proposes that donors in Group 3 (donors with negative NAT who have a repeatedly reactive screening test for antibody, but negative or indeterminate HIV-1 Western blot results) also may be considered. The proposal also suggests re-testing after 8 weeks using both HIV NAT and anti-HIV-1/2 EIA. Details of the algorithm will be addressed through a series of questions:

- In Question 1, FDA will be asking the Committee whether it is useful to consider for reentry donors in "Group 1" (donors with positive, but

unconfirmed, screening tests both by NAT and serology). The issue is that within this group of donors, the number who may be eligible to reenter is expected to be very small (estimated at 100 donors per year), so that considering this group for reentry may not be cost-effective or yield-effective for the blood establishment.

- In Question 2, FDA will be asking whether possible reentry should apply to the subset of donors in “Group 3” who have Indeterminate Western Blots with Viral Bands Present. The issue here is whether follow-up studies on donors whose blots are indeterminate but have viral bands show that they are actually not infected with HIV. Data presented on Western Blot indeterminates at the June, 1996 BPAC led to a conclusion by the Committee that the rate of infection in persons with an indeterminate Western Blot is very low, and that reentry could be attempted for this group. It is proposed that negative results of NAT testing are a sufficient basis to negate concerns over an indeterminate Western blot containing viral bands, provided that a suitable screening test for antibodies to HIV also is negative on re-testing.
- Question 3 addresses whether 8 weeks is an adequate period to wait before follow-up testing of the donor by both NAT and antibody EIA. The issue is whether an 8-week follow-up period encompasses the pre-seroconversion window period with sufficient confidence that negative serology rules out HIV infection. Absent evidence for seroconversion, the negative NAT on follow-up testing would be taken as evidence that any prior positive (but unconfirmed) NAT result was an error.
- Question 4 addresses the case in which follow-up testing by NAT is negative, but there is a persistent antibody EIA Repeatedly Reactive result. An option to consider is whether the donor can be further tested by Western blot. If the Western blot test result is negative, or an indeterminate pattern has not progressed, can the donor be treated de-novo as a member of “Group 3” and reconsidered for reentry after a second waiting period of 8 weeks? Many blood establishments would like to continue to follow-up such donors; however, if a significant percentage of them actually prove to be infected, concern has been raised about their continuing to visit the donor setting for follow-up.

PROPOSAL FOR HCV REENTRY:

Options for HCV reentry are summarized in **ATTACHMENT 3**. Similar to the reentry options for HIV, donors are grouped according to the screening test results. Again, FDA proposes that reentry should be considered for donors in Groups 2 and 3, and seeks advice from the Committee on details of the proposal.

- In Question 1, FDA will ask whether it is useful to attempt reentry for “Group 1” donors. The issue here is similar to that in Question 1 for HIV, namely whether it is practical to consider reentry for donors who are screening test reactive both on NAT and serology.
- Question 2 addresses whether “Group 3” donors should include those with an Indeterminate RIBA. The pertinent data will address the prevalence of HCV infection in RIBA Indeterminate donors.
- Question 3 asks if waiting at least 6 months after the index donation (i.e., the one that tested repeatedly reactive in an EIA screening test) is an adequate period of time. The current FDA recommendation is that a minimum time period of 6 months elapse between the index donation and the follow-up sample to evaluate any donor for possible reentry. The answer to this question depends on data that shows whether a 6-month follow-up period encompasses with sufficient confidence the pre-seroconversion window period.

FDA’s current thinking is to give the blood establishment the option of following up with an HCV NAT test at any time up to 6 months after the index donation due to concerns about intermittent HCV viremia and a possible true-negative NAT on later follow-up testing. This optional NAT would be performed for purposes of donor counseling and, if it’s Positive, to exclude the possibility of reentry. If that NAT test is Negative or not done, the donor may be followed-up with NAT and antibody EIA after an appropriate period of time to qualify for reentry.

- In Question 4, FDA will ask whether a donor with negative NAT, but with a persistent antibody EIA Repeatedly Reactive result may, at the option of the blood establishment, be reconsidered for reentry in a “second cycle” of re-testing provided that an appropriate RIBA test is negative.

The presentations at the BPAC meeting are intended to focus on the data the Committee will need to address the questions below. Dr. Michael Busch will present a scientific overview, including data for both HIV and HCV on time to viremia and on the duration of the viremic pre-seroconversion window period, and evidence for and against transient viremia in the eclipse phase and immunosilent infections. Dr. Susan Stramer and Dr. Susan Galel will present data obtained under IND from screening and follow-up studies using the GenProbe and Roche NAT testing systems, respectively.

REFERENCES:

1. Busch MP. Closing the windows on viral transmission by blood transfusion. In: Stramer SL, ed. *Blood Safety in the New Millenium*, Bethesda, MD: American Association of Blood Banks, 2001.
2. Nucleic acid amplification testing of blood donors for transfusion-transmitted infectious disease. Report of the Interorganizational Task Force on Nucleic Acid Amplification Testing of Blood Donors. *Transfusion* 2000;40:143-159.
3. Busch MP, Dodd RY. NAT and blood safety: what is the paradigm? (editorial) *Transfusion* 2000;40:1157-1160.
4. Stramer SL, Cagliotti S, Strong DM. NAT of the United States and Canadian blood supply. *Transfusion* 2000;40:1165-1168.
5. Dodd RY, Stramer SL. Indeterminate results in blood donor testing: what you don't know can hurt you. *Transfusion Med Rev* 2000;14:151-160.

QUESTIONS FOR THE COMMITTEE:

Reentry for Donors Deferred Because of HIV Test Results

1. Is it useful to consider reentry for donors (Group 1) with NAT Positive / Anti-HIV-1/2 EIA RR / HIV-1 Western Blot Indeterminate or Negative results ?
2. Should reentry be considered for donors (in Group 3) with NAT Negative / Anti-HIV-1/2 EIA RR / HIV-1 Western Blot Indeterminate, Viral Bands Present results ?
3. What should be the minimum time period for waiting prior to follow-up testing ?
4. Should the blood establishment have the option of continuing to follow-up a donor with NAT Negative / persistent Anti-HIV-1/2 EIA RR results for possible reentry ?

Reentry for Donors Deferred Because of HCV Test Results

1. Is it useful to consider reentry for donors (Group 1) with NAT Positive / Anti-HCV EIA RR / RIBA 3.0 Indeterminate or Negative results ?
2. Should reentry be considered for donors (in Group 3) with NAT Negative / Anti-HCV EIA RR / RIBA 3.0 Indeterminate results ?
3. What should be the minimum time period for waiting prior to follow-up testing ?
4. Should the blood establishment have the option of continuing to follow-up a donor with NAT Negative / persistent Anti-HCV EIA RR results for possible reentry ?