**Date:** August 8, 1995

**From:** Director, Center for Biologics Evaluation and Research (CBER)

**Subject:** Recommendations for Donor Screening with a Licensed Test for HIV-1 Antigen

**To:** All Registered Blood and Plasma Establishments

## INTRODUCTION

This memorandum provides the recommendations of the Food and Drug Administration (FDA) on the implementation of donor screening tests for human immunodeficiency virus, type 1 (HIV-1) antigen(s). The attached recommendations supersede previous FDA recommendations contained in a memorandum of October 4, 1989, following licensure of the first test for HIV-1 antigen(s).

## BACKGROUND

On March 23, 1989, the Blood Products Advisory Committee (BPAC) of the Food and Drug Administration recommended licensure of a test for the detection of HIV-1 antigen(s) in serum or plasma (HIVAG-1™, Abbott Laboratories, North Chicago, Illinois) as an aid in determining the diagnosis and prognosis of patients with HIV-1 infection, but not as a screening test for blood and plasma donors. Consistent with the BPAC recommendation, FDA approved the test with the following label restriction, "This test is not intended as a screen for donated blood or plasma."

The rationale for this decision was the absence of known HIV transmission by plasma derivatives since 1987, and the lack of detection of antigen positive, antibody negative donations in large scale donor screening studies conducted both within the United States and Europe[1,2]. These and other studies were interpreted to imply that detection of HIV-1 antigen in the absence of antibody would be a very rare event in U.S. donor screening, although the frequency of detection could not be estimated. Based on the available data, FDA did not approve HIV-1 antigen testing for routine donor screening.

Recently, the role of HIV-1 antigen testing in the donor setting has been reconsidered for several reasons. First,

there have been four documented instances of HIV-1 transmission by HIV-1 antigen positive blood donations from three HIV-1 antibody negative donors. All four cases were identified by retrospective analysis of stored samples from previous donations of the seroconverting donors.[3-5]

Second, there have been more recent estimates of the residual risk of HIV transmission by screened blood and the efficacy of antigen testing to detect seronegative, infectious donations. Based on studies involving 19 blood centers within the U.S., Lackritz, et al. estimated that the current HIV risk per unit is 1:440,000 - 1:640,000[6], compared with risk estimates in 1989 of 1:38,000 to 1:150,000[7,8]. A risk of 1:440,000 corresponds to approximately 41 cases of recipient exposure per year out of 18 million units transfused.

Busch, et al. estimated that the antibody negative infectious "window period" is approximately 22-25 days for screening with combination assays for antibodies to HIV-1 and HIV-2 as determined in 81 seroconverting homosexual men or injection drug users.[9] The authors estimated that HIV antigen screening could reduce the "window period" by about 6 days while testing by polymerase chain reaction (PCR) for RNA could reduce the "window period" by about 11 days. As a result, it is estimated that donor screening by HIV-1 antigen can be expected to prevent up to 25% of the current "window period" cases by detection of about 5-10 cases of antigen-positive/ antibody-negative collections per year.[10] Screening for HIV-1 antigen also may contribute to the safety of plasma derivatives by reducing the frequency of HIV contamination in plasma pools for fractionation.

In September, 1994, FDA sponsored a "Conference on the Feasibility of Genetic Technology to Close the HIV Window in Donor Screening" to address the value of direct viral detection in donor screening. For a variety of reasons, the majority of participating experts expressed the opinion that genetic techniques, although capable of HIV-1 detection prior to seroconversion, were not ready for use in mass screening. This meeting did, however, spark renewed interest in considering other direct viral detection methods for donor screening, such as HIV-1 antigen testing, as an interim measure to further reduce the current low risk of HIV-1 transmission through transfusions of blood and blood products.

To further address direct viral detection methods, FDA brought

the issue of donor screening for HIV-1 antigen to a public meeting of the BPAC on June 23, 1995. The BPAC members agreed unanimously that the current estimates of HIV-1 prevention by antigen screening of blood donors are sufficient to determine efficacy of test kits for donor screening. After hearing the most recent available data on HIV-1 risk in the blood supply, the estimated efficacy of antigen screening, and other issues bearing on a risk/benefit assessment (e.g. "magnet effect" of high risk donors seeking testing, cost analysis, etc.), 9 of the 15 BPAC members present were of the opinion that donor screening for HIV-1 antigen by candidate test kits is not likely to provide a significant public health benefit which outweighs the potential risks.

After considering the available information and the opinions of the BPAC members, FDA now is recommending that blood establishments should implement donor screening for HIV-1 antigen using licensed tests that are approved for this indication. FDA is recommending implementation of HIV-1 antigen screening because of the benefit that it will provide to a small number of blood product recipients, as a partial preventive measure against the possibility of any increase in HIV-1 "window period" donations and to decrease the virus burden in plasma pools for fractionation. Because HIV-1 antigen testing will only reduce but not eliminate the residual risk of HIV-1 from transfusion, the FDA regards such screening as only an interim measure pending the availability of better technology for this purpose. FDA encourages continued development of new methods to further reduce the risk of HIV transmissions in the "window period".

Although currently there are no tests for HIV-1 antigen(s) approved for donor screening, FDA is issuing recommendations on donor screening for HIV-1 antigen(s) in advance of the availability of such tests in order to provide blood and plasma establishments with maximum time to prepare for this testing.

Questions concerning these recommendations may be directed to the Division of Transfusion Transmitted Diseases, FDA/CBER (HFM-310), 1401 Rockville Pike, Rockville, MD 20852; FAX: (301) 594-6989.

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RECOMMENDATIONS FOR DONOR SCREENING
WITH A TEST FOR HIV-1 ANTIGEN(S)

TERMINOLOGY

The following terms apply to HIV-1 antigen testing:

| | |
|---|---|
| Initially reactive: | Initial EIA test is reactive. |
| Repeatedly reactive: | One or both duplicate EIA retests is (are) reactive. |
| NEGATIVE: | Initial EIA test is not reactive; or, initial EIA test is reactive and both duplicate EIA retests are not reactive. |
| POSITIVE: | EIA test is repeatedly reactive and the neutralization test is positive (neutralizing). |
| INDETERMINATE: | EIA test is repeatedly reactive and the neutralization test is either negative (non-neutralizing) or indeterminate (invalid). |

Donor specimens that are repeatedly reactive in the screening assay which are neutralizing according to the criteria set forth by the test kit manufacturer are considered **POSITIVE** for HIV-1 antigen(s). Donor specimens that are repeatedly reactive in the screening assay, but which are negative in the neutralization test are unlikely to contain HIV-1 antigen(s). However, they should not be regarded as negative because of the possible occurrence of false-negative neutralization tests. Therefore, specimens that are repeatedly reactive in the screening assay but which are negative or indeterminate (invalid) by the criteria set forth for neutralization by the manufacturer should be considered **INDETERMINATE**.

RECOMMENDATIONS

A. Implementation of Donor Screening for HIV-1 Antigen(s)

1. All donations of Whole Blood, blood components, Source Leukocytes and Source Plasma should be screened for HIV-1 antigen(s) by an FDA licensed test labeled specifically for use in donor screening. FDA believes that this recommendation should be implemented within three months of the commercial availability of the first such test. Following the date of implementation, only units from donors found negative on HIV-1 antigen screening and acceptable by all other criteria should be released for use in transfusion or for further manufacturing into injectable products. **Antigen testing should be performed <u>in addition to</u> required testing for antibodies to HIV-1 and HIV-2 (see previous FDA recommendations of April 1992)**.

2. Within three months of the commercial availability of the first FDA licensed HIV-1 antigen test labeled specifically for use in donor screening, all inventoried units of Whole Blood, blood components, Source Leukocytes and Source Plasma available for release should be screened for HIV-1 antigen(s).

3. Blood establishments should cooperate with consignees to insure that inventoried within-date units intended for use in transfusion which were distributed prior to test implementation are either replaced with screened units or else tested for HIV-1 antigen(s) as soon as feasible.

B. Disposition and Labeling of Units

1. Units from Donations Negative for HIV-1 Antigen

   a. Products for transfusion: The instruction circular should state, consistent with 21 CFR 606.122(h), that the product was prepared from blood that was negative in a screening test for HIV-1 antigen(s). Blood establishments should maintain a record of the date of implementation of testing for HIV-1 antigen(s).

   b. Products for further manufacturing use: The container label should bear the statement, "Negative by a test for HIV-1 antigen(s)" or an equivalent statement. The statement regarding

anti-HIV test results, HBsAg test results [21 CFR 640.70(a)(8)] and anti-HCV test results may be combined with the statement regarding the HIV-1 antigen test results. For example, the statement could be: "Negative by tests for HIV-1 antigen(s), antibodies to HIV and HCV, and nonreactive for HBsAg."

2. Units from Repeatedly Reactive Donations

a. Units of Whole Blood, blood components, Source Leukocytes and Source Plasma obtained from a donor whose blood sample is found to be **repeatedly reactive** using a licensed screening test for HIV-1 antigen(s) should be quarantined to prevent inappropriate release. Quarantined units should either be destroyed or not used for transfusion or for further manufacturing into injectable products, except as approved by the Director, CBER.

It is recommended that blood or blood components be withheld from autologous use if HIV-1 antigen screening tests are repeatedly reactive. However, such products may be distributed for autologous use only provided that: (1) a written, signed and dated request is received from the patient's physician; (2) written permission is obtained from the transfusion service to receive the products (if applicable); (3) the transfusion service takes responsibility for ensuring that there is documented verification of the accurate identity of the transfusion recipient; and (4) the products are labeled "BIOHAZARD" and "FOR AUTOLOGOUS USE ONLY."

b. Establishments which intend to ship for further manufacture into non-injectable products, units which are inadvertently collected from donors who test repeatedly reactive for HIV-1 antigen(s) should use FDA approved labels and maintain shipping documents for review at the time of FDA inspection.

c. There are few approved uses of HIV-1 antigen repeatedly reactive products other than for

research and the manufacture of reagents required for HIV testing. The intentional collection of repeatedly reactive units for use in such products, as well as manufacture, special labeling and distribution, requires advance approval of a specific license application or supplement by the Director, CBER.

d. Units which are not destroyed should be labeled with four cautionary statements as follows:

"NOT FOR TRANSFUSION" [21 CFR 606.121 (f)]

"BIOHAZARD"

"Reactive by a test for HIV-1 antigen(s). The risk of transmission of HIV is present."

and

"For further manufacture into in-vitro diagnostic reagents for which there are no alternative sources" or "For laboratory research use only."

3. Untested Blood and Blood Components

In the case of rare products which cannot be tested because they were placed in frozen storage before licensed HIV-1 antigen tests suitable for donor screening were available and for which there is no available substitute product (e.g. rare red blood cell phenotypes), a statement such as one of the following should be applied:

"CAUTION: This product was prepared before testing for HIV-1 antigen(s) was implemented and the subsequent HIV status of the donor is not known," or

"This product was prepared before testing for HIV-1 antigen(s) was implemented. The donor was tested on (Date), more than eight weeks after the date of collection, and was found to be NEGATIVE for HIV-1 antigen(s) and for antibodies to HIV-1 and HIV-2."

C. Donor Deferral

Donors of Whole Blood, blood components, Source Leukocytes and Source Plasma whose blood specimens are found to be **repeatedly reactive** using a licensed screening test for HIV-1 antigen(s) should be further tested by a neutralization procedure according to the manufacturer's instructions in the package insert in order to determine their deferral status. The results of a neutralization test may also be useful in donor notification and counseling. The same specimen as used for initial screening or another specimen from the same collection should be used for this additional, more specific, testing **as long as the specimen has been stored properly as outlined in the package labeling for the HIV-1 antigen(s) detection kit being used.**

1. Donors whose blood samples are POSITIVE for HIV-1 antigen(s) based on the neutralization test should be **permanently deferred**.

2. Donors whose blood samples are INDETERMINATE based on the neutralization test or untested by neutralization should be temporarily deferred from donation for a minimum of eight weeks. If a temporarily deferred donor re-donates or is otherwise retested after a period of at least eight weeks:

   a. The donor can automatically be reinstated and any current collection may be used if all donor screening tests (including HIV antigen) are performed and found NEGATIVE, and the donor meets all other suitability criteria.

   b. The donor is permanently deferred if the screening test for HIV antigen is repeatedly reactive on any subsequent evaluation or donation, regardless of the result of the neutralization test.

3. The names of donors with repeatedly reactive screening test results should be entered on the deferral registry in such a way that they can be identified as being permanently or temporarily deferred [21 CFR 606.160 (e)]. Confidentiality of

the results should be protected. It should be ensured that products from unsuitable donors are excluded from use without disclosing the reason to unauthorized personnel. The deferral system should also ensure that products obtained from subsequent donations of unsuitable donors will not be distributed [21 CFR 606.160 (e)].

D. Public Health Service (PHS) Recommendations for Donor Notification and Counseling

In a blood or plasma donor population, the vast majority of repeatedly reactive HIV-1 antigen screening results are expected to be falsely positive. All samples repeatedly reactive for HIV-1 antigen(s) by EIA should be promptly tested by the neutralization test to determine whether the donor is truly POSITIVE for HIV-1 antigen(s). Because of the potential deterioration of HIV antigen(s) on sample storage, care should be exercised to follow the sample storage and time restrictions specified in the test kit package insert. The neutralization test should be done before informing donors of their repeatedly reactive test results. Donor notification should contain information about the significance of the test results and suggest medical follow-up.

Individuals with POSITIVE results based on an HIV-1 antigen neutralization test are presumed to be infected with HIV. Donors with POSITIVE results on an HIV-1 antigen neutralization test should be notified and counseled regarding evidence of HIV infection. Such results should be confirmed by medical follow-up including testing for antibodies to HIV-1 and HIV-2 after a period of at least eight weeks.

The HIV status of individuals with INDETERMINATE results is not clear and the donors should be further evaluated. Because of the potential for the rapid degradation of HIV-1 antigen in improperly stored samples, clarification of the neutralization test may be obtained by testing a fresh specimen or by testing the donor for antibodies to HIV-1 and HIV-2 after a period of at least eight weeks. If INDETERMINATE results persist on retesting after at least eight weeks in the absence of seroconversion to HIV-1 or HIV-2, the individual may be considered negative for purposes of counseling. However, these individuals

should be advised that they are no longer acceptable as donors because of their test results.

E. Exclusion/Retrieval of Potentially Contaminated Units from Prior Collections and Notification of Consignees

See FDA's memorandum dated April 23, 1992 for FDA recommendations regarding units from prior collections from donors found repeatedly reactive for antibodies to HIV-1 or HIV-2. FDA further recommends the quarantine of previously collected units of Whole Blood, blood components, Source Leukocytes or Source Plasma from any person who tests repeatedly reactive by a screening test for HIV-1 antigen(s) in the absence of a repeatedly reactive screening test(s) for antibodies to HIV-1 and HIV-2.

1. Retrieval and Quarantine of Prior Collections

Blood centers should within 72 hours identify and quarantine all in-date units collected within the three months prior to the donor's repeatedly reactive screening test for HIV-1 antigen(s). The consignees of such units should be notified so that the units that they hold also can be quarantined. The quarantined units should not be transfused or used in further manufacturing pending the result of subsequent donor testing. For plasma for fractionation, the retrieval can be limited to units which have not already been pooled or further processed.

2. Release of Units from Quarantine

Previously collected units may be released from quarantine if the donor subsequently qualifies for reentry based on negative tests for both HIV-1 antigen(s) and antibodies to HIV-1 and HIV-2 at least eight weeks after the repeatedly reactive collection. If retesting of the donor is not performed within six months of the repeatedly reactive result, any quarantined units from prior collections should be destroyed or relabeled with four cautionary statements as follows:

"NOT FOR TRANSFUSION" [21 CFR 606.121 (f)]

"BIOHAZARD"

"This product was collected from a donor later known to be reactive for HIV-1 antigen(s). The risk of transmission of HIV is present."

and

"For further manufacture into in-vitro diagnostic reagents for which there are no alternative sources" or "For laboratory research use only."

F. Notification of Consignees of Neutralization Test Results

Notification of consignees of the results of neutralization tests for donors with repeatedly reactive screening tests for HIV-1 antigen(s) should be performed so that transfusion services can carry out recipient tracing and notification through the attending physicians. This testing and notification should be completed as soon as feasible (within two weeks if possible) following the repeatedly reactive screening test. (Unless the neutralization test is completed within the maximum storage time allowed for the test kit being used, a fresh specimen of blood should be used for neutralization testing.) It is not intended that consignees should initiate recipient tracing based only on a repeatedly reactive donor screening test result for HIV-1 antigen(s) prior to the availability of the result of the neutralization test.

For cases in which units were obtained from the donor during the three month period prior to the repeatedly reactive donation, blood centers should notify consignees of the results of a POSITIVE test on the donor's current sample, based on additional testing by neutralization.

If the test result is INDETERMINATE based on a neutralization test that is negative (non-neutralizing) or indeterminate (invalid), but the test sample has not been stored appropriately according to the instructions in the package insert, a fresh sample should be obtained as soon as possible and tested by both the screening EIA and neutralization test for HIV-1 antigen(s) prior to

consignee notification.

If the neutralization test is INDETERMINATE, based on a fresh or properly stored sample, the consignee should be notified. However, a judgement by the medical director should be made regarding the potential benefits of recipient tracing prior to resolution of the HIV status of the donor through follow-up testing for antibodies to HIV.

Whenever possible, a follow-up sample from the donor at least eight weeks later should be tested for antibodies to HIV-1 and HIV-2 to rule-in or exclude HIV infection.

The recommendations contained in this memorandum may be implemented without prior approval from FDA. Licensed establishments implementing these recommendations should submit by official correspondence a statement to their product license file indicating the date that revised standard operating procedures consistent with these recommendations have been established and implemented. If an establishment believes that an alternative approach would provide equivalent protection, the establishment is invited to discuss the approach with FDA for FDA's evaluation.

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2. Busch MP, PE Taylor, BA Lenes, et al. Screening of selected male blood donors for p24 antigen of human immunodeficiency type 1. Transfusion Safety Study Group. NEJM 323:1308-12; 1990.

3. Gilcher RO, J Smith, S Thompson, et al. Transfusion-associated HIV from anti-HIV non-reactive, HIV antigen reactive donor blood (Abstract #S-237). ISBT-AABB Joint Congress, Los Angeles, CA, Nov 1990.

4. Irani MS, AW Dudley Jr, LJ Lucco. Case of HIV-1 transmission by antigen-positive, antibody negative blood (letter). NEJM 325:1174-5; 1991.

5. Roberts CS, JN Longfield, RC Platte, et al. Transfusion-associated human immunodeficiency virus type 1 from screened antibody-negative blood donors. Arch Pathol Lab Med 118:1188-92; 1994.

6. Lackritz EM, GA Satten, CP Raimondi, et al. Estimated risk of HIV transmission by screened blood in the U.S. Abstracts, 2nd International Conference on Human Retroviruses and Related Infections, Washington, DC. January, 1995. [Updated at the 48th Meeting of the Blood Products Advisory Committee, Bethesda, MD, June 23, 1995.]

7. Ward JW, SD Holmberg, JR Allen, et al. Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV antibody. NEJM 318:473-8; 1988.

8. Cumming PD, EL Wallace, JB Schorr, RY Dodd. Exposure of patients to human immunodeficiency virus through the transfusion of blood components that test antibody-negative. NEJM 321:941-6; 1989.

9. Busch MP, LLL Lee, GA Satten, et al. Time Course of detection of viral and serologic markers preceding human immunodeficiency virus type 1 seroconversion: implications for screening of blood and tissues donors. Transfusion 35(2):91-7; 1995.

10. Busch MP and HJ Alter. Will human immunodeficiency virus p24 antigen screening increase the safety of the blood supply and, if so, at what cost? Transfusion 35(7):536-9; 1995.

Figure 1

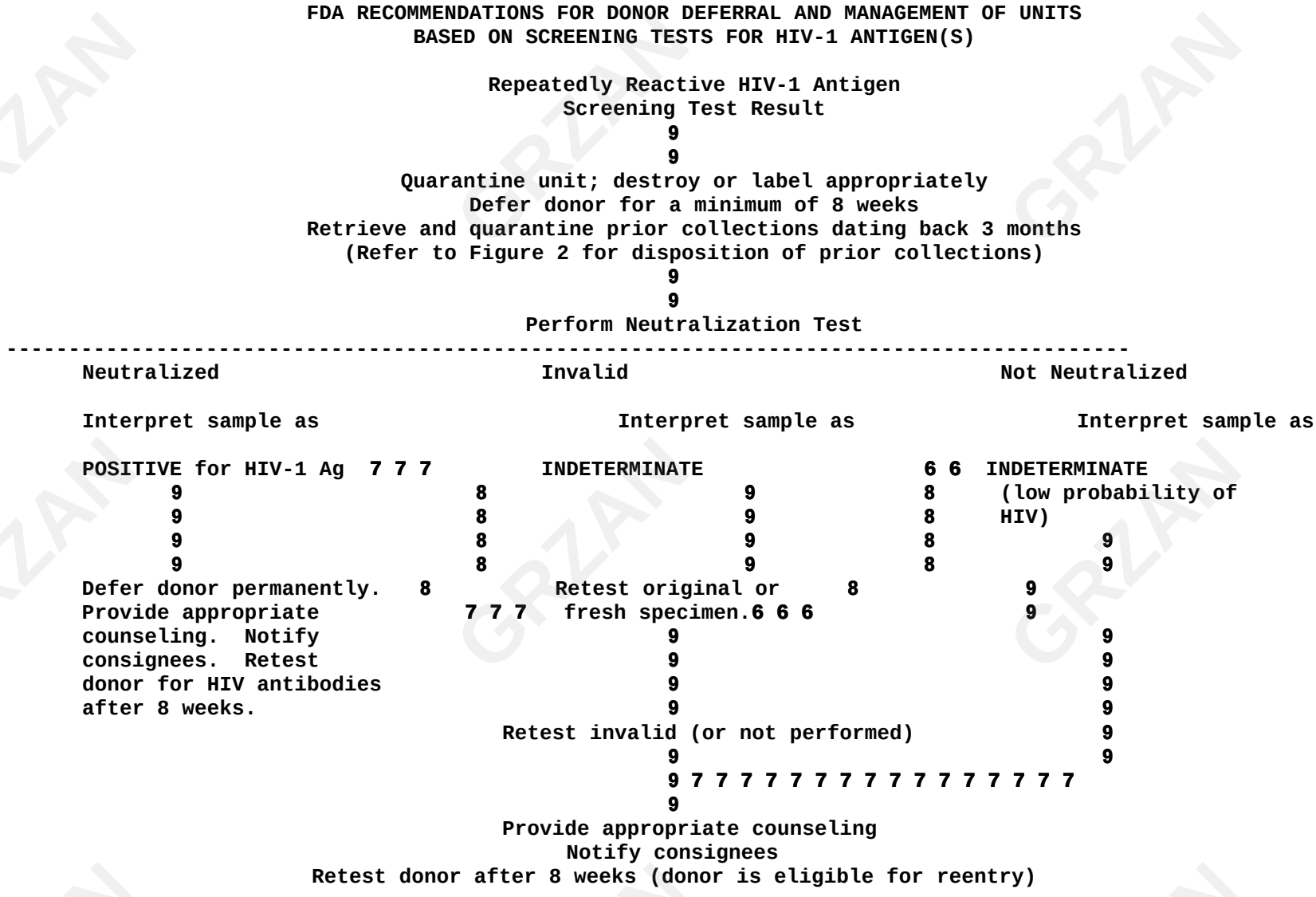

FDA RECOMMENDATIONS FOR DONOR DEFERRAL AND MANAGEMENT OF UNITS
BASED ON SCREENING TESTS FOR HIV-1 ANTIGEN(S)
Repeatedly Reactive HIV-1 Antigen
Screening Test Result
Quarantine unit; destroy or label appropriately
Defer donor for a minimum of 8 weeks
Retrieve and quarantine prior collections dating back 3 months
(Refer to Figure 2 for disposition of prior collections)
Perform Neutralization Test
Neutralized
Interpret sample as
POSITIVE for HIV-1 Ag
Defer donor permanently.
Provide appropriate
counseling. Notify
consignees. Retest
donor for HIV antibodies
after 8 weeks.
Invalid
Interpret sample as
INDETERMINATE
Retest original or
fresh specimen.
Retest invalid (or not performed)
Not Neutralized
Interpret sample as
INDETERMINATE
(low probability of
HIV)
Provide appropriate counseling
Notify consignees
Retest donor after 8 weeks (donor is eligible for reentry)

Figure 2

**FDA RECOMMENDATIONS FOR DONOR REENTRY AND FOR DISPOSITION OF QUARANTINED UNITS FROM PRIOR (NEGATIVE) COLLECTIONS FOLLOWING A REPEATEDLY REACTIVE SCREENING TEST FOR HIV-1 ANTIGEN(S)**

**Donor is eligible for reentry based on a NEGATIVE or INDETERMINATE test for HIV-1 antigen(s) including Neutralization Testing**

**Obtain follow-up specimen ≥8 weeks after repeatedly reactive test**

**Perform screening tests for HIV-1 Antigen(s) and for antibodies to HIV-1 and HIV-2[1]**

| Repeatedly Reactive on any screening test | Negative for all markers |
|---|---|
| 9 | 9 |
| 9 | 9 |
| 9 | 9 |
| 9 | 9 |
| Defer donor permanently. Destroy or suitably label current unit and units from prior (negative) collections. | Reenter donor. Current unit may be used if donor is otherwise suitable. Quarantined units from prior (negative) collections may be released. |

[1]If retesting of the donor is not performed within six months, any quarantined units from prior collections should be destroyed or suitably relabeled.