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

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Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at anytime. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number FDA-2005-D-0140.

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
May 2010
Updated December 2017

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

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Note: Changes have been made to update the "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," dated May 2010, including:

- Revised recommendations for reentry of donors deferred because of reactive HCV test results in Section V.B. The recommendations have been revised because of the discontinuation of the CHIRON® RIBA® HCV 3.0 SIA (RIBA), that was intended for use as an additional, more specific test on human serum or plasma specimens found to be repeatedly reactive using a licensed anti-HCV screening test.

- Updated the definition of "Discriminatory NAT" in Section II. and made corresponding editorial revisions to recommendations in Section IV.C. and Sections V.A and V.B. to reflect approval of multiplex NAT assays that directly detect HIV-1 RNA and HCV RNA and simultaneously detect and discriminate HIV RNA and HCV RNA.

- Updated regulation citations for consistency with the current Code of Federal Regulations.

- Updated the Background and Discussion in Section III. to include the current estimates of HIV-1 and HCV in blood donations and the donor screening tests licensed since publication of the May 2010 guidance.

U.S. Department of Health and Human Services
Food and Drug Administration
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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

Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, the Food and Drug Administration (FDA), are providing recommendations to you, blood and plasma establishments, manufacturers, and testing laboratories for testing individual samples or pooled samples from donors of human blood and blood components for Human Immunodeficiency Virus Type 1 (HIV-1) ribonucleic acid (RNA) and Hepatitis C Virus (HCV) RNA using the Nucleic Acid Test (NAT). This guidance also contains recommendations regarding product disposition and donor management based on the results of NAT testing for markers of HIV-1 and HCV infection on samples, collected at the time of donation, from donors of human blood and blood components.

This guidance amends the guidance entitled, "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" dated May 2010 (75 FR 22814). The May 2010 guidance finalized the draft guidance of the same title, dated July 2005 and also superseded the recommendations for reentry of donors deferred because of anti-HIV-1 test results, HIV-1 p24 antigen test results, and anti-HCV test results that were provided in the FDA memoranda entitled, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV-1) Transmission by Blood and Blood Products" April 23, 1992; "Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)" August 5, 1993; "Recommendations for Donor Screening with a Licensed Test for HIV-1 Antigen" August 8, 1995 (Refs. 1 through 3).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. DEFINITIONS

Anti-HIV-1 or -2 Test or Anti-HIV-1/2 Test or Anti-HCV Test: A screening test, such as an enzyme immunoassay, performed on donations of blood and blood components, that FDA has licensed, approved or cleared for such use (hereinafter referred to as "licensed").

Deconstruction: Resolution of the reactivity of a minipool by testing subpools (original or freshly made) or samples from individual donors that formed the minipool. Deconstruction of a reactive minipool to individual units is a required step for all approved tests.[1]

Discriminatory NAT: A NAT that uses specific primers for HIV-1 or HCV to identify the RNA in a reactive multiplex NAT sample that might contain either HIV-1 RNA or HCV RNA based on the assay. Performing a Discriminatory NAT assay on a reactive sample is a required step for those establishments using certain multiplex tests that do not simultaneously detect and discriminate HIV RNA and HCV RNA in the same reaction.[2]

Donor Reentry: A procedure that qualifies a deferred donor as eligible to donate again. Donor reentry procedures may be used following a false positive test result and typically require the passage of time to allow for possible seroconversion prior to the performance of additional serologic testing and NAT (see sections V.A. and V.B. of this document).

Lookback: A series of actions taken by a blood establishment based on donor test results indicating infection with HIV-1 or HCV. These actions relate to the donor's prior donations that possibly were donated during the window period when HIV-1 or HCV RNA and antibody were not detectable by screening tests but the infectious agent might be present in the donor's blood. These actions include: quarantining the remaining inventory of prior collections from that donor, notifying consignees to quarantine prior collections, further testing of the donor, destroying or re-labeling potentially infectious prior collections, and when appropriate, notifying transfusion recipients who received human blood or blood components from that donor.

Minipool: A pool of donor samples on which NAT (minipool NAT or MP-NAT) is performed as a screening test. A minipool is formed by pooling of samples from subpools or by directly pooling samples from individual donors.

Multiplex NAT: A NAT that simultaneously detects HIV-1 RNA and HCV RNA.

Single Virus NAT: A NAT that separately detects either HIV-1 RNA or HCV RNA.

Subpool: A pool of donor samples that was used with other (sub)pools to form the minipool or that was formed as a result of "deconstruction" of the minipool.

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[1] Under Title 21 of the Code of Federal Regulations (CFR) 610.40(b) (21 CFR 610.40(b)), you must use screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions.
[2] *Id.*

III. BACKGROUND AND DISCUSSION

FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products. Blood donors are now asked specific and very direct questions about risk factors that could indicate possible infection with a transmissible disease. This "up-front" screening eliminates approximately 90 percent of ineligible donors. In addition, FDA requires blood centers to maintain lists of deferred donors to prevent the use of collections from them.

During the past decade blood establishments have implemented new donor screening tests, including sensitive tests for viral antibody, antigen (for HIV-1), and nucleic acids, and there has been a dramatic reduction in the transmission of HIV-1 and HCV by human blood and blood components. Sources of remaining risk for HIV-1 and HCV transmission by human blood products include: 1) marker-negative "window period" donations (made during the period that the donor is infected with a virus, but neither the virus nor antibodies to the virus are detectable by current tests); 2) donors infected with genetic and immunovariant viral strains; 3) persistent antibody-negative (immunosilent) carriers; and 4) laboratory errors. According to a recent report, donations during the window period constitute most of the risk of HIV-1 and HCV transmission (Ref. 4). Therefore, measures to reduce the window period might further reduce the residual risk of HIV-1 and HCV transmission by human blood and blood components.

Studies performed using seroconversion panels indicate the value of NAT in reducing the window period for HIV-1 and HCV. The estimated mean window-period reduction for HIV-1 RNA by pooled sample NAT is approximately 11 to 15 days relative to antibody testing and 5 to 9 days relative to HIV-1 p24 antigen testing (Refs. 5 through 7). NAT for detection of HCV has been estimated to reduce the window period by 50 to 60 days relative to that for HCV antibody. During a ten-year period (1999-2008), approximately 66 million donations were screened with 32 HIV (1:2 million) and 244 HCV (1:270,000) NAT yield (RNA-positive but antibody-negative) donations identified (Ref. 6). Subsequent to implementation of NAT, the residual risk of HIV-1 and HCV in screened human blood and blood component donations in 2007-2008 was estimated to be approximately 1 in 1,467,000 donations for HIV-1 and 1 in 1,149,000 donations for HCV (Ref. 6).

In September 1994, we held a workshop to discuss the potential application of nucleic acid based methods to donor screening for HIV-1. We concluded at the time that these methods clearly were sensitive, but they were not ready for implementation on a large scale.

The industry actively pursued the development of NAT for screening donors of human blood and blood components. There was much interest in testing pools of plasma donor samples (minipools) by NAT because of the cost and labor intensiveness of testing individual donor samples. By 1997, some manufacturers in Europe had voluntarily instituted NAT on minipools. In 1998, the European Union issued a directive that by July 1, 1999, HCV RNA testing would be required in Europe for all plasma for fractionation and that the requirement for HIV-1 RNA testing would follow at a later date.

Large-scale clinical studies were needed to demonstrate the efficacy of NAT because of the expected low frequency of window period donations. Test kit manufacturers and testing laboratories submitted Investigational New Drug applications (INDs) describing their test method and in-house validation of that method. Blood organizations and establishments intending to use the assay for donor screening also filed INDs to describe their clinical trial protocol for validation of pooled-donor sample NAT (MP-NAT) and individual donor sample NAT (ID-NAT).

In December 1999, we issued a guidance for industry on the validation of NAT methods to screen plasma donors (Ref. 8). This document provided guidance on test standards, manufacturing requirements, and clinical trial requirements for licensure of the test method for use in donor screening for transfusion-transmitted viruses.

In September 2001, we licensed the first NAT system, the National Genetics Institute (NGI) UltraQual HIV-1 and HCV Reverse Transcription Polymerase Chain Reaction (RT-PCR) assays. Under that license, NGI performs RT-PCR assays on pooled samples from donors of Source Plasma.

In February 2002, we licensed the Procleix HIV-1/HCV Assay, a qualitative NAT for detection of HIV-1 RNA and/or HCV RNA in plasma from donors of human blood and blood components for transfusion. This assay was approved for use with individual donor samples or pooled donor samples.

In December 2002, we licensed the COBAS AmpliScreen HCV Test, v 2.0 and the COBAS AmpliScreen HIV-1 Test, v 1.5. These tests are qualitative in vitro tests for the direct detection of HCV RNA and HIV-1 RNA in plasma samples from human donors, including donors of Whole Blood, blood components, and Source Plasma, and from other living donors. These assays were approved for use with individual donor samples or pooled donor samples.

In October 2004, we issued a final guidance, "Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV" dated October 2004 (October 2004 guidance). That guidance combined and finalized the draft guidance "Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV" dated December 2001, and the draft guidance "Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components for Transfusion to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV" dated March 2002.

The October 2004 guidance informed establishments collecting blood and blood components that we have licensed NAT to screen blood donors for HIV-1 RNA and HCV RNA and that these licensed tests could detect evidence of infection at a significantly earlier stage than is possible under previously approved tests using antibody or antigen detection technology, including the HIV-1 p24 antigen test. We also informed those establishments that we believe these newly

licensed tests are now widely available and meet the criteria in 21 CFR 610.40(b) for screening tests that are necessary to reduce adequately and appropriately the risk of transmission of communicable disease through blood and blood products.

In the October 2004 guidance, we recommended the use of HIV-1 NAT and HCV NAT on units that are not reactive on a donor-screening test for the detection of antibodies to HIV-1 or HCV, respectively. However, for donations that are reactive on a test for the detection of antibodies to HIV-1 or HCV and are to be discarded or used in the manufacture of non-injectable products, we do not consider HIV-1 NAT and HCV NAT to be necessary as part of the adequate and appropriate testing required under 21 CFR 610.40(b). We informed the establishments that even though testing for these products is not required under 21 CFR 610.40(b), they may decide to perform HIV-1 NAT and HCV NAT for these donations in order to obtain useful information regarding the donor's infection status. This information might be useful as part of donor notification.

In October 2006, we licensed the Procleix Ultrio Assay, a qualitative in vitro assay system to screen for HIV-1 RNA and HCV RNA in plasma and serum specimens from human donors, including donors of Whole Blood, blood components, and Source Plasma, and from other living donors. This assay was also approved for use with individual donor samples or pooled donor samples.

In February 2007, we licensed the BioLife Plasma Services HIQ-PCR HIV-1 RT-PCR assay and the HIQ-PCR HCV RT-PCR assay for the qualitative detection of HIV-1 RNA and HCV RNA, respectively, in pools of human Source Plasma.

In December 2008, we licensed the cobas TaqScreen MPX Test, a qualitative in vitro screening test for individual human donors, including donors of Whole Blood and blood components, and other living donors, for the presence of HIV-1 Group M RNA, HCV RNA, and Hepatitis B Virus (HBV) DNA. Plasma from all donors may be screened as individual specimens. For donations of Whole Blood and blood components, plasma specimens may be tested individually or in pools.

In May 2012, we licensed the Gen-Probe Procleix Ultrio Plus Assay, a qualitative in vitro test for use on the Procleix TIGRIS System to screen for HIV-1 RNA, HCV RNA and HBV DNA in plasma and serum specimens from individual human donors, including donors of whole blood, blood components, and source plasma, and from other living donors. This assay was also approved for use with individual donor samples or pooled donor samples.

In December 2014, we licensed the cobas TaqScreen MPX Test, version 2.0, for use the cobas s 201 system, a qualitative in vitro screening test for the direct detection of HIV-1 Group M RNA, HIV-1 Group O RNA, HIV-2 RNA, HCV RNA and HBV DNA in plasma specimens from individual human donors, including donors of Whole Blood, blood components, Source Plasma and other living donors. Plasma specimens may be tested individually or in pools. For an individual specimen, results are simultaneously detected and discriminated for HIV, HCV, and HBV.

In October 2016, we licensed the cobas MPX Test, for use on the cobas 6800/8800 Systems, a qualitative in vitro test screening test for the direct detection of HIV-1 Group M RNA, HIV-1 Group O RNA, HIV-2 RNA, HCV RNA, and HBV DNA in human plasma and serum. The cobas MPX Test simultaneously detects and discriminates for HIV, HCV and HBV and does not discriminate between HIV-1 Group M, HIV-1 Group O, and HIV-2.

This guidance is intended to assist you with testing, product disposition, donor deferral, donor notification, donor reentry, and lookback. We have written this document in general form because other NAT may be approved in the future. However, where appropriate, we will identify sections that apply to NAT that are already approved. You must follow manufacturers' instructions regarding testing under 21 CFR 610.40(b).

A. NAT Algorithms

Under 21 CFR 610.40(b), you must use screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions. If you perform NAT on pooled samples and obtain a reactive NAT result on a minipool, the manufacturer's instructions instruct you to perform subsequent testing to identify the individual unit(s) that contains the RNA identified in the minipool test. Once you have identified a positive unit, either by subsequent testing of a minipool or by initial individual donor sample testing, you must not use the donation for transfusion or for manufacturing into injectable products (21 CFR 610.40(h)(1)) unless an exception applies (21 CFR 610.40(h)(2)). You must defer the donor (21 CFR 610.41(a)), and you must inform the donor of the deferral and the reason for the deferral, including test results if they were the basis for the deferral (21 CFR 630.40). You must also perform "lookback" to identify blood products previously donated (21 CFR 610.46 and 610.47). A reactive NAT result may indicate ongoing infection of the donor. Thus, prior donations from that donor, although NAT-non-reactive, may pose a risk to transfusion recipients.

In the FEDERAL REGISTER of August 24, 2007 (72 FR 48765), FDA published the final rule entitled "Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting Hepatitis C Virus Infection ("Lookback")" (Lookback rule) (Ref. 9). The Lookback rule established lookback requirements related to HCV infection and revised the requirements related to HIV infection. It requires that you perform lookback for HIV-1 and for HCV when donor samples test reactive using HIV-1 NAT or HCV NAT. Donors infected with HIV-1 or HCV may experience intermittent viremias for a variable period of time prior to a persistently detectable viremia or an antibody response. Since these episodes of transient viremia may extend over a longer window period than previously estimated, the Lookback rule requires you to review all records for a period of 12 months before the donor's reactive NAT. A 12-month timeframe is necessary to encompass with sufficient confidence the window period for HIV-1 or for HCV prior to the detection of antibody.

We have not established an alternative (possibly shorter than 12 months) lookback period based on the last non-reactive NAT, in order to minimize operational complexity and because the appropriate period has not been well established scientifically.

At the meeting of the Blood Products Advisory Committee (BPAC) in March 2001[3], FDA requested advice on appropriate algorithms for management of donations of human blood and blood components tested by pooled donor sample NAT for both HIV-1 RNA and HCV RNA. In particular, FDA sought comment on actions to be taken in the event of discrepant testing results, such as when the minipool is reactive but individual donor samples test non-reactive. Data generated using NAT under IND that was presented in the BPAC meeting showed that in each discrepant case it was the minipool that was falsely reactive, due to contamination either during specimen handling or during the assay run. In response to FDA questions the BPAC voted to consider the NAT result on samples from individual donors as the definitive test result, and recommended release from quarantine for donations from those donors, on the basis of non-reactive individual test results.

This guidance contains four recommended algorithms for use when NAT-reactive results are obtained on individual samples or pooled samples from donors of human blood and blood components. Note that these algorithms apply when only the HIV-1 NAT or HCV NAT result is reactive (i.e., serologic tests for HIV-1/2 and HCV are negative). This guidance also contains recommendations on product disposition, donor deferral criteria, follow-up testing of the donor, donor notification, and lookback (product retrieval and recipient notification). This guidance is not intended to replace manufacturers' instructions for testing using approved tests.

The first and second algorithms (see sections IV.A. and IV.B, Figures 1 and 2, and Tables 1 and 2 of this document) recommend actions to deconstruct a reactive minipool by testing archived or freshly pooled subpools or by testing individual donor samples. The third and fourth algorithms (see sections IV.C. and IV.D, Figures 3 and 4, and Tables 3 and 4 of this document) recommend actions to be taken when a NAT-reactive result is obtained on an individual sample from a donor of human blood or blood components.

B. Donor Reentry

Each year many donors are deferred from donating blood for an indefinite period because of a false positive test result on a serologic test, followed by a negative or indeterminate supplemental test for antibodies to HIV-1 or HCV. In addition to these deferrals the implementation of NAT for HIV-1 RNA and HCV RNA has resulted in additional deferrals of donors each year due to potentially false reactive NAT results.

These deferred donors may be eligible to be considered for reentry to donate blood or blood components. Under 21 CFR 610.41(b), a deferred donor subsequently may be found to be eligible as a donor by a re-qualification method or process found acceptable

[3] https://wayback.archive-it.org/7993/20170403222320/https://www.fda.gov/ohrms/dockets/ac/cber01.htm#Blood%20Products

for such purposes by FDA. However, some establishments are not attempting to reenter donors because of the complexity of the current reentry algorithms and concerns about inappropriately reentering a donor. Although we do not require reentry of donors deferred because of false positive test results, we issued guidance in April 1992 on reentry of donors deferred because of a repeatedly reactive (RR) test for antibodies to HIV-1 or HIV-2, and in August 1993 on reentry of donors deferred because of a RR test for antibodies to HCV (Refs. 1 and 3).

This guidance contains recommendations for reentry of donors deferred because of reactive HIV-1 NAT or HCV NAT or certain other test results in accordance with 21 CFR 610.41(a). We find these reentry methods to be acceptable within the meaning of 21 CFR 610.41(b). Note that the reentry of a donor permits prospective donations from a reentered donor who meets donor eligibility criteria. It does not affect the status of previous collections from that donor, including donations subject to lookback.

Reentry of Donors (HIV Test Results)

In this guidance, we recommend that you consider for reentry three groups of donors deferred because of reactive HIV-1 NAT or RR anti-HIV-1 or -2 test or RR anti-HIV-1/2 test or RR HIV-1 p24 antigen test results (see section V.A., Figure 5, and Table 5 of this document). These three groups of donors include:

1. Donors with a reactive HIV-1 NAT result but who were seronegative for antibodies to HIV-1 and HIV-2;

2. Donors with non-reactive HIV-1 NAT (or NAT was not performed) who had a RR anti-HIV-1/2 test and an HIV-1 Western Blot (WB) or immunofluorescence assay (IFA) that was indeterminate (viral bands may be present), unreadable, negative, or was not performed; and

3. Donors with a positive or indeterminate result on the HIV-1 p24 Neutralization test (Ref. 2), even on more than one occasion. This last group of donors may be eligible for reentry because there are many donors who had (false) positive Neutralization test results who are currently non-reactive by HIV-1 NAT and negative by an anti-HIV-1 or anti-HIV-1/2 test.

FDA no longer recommends that blood and plasma establishments using certain approved NAT methods perform screening for HIV-1 p24 antigen. If antigen testing continues to be performed concurrent with NAT and antibody testing, donors deferred because of HIV-1 p24 test results would continue to be eligible for reentry.

Data presented at the June 2001 BPAC meeting demonstrated that an 8-week waiting period encompasses the pre-seroconversion window period for HIV-1 with sufficient confidence that negative tests, after at least 8 weeks have passed, rule out HIV-1 infection

(Ref. 10). Absent evidence for seroconversion, a negative NAT on follow-up testing provides evidence that the prior reactive (but unconfirmed) NAT result was likely an error.

Accordingly, for all three groups of donors, after a minimum time period of 8 weeks we recommend that you take a follow-up sample from the donor for testing by both HIV-1 ID-NAT and an anti-HIV-1/2 test. Performing follow-up testing first on a new sample from the donor, collected before another donation, may prevent a potentially contaminated unit from being collected and placed in inventory at the blood establishment. If the ID-NAT is non-reactive and the anti-HIV-1/2 test is negative on the follow-up sample, the donor may be reentered. The donor would then be tested again at the time of his/her next donation using the battery of screening tests required under 21 CFR 610.40. That donation may be tested by NAT as part of a minipool (i.e., MP-NAT) or as an individual donation (i.e., ID-NAT). Thus, two HIV-1 NAT tests would be performed and must be non-reactive and two anti-HIV-1/2 tests would be performed and must be negative before a unit from that donor could be used. For purposes of donor counseling, you may choose to test the deferred donor with an HIV-1 NAT and an anti-HIV-1/2 test at any time prior to the end of this 8-week waiting period after the original donation. However, if an HIV-1 NAT is reactive prior to the end of this 8-week waiting period, the donor would not be eligible for reentry and we recommend that you defer the donor permanently. If an anti-HIV-1/2 test is RR prior to the end of this 8-week waiting period, and a licensed supplemental test for antibodies to HIV-1 (i.e., WB or IFA), if performed, is not positive, you may take another follow-up sample from the donor for testing by both HIV-1 ID-NAT and an anti-HIV-1/2 test after another 8-week waiting period has passed.

Reentry of Donors (HCV Test Results)

In this guidance, we recommend that you consider for reentry two groups of donors deferred because of reactive HCV NAT or RR anti-HCV test results (see section V.B., Figure 6, and Table 6 of this document). These two groups of donors include:

1. Donors with a reactive HCV NAT result but who were seronegative for antibodies to HCV; and

2. Donors with a non-reactive HCV NAT result (or NAT was not performed) who had RR anti-HCV test results[4]. This group includes donors who were RR on a second, different licensed screening test for HCV antibody, if it was used in further testing of the index donation.

Data presented at the June 2001 BPAC meeting demonstrated that a 6-month follow-up period encompasses the pre-seroconversion window period with sufficient confidence that negative tests after at least 6 months have passed rule out HCV infection (Ref. 10).

[4] This group includes deferred donors with an historical HCV RIBA that was indeterminate, negative or was not performed.

For purposes of reentering both of these groups of deferred donors we recommend that you take a follow-up sample from the donor after a minimum period of 6 months from the original donation for testing by an HCV ID-NAT and two different, licensed anti-HCV screening tests. Current scientific data indicate that detectable viremia may be intermittent or may be resolved in about 15-25% of cases of HCV infection (Refs. 11 and 12). If the ID-NAT is non-reactive and both anti-HCV tests are negative on the follow-up sample, the donor may be reentered. The donor would then be tested again at the time of his/her next donation using the battery of screening tests required under 21 CFR 610.40(b). That donation may be tested by NAT as part of a minipool (i.e., MP-NAT) or as an individual donation (i.e., ID-NAT). Thus, two HCV NAT tests would be performed and must be non-reactive and three anti-HCV tests would be performed and must be negative before a unit from that donor could be used.

If the ID-NAT is non-reactive and both of the licensed anti-HCV tests are RR after a 6-month waiting period, we recommend that you defer the donor permanently.

For purposes of donor counseling and to detect possible HCV viremia, you may also choose to test the deferred donor with an HCV NAT and two different, licensed anti-HCV screening tests at any time prior to the completion of this 6-month period after the original donation. If an HCV NAT is reactive prior to the end of this 6-month period, the donor would not be eligible for reentry and we recommend that you defer the donor permanently. If an HCV NAT is non-reactive and one anti-HCV test is RR prior to the end of the 6-month period, you may take one more follow-up sample from the donor for testing by HCV ID-NAT and two different, licensed anti-HCV screening tests after a second 6-month waiting period. If an anti-HCV test is still RR on a second follow-up sample at any time after the original donation, we recommend that you defer the donor permanently.

IV. RECOMMENDATIONS FOR NAT ALGORITHMS

As discussed in sections A and B below, currently approved tests on minipools of donor samples for HIV-1 RNA and HCV RNA may be either Multiplex NAT for the simultaneous detection of HIV-1 RNA and HCV RNA or Single Virus NATs conducted separately for the RNA of the two viruses.

A. Testing, Product Disposition, Donor Management, and Lookback for a Minipool that is Reactive on a Multiplex NAT (MP-NAT): Resolution by Testing Subpools or by Testing Individual Donor Samples

If you obtain a reactive Multiplex HIV-1 RNA/HCV RNA NAT result for a minipool, the test instructions for use instruct you to perform subsequent testing to identify the donor sample(s) that are NAT-reactive as the basis for the NAT-reactive result on the pool. In

general, the manufacturer's instructions for a licensed NAT describe two methods for resolving a minipool that is reactive on a Multiplex NAT, and you must follow the instructions in the package insert that provide specific testing algorithms (21 CFR 610.40(b)).

METHOD 1: Deconstruction of the NAT-reactive minipool may be performed by testing the subpools (original or freshly made) that formed the minipool. This deconstruction of the minipool to identify the donor sample(s) that are NAT-reactive as the basis for the NAT-reactive result on the pool may involve several layers of testing using original or freshly pooled subpools, followed by testing of individual donor samples in the reactive subpool(s) (see Figure 1 and Table 1 below).

1. If you test subpools that were used to construct a Multiplex NAT-reactive minipool, in accordance with the manufacturer's instructions you must test the original subpools or freshly pooled subpools using the same Multiplex NAT method that was used in the original NAT on the minipool (21 CFR 610.40(b)).

NOTE: In some cases the manufacturer's instructions provide for a different sample preparation procedure. However, the primers and probes would be the same as those used in the original NAT on the minipool.

a. If all subpools are non-reactive, we recommend that you release from quarantine all individual donations that comprise the non-reactive subpools, provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release.

NOTE: Laboratory control procedures must make adequate provisions for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments (21 CFR 606.140(b)). This includes monitoring the frequency of reactive minipools that, upon deconstruction, remain unresolved. Laboratory control procedures must also include adequate identification and handling of all test samples (21 CFR 606.140(c)). Use of supplies and reagents must be in a manner consistent with the instructions provided by the manufacturer (21 CFR 606.65(e), 21 CFR 610.40(b)). You must conduct and record a thorough investigation including the conclusions and followup, of any unexplained discrepancy (21 CFR 606.100(c)), such as when the frequency of unresolved reactive minipools exceeds the threshold defined in your laboratory control procedures, or when there are indications of possible laboratory contamination of negative donor samples with positive samples. This investigation must include a determination of the cause of the initial reactivity of the unresolved minipool.

b. If one or more of the subpools are reactive, we recommend that you release from quarantine the individual donations that comprise the non-reactive subpools, provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release. Consistent with

the manufacturer's instructions, you must test the individual donor samples that comprise the reactive subpool(s) using the same Multiplex NAT method that was used in the original NAT on the minipool (21 CFR 610.40(b)).

(1) If all individual donor samples are non-reactive, we recommend that you release from quarantine all individual donations (if serologic tests on those donor samples are negative and the donations are otherwise suitable for release). See the NOTE in section IV.A.1.a. of this document on laboratory control procedures and the possible need to conduct additional analyses to determine the cause of the initial reactivity of the unresolved minipool.

(2) If one or more individual donor sample(s) are reactive, perform the steps in section IV.C.1. of this document (including testing using Discriminatory NAT when necessary, product disposition, donor management, and lookback).

We recommend that you release from quarantine all non-reactive individual donations provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release.

METHOD 2: For comparatively small minipools, for example, minipools that consist of up to 24 individual samples, deconstruction of the NAT-reactive minipool may be performed by directly testing the individual donor samples that formed the minipool (see Figure 1 and Table 1 below).

2. If you directly test the samples from individual donors that constituted the Multiplex NAT-reactive minipool, in accordance with the manufacturer's instructions you must test the individual donor samples using the same Multiplex NAT method that was used in the original NAT on the minipool (21 CFR 610.40(b)).

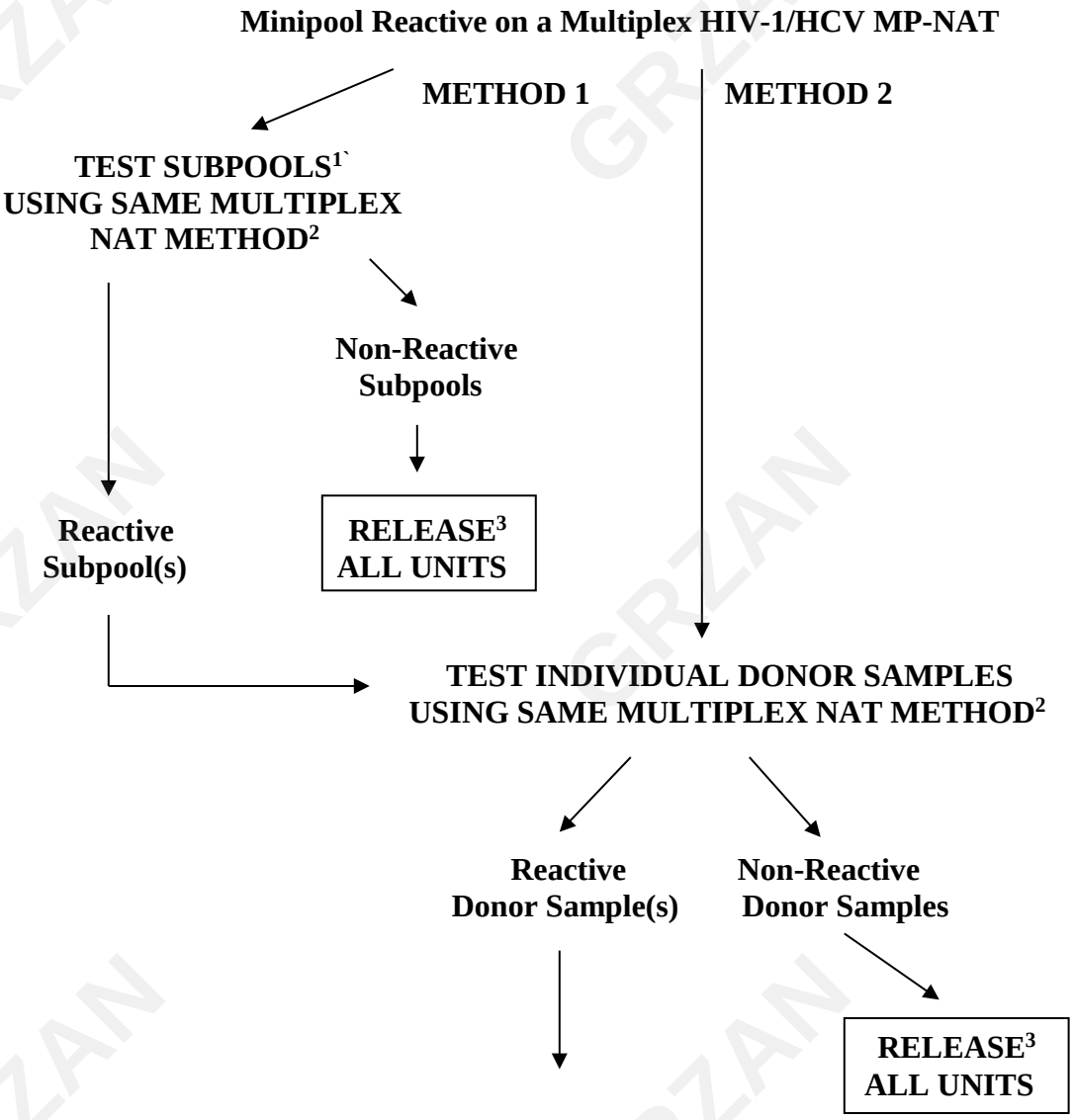
NOTE: In some cases the manufacturer's instructions provide for a different sample preparation procedure. However, the primers and probes would be the same as those used in the original NAT on the minipool.

a. If all individual donor samples are non-reactive, we recommend that you perform the steps in section IV.A.1.b.(1) of this document.

b. If one or more individual donor sample(s) are reactive, perform the steps in section IV.C.1. of this document (including testing using Discriminatory NAT when necessary, product disposition, donor management, and lookback).

We recommend that you release from quarantine all non-reactive individual donations provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release.

FIGURE 1. Testing, Product Disposition, Donor Management, and Lookback for a Minipool that is Reactive on a Multiplex NAT (MP-NAT): Resolution by Testing Subpools or by Testing Individual Donor Samples



PERFORM THE STEPS IN FIGURE 3 FOR TESTING USING DISCRIMINATORY NAT, PRODUCT DISPOSITION, DONOR MANAGEMENT, AND LOOKBACK

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[1] Several layers of deconstruction using original or freshly pooled subpools, may be needed.
[2] In some cases a different sample preparation procedure may be used per manufacturer's instructions. However, primers and probes should be same as those used in the NAT on the minipool.
[3] Units may be released only if serologic tests for HIV-1 and HCV are negative and the units are otherwise suitable for release.

TABLE 1. Testing, Product Disposition, Donor Management, and Lookback for a Minipool that is Reactive on a Multiplex NAT (MP-NAT): Resolution by Testing Subpools or by Testing Individual Donor Samples

<table>
<tr><th>If:</th><th>Then:</th><th>After that if:</th><th>Then:</th><th>After that if:</th><th>Then:</th></tr>
<tr><td rowspan="4">Minipool Reactive on a Multiplex HIV-1/HCV MP-NAT</td><td rowspan="2">METHOD 1: Test subpools[1] using same Multiplex NAT method[2]</td><td>Reactive subpool(s)</td><td>Test the individual donor samples using same Multiplex NAT method[2]</td><td>Reactive donor sample(s)</td><td>Perform the steps in Table 3 for testing (discriminatory NAT), product disposition, donor manage-ment, lookback</td></tr>
<tr><td>Non-reactive subpool(s)</td><td>Release[3] all units</td><td>Non-reactive donor samples</td><td>Release[3] all units</td></tr>
<tr><td rowspan="2">OR

METHOD 2: Test the individual donor samples using same Multiplex NAT method[2]</td><td>Reactive donor sample(s)</td><td>Perform the steps in Table 3 for testing (discriminatory NAT), product disposition, donor management, lookback</td><td rowspan="2"></td><td rowspan="2"></td></tr>
<tr><td>Non-reactive donor samples</td><td>Release[3] all units</td></tr>
</table>

[1] Several layers of deconstruction using original or freshly pooled subpools may be needed.
[2] In some cases a different sample preparation procedure may be used per manufacturer's instructions. However, primers and probes should be same as those used in the NAT on the minipool.
[3] Units may be released only if serologic tests for HIV-1 and HCV are negative and the units are otherwise suitable for release.

B. Testing, Product Disposition, Donor Management, and Lookback for a Minipool that is Reactive on a Single Virus NAT (MP-NAT): Resolution by Testing Subpools or by Testing Individual Donor Samples

If you obtain a reactive result for a NAT for HIV-1 RNA and/or HCV RNA performed separately on a minipool, the test instructions for use instruct you to perform subsequent testing to identify the donor sample(s) that are NAT-reactive as the basis for the NAT-reactive result on the pool. In general, the manufacturer's instructions for a licensed NAT describe two methods for resolving a minipool that is reactive on a Single Virus NAT, and you must follow the instructions in the package insert that provide specific testing algorithms (21 CFR 610.40(b)).

METHOD 1: Deconstruction of the NAT-reactive minipool may be performed by testing the subpools (original or freshly made) that formed the minipool. This deconstruction of the minipool to identify the donor sample(s) that are NAT-reactive as the basis for the NAT-reactive result on the pool, may involve several layers of testing using original or freshly pooled subpools, followed by testing of individual donor samples in the reactive subpool(s) (see Figure 2 and Table 2).

1. If you test subpools that were used to construct a NAT-reactive minipool, in accordance with the manufacturer's instructions you must test the original subpools or freshly pooled subpools using the same Single Virus NAT method that was used in the original NAT on the minipool (21 CFR 610.40(b)).

   NOTE: In some cases the manufacturer's instructions provide for a different sample preparation procedure. However, the primers and probes would be the same as those used in the original NAT on the minipool.

   a. If all subpools are non-reactive, we recommend that you release from quarantine all individual donations that comprise the non-reactive subpools provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release. See the NOTE in section IV.A.1.a. on laboratory control procedures and the possible need to conduct additional analyses to determine the cause of the initial reactivity of the unresolved minipool.

   b. If one or more of the subpools are reactive, we recommend that you release from quarantine the individual donations that comprise the non-reactive subpools provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release. Consistent with the manufacturer's instructions, you must test the individual donations that comprise the reactive subpool(s) using the same Single Virus NAT method that was used in the original NAT on the minipool (21 CFR 610.40(b)).

(1) If all individual donor samples are non-reactive, we recommend that you release from quarantine all individual donations provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release. See the NOTE in section IV.A.1.a. of this document on laboratory control procedures and the possible need to conduct additional analyses to determine the cause of the initial reactivity of the unresolved minipool.

(2) If one or more individual donor sample(s) are reactive, perform steps 1 through 4 in section IV.D. of this document (including product disposition, donor management, and lookback).

We recommend that you release from quarantine all non-reactive individual donations provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release.

METHOD 2: For comparatively small minipools, for example, minipools that consist of up to 24 individual samples, deconstruction of the NAT-reactive minipool may be performed by directly testing the individual donor samples that formed the minipool (see Figure 2 and Table 2 below).

2. If you directly test the samples from individual donors that constituted the NAT-reactive minipool, in accordance with the manufacturer's instructions you must test the individual donor samples using the same Single Virus NAT method that was used in the original NAT on the minipool (21 CFR 610.40(b)).

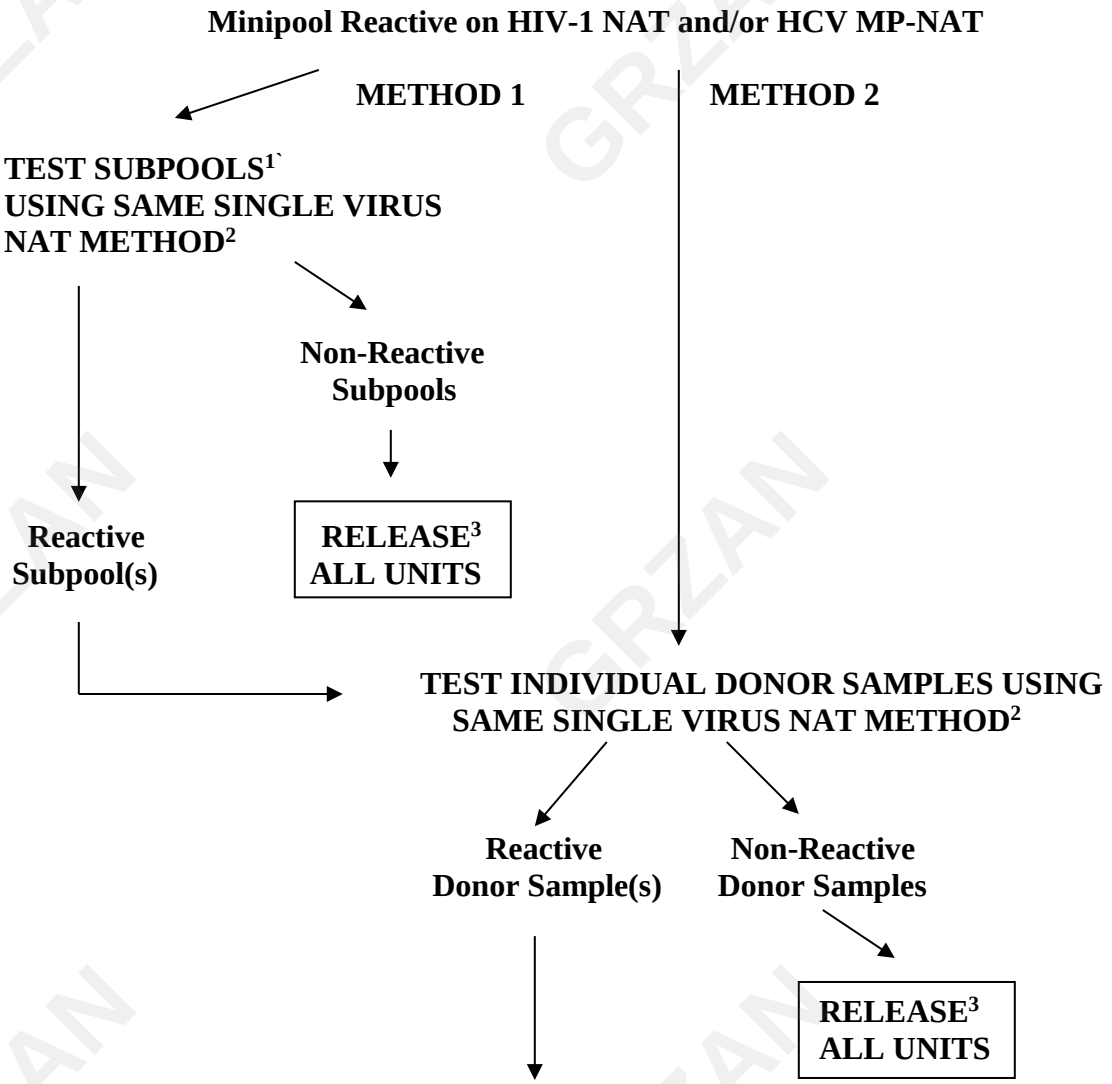
NOTE: In some cases the manufacturer's instructions provide for a different sample preparation procedure. However, the primers and probes would be the same as those used in the original NAT on the minipool.

a. If all individual donor samples are non-reactive, we recommend that you perform the steps in section IV.B.1.b.(1) of this document.

b. If one or more individual donor sample(s) are reactive, perform steps 1 through 4 in section IV.D. of this document (including product disposition, donor management, and lookback).

We recommend that you release from quarantine all non-reactive individual donations provided that serologic tests on those donor samples are negative and the donations are otherwise suitable for release.

FIGURE 2. Testing, Product Disposition, Donor Management, and Lookback for a Minipool that is Reactive on a Single Virus NAT (MP-NAT): Resolution by Testing Subpools or by Testing Individual Donor Samples



[1] Several layers of deconstruction using original or freshly pooled subpools, may be needed.
[2] In some cases a different sample preparation procedure may be used per manufacturer's instructions. However, primers and probes should be same as those used in the NAT on the minipool.
[3] Units may be released only if serologic tests for HIV-1 and HCV are negative and the units are otherwise suitable for release.

TABLE 2. Testing, Product Disposition, Donor Management, and Lookback for a Minipool that is Reactive on a Single Virus NAT (MP-NAT): Resolution by Testing Subpools or by Testing Individual Donor Samples

If:	*Then:*	*After that if:*	*Then:*	*After that if*:	*Then:*
Minipool Reactive on HIV-1 MP-NAT and/or HCV MP-NAT	**METHOD 1: Test subpools[1] using same Single Virus NAT method[2]**	**Reactive subpool(s)**	**Test the individual donor samples using same Single Virus NAT method[2]**	**Reactive donor sample(s)**	**Perform the steps in Table 4 for product disposition, donor management, and lookback**
				Non-reactive donor samples	**Release[3] all units**
		Non-reactive subpool(s)	**Release[3] all units**		
	OR **METHOD 2: Test the individual donor samples using same Single Virus NAT method[2]**	**Reactive donor sample(s)**	**Perform the steps in Table 4 for product disposition, donor management, and lookback**		
		Non-reactive donor samples	**Release[3] all units**		

[1] Several layers of deconstruction using original or freshly pooled subpools may be needed.
[2] In some cases a different sample preparation procedure may be used per manufacturer's instructions. However, primers and probes should be same as those used in the NAT on the minipool.
[3] Units may be released only if serologic tests for HIV-1 and HCV are negative and the units are otherwise suitable for release.

As discussed in Sections C and D below, currently approved tests on individual donor samples for HIV-1 RNA and HCV RNA may be either Multiplex NAT for the simultaneous detection of HIV-1 RNA and HCV RNA, or Single Virus NATs conducted separately for the RNA of the two viruses.

C. 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

If you obtain a reactive Multiplex HIV-1 RNA/HCV RNA NAT result on an individual donor sample (ID-NAT), you must do the following (see Figure 3 and Table 3):

1. Follow the manufacturer's instructions, which instruct you to test the reactive donation using Discriminatory NATs, when necessary (21 CFR 610.40(b)).

   a. If the sample is reactive for HIV-1 RNA and/or HCV RNA, you must quarantine the unit (21 CFR 610.40(h)). You must not ship or use the unit unless one of the exceptions described in 21 CFR 610.40(h)(2) applies.

   If you choose not to destroy the unit, you may release it for research or further manufacture with written approval from FDA (21 CFR 610.40(h)(2)(ii)(A). If released for one of these uses, you must appropriately label such blood or blood components as required under 21 CFR 606.121 and with the "BIOHAZARD" legend (21 CFR 610.40(h)(2)(ii)(B)). Under 21 CFR 610.40(h)(2)(ii)(C), except for autologous donations, you must label such human blood and blood components as reactive for the appropriate screening test for evidence of infection due to the identified communicable disease agent(s). We recommend that you use one of the following statements, as applicable:

   - "Reactive for HIV-1 RNA" or
   - "Reactive for HCV RNA" or
   - "Reactive for HIV-1 RNA and HCV RNA".

   Under 21 CFR 610.40(h)(2)(ii)(E), you must also include the following statement, as applicable:

   - "Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources" or
   - "Caution: For Laboratory Research Use Only".

   You must defer the donor (21 CFR 610.41). The donor may be eligible for reentry (see sections V.A. and V.B.). You must notify the donor of his/her deferral, providing information about the test results that were the basis for the deferral (21 CFR 630.40).

Under 21 CFR 610.46 and 21 CFR 610.47 you must perform lookback (product quarantine/retrieval and notification of recipients of prior collections) for HIV-1 and/or HCV, respectively, as follows:

- If you are an establishment that collects Whole Blood or blood components, including Source Plasma and Source Leukocytes, within 3 calendar days after a donor tests reactive for evidence of HIV-1 and/or HCV infection using the Discriminatory NATs, you must review records dating back 12 months prior to the donor's reactive NAT to identify blood and blood components previously donated by the donor. You must quarantine identified in-date blood and blood components if intended for transfusion or if intended for further manufacture into injectable products (except if pooled), notify consignees so that they may quarantine previously collected in-date blood and blood components, and notify transfusion recipients.

- If you are a consignee of Whole Blood or blood components, including Source Plasma and Source Leukocytes, when notified by the collecting establishment you must quarantine identified previously collected in-date blood and blood components if intended for transfusion or if intended for further manufacture into injectable products (except if pooled). You must notify transfusion recipients who were transfused with blood and blood components collected during the 12 months before the date of the Discriminatory NAT-reactive donation, or notify the recipient's physician of record, of the need for recipient HIV-1 or HCV testing and counseling. You must make reasonable attempts to perform the notification within 12 weeks after receiving the donor's Discriminatory NAT-reactive result for HIV-1 or HCV. If both Discriminatory NATs were reactive, notification of transfusion recipients should specify that the patient should be tested for both HIV-1 and HCV.

b. If the Discriminatory NATs are non-reactive for both HIV-1 RNA and HCV RNA, the sample is "Non-Discriminated Reactive" (NDR)

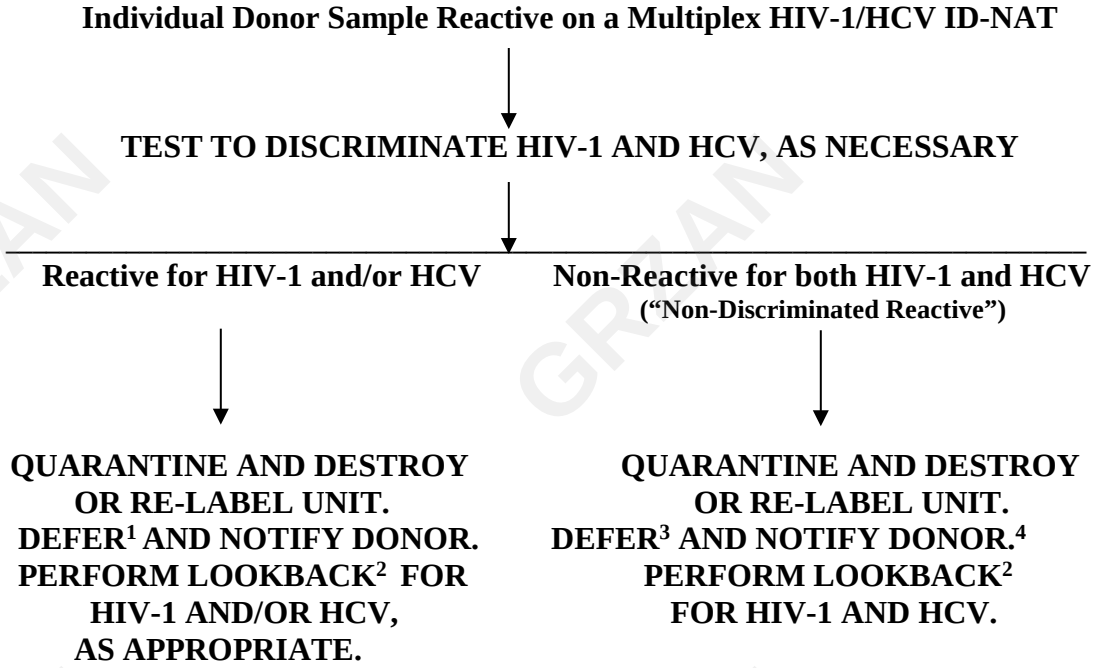
You must quarantine the unit and destroy or re-label the unit as described in section IV.C.1.a.

You must defer the donor (21 CFR 610.41). We recommend that you defer the donor for 6 months. The donor is eligible for reentry after the 6-month waiting period. If you chose to reenter the donor, you may do so at that time without testing a follow-up sample. You must notify the donor of his/her deferral, providing information about the test results that were the basis for the deferral (21 CFR 630.40). We recommend that you counsel the donor that the

initial test result was very likely a false positive result and that the donor is not infected, but that because of the initial reactive test result he or she will be deferred for 6 months.

You must perform lookback for HIV-1 and HCV under 21 CFR 610.46 and 610.47, respectively, as described in section IV.C.1.a. above.

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



[1]The donor may be eligible for reentry (see Figures 5 and 6).

[2] If both Discriminatory NATs were reactive or if both Discriminatory NATs were non-reactive, notification of transfusion recipients should specify that the patient should be tested for both HIV-1 and HCV.

[3] We recommend that you defer the donor for 6 months and, if you choose to reenter the donor, you may do so at that time without testing a follow-up sample.

[4] We recommend that you counsel the donor that the test result was very likely a false positive result and that the donor is not infected, but that because of the initial reactive test result he or she will be deferred for 6 months.

TABLE 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

If:	*Then:*	*After that if:*	*Then:*
Individual Donor Sample Reactive on a Multiplex HIV-1 /HCV ID-NAT	**Test to discriminate HIV-1 and HCV, as necessary**	**Reactive for HIV-1 and/or HCV**	**Quarantine and destroy or re-label unit; Defer[1] and notify donor; perform lookback[2] for HIV-1 and/or HCV, as appropriate**
		Non-Reactive for both HIV-1 and HCV	**Quarantine and destroy or re-label unit; Defer[3] and notify donor[4]; perform lookback[2] for HIV-1 and HCV**

[1]The donor may be eligible for reentry (see Tables 5 and 6).
[2] If both Discriminatory NATs were reactive or if both Discriminatory NATs were non-reactive, notification of transfusion recipients should specify that the patient should be tested for both HIV-1 and HCV.
[3] We recommend that you defer the donor for 6 months and, if you choose to reenter the donor, you may do so at that time without testing a follow-up sample.
[4] We recommend that you counsel the donor that the test result was very likely a false positive result and that the donor is not infected, but that because of the initial reactive test result he or she will be deferred for 6 months.

D. Testing, Product Disposition, Donor Management, and Lookback for an Individual Donor Sample that is Reactive on a Single Virus NAT (ID-NAT) after Negative Antibody Screening Tests

If you obtain a reactive HIV-1 RNA NAT and/or reactive HCV RNA NAT result for an individual donor sample from a test other than a Multiplex NAT, you must do the following (see Figure 4 and Table 4):

1. Quarantine the unit (21 CFR 610.40(h)). You must not ship or use the unit unless one of the exceptions described in 21 CFR 610.40(h)(2) applies. If you choose not to destroy the unit, you may release it for research or further manufacture with written approval from FDA. If released for one of these uses, you must appropriately label the unit as described in section IV.C.1.a. (21 CFR 606.121).

2. Defer the donor (21 CFR 610.41). The donor may be eligible for reentry (see sections V.A. and V.B.).

3. Notify the donor of his/her deferral, providing information about the test results that were the basis for the deferral (21 CFR 630.40).

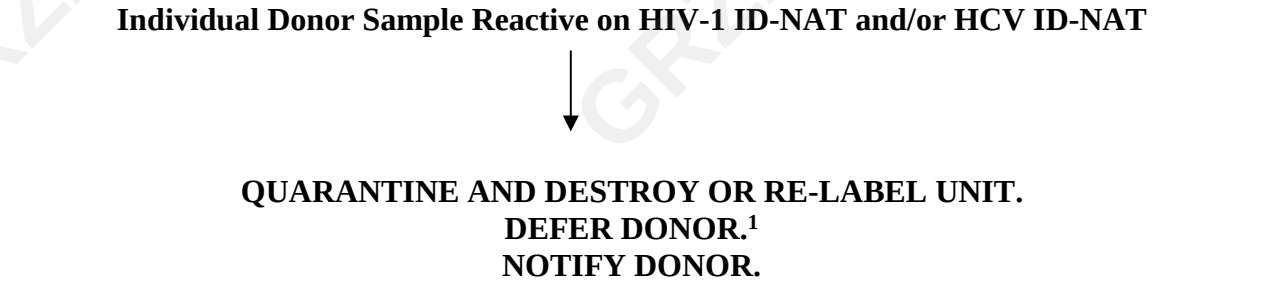
4. Perform lookback (product quarantine/retrieval and notification of recipients of prior collections) for HIV-1 and/or HCV under 21 CFR 610.46 and 21 CFR 610.47 respectively, as appropriate.

    - If you are an establishment that collects Whole Blood or blood components, including Source Plasma and Source Leukocytes, within 3 calendar days after a donor tests reactive for evidence of HIV-1 and/or HCV infection you must review records dating back 12 months prior to the donor's reactive NAT to identify blood and blood components previously donated by the donor. You must quarantine identified in-date blood and blood components if intended for transfusion or if intended for further manufacture into injectable products (except if pooled), notify consignees so that they may quarantine previously collected in-date blood and blood components, and notify transfusion recipients.

    - If you are a consignee of Whole Blood or blood components, including Source Plasma and Source Leukocytes, when notified by the collecting establishment you must quarantine identified previously collected in-date blood and blood components if intended for transfusion or if intended for further manufacture into injectable products (except if pooled). You must notify transfusion recipients who were transfused with blood and blood components collected during the 12 months before the date of the NAT-reactive donation, or notify the recipient's physician of record, of the need for recipient HIV-1 or HCV testing and counseling. You must make reasonable

attempts to perform the notification within 12 weeks after receiving the donor's reactive NAT screening test result for HIV-1 or HCV. If both Single Virus NATs were reactive, notification of transfusion recipients should specify that the patient should be tested for both HIV-1 and HCV.

FIGURE 4. Testing, Product Disposition, Donor Management, and Lookback for an Individual Donor Sample that is Reactive on a Single Virus NAT (ID-NAT) after Negative Antibody Screening Tests



[1]The donor may be eligible for reentry (see Figures 5 and 6).

TABLE 4. Testing, Product Disposition, Donor Management, and Lookback for an Individual Donor Sample that is Reactive on a Single Virus NAT (ID-NAT) after Negative Antibody Screening Tests

If:	***Then:***
Individual Donor Sample Reactive on HIV-1 ID-NAT and/or HCV ID-NAT	**Quarantine the unit**
	Destroy or re-label the unit
	Defer the donor[1]
	Notify the donor
	Perform lookback for HIV-1 and/or HCV, as appropriate

[1] The donor may be eligible for reentry (see Tables 5 and 6).

V. RECOMMENDATIONS FOR DONOR REENTRY

Note that the reentry of a donor permits prospective donations from a reentered donor who meets donor eligibility criteria. It does not affect the status of previous collections from that donor, including donations subject to lookback.

A. Reentry for Donors Deferred Because of Reactive HIV-1/2 Test Results

Currently, FDA has not found acceptable a process for reentry of deferred donors with the following HIV-1 test results:

- NAT-reactive for HIV-1 (e.g., a Discriminatory NAT after a reactive Multiplex NAT or by a Single Virus NAT for HIV-1 RNA) and anti-HIV-1 or -2 or anti-HIV-1/2 test RR (regardless of HIV-1 WB or IFA or HIV-1 p24 EIA test result);

  OR

- NAT-reactive for HIV-1 (e.g., a Discriminatory NAT after a reactive Multiplex NAT or by a Single Virus NAT for HIV-1 RNA) and HIV-1 p24 EIA RR (regardless of anti-HIV-1 or -2 or anti-HIV-1/2 test result);

  OR

- NAT-non-reactive for HIV-1 (or HIV-1 NAT not performed) and anti-HIV-1 or -2 or anti-HIV-1/2 test RR, HIV-1 WB positive (regardless of HIV-1 p24 EIA test result).

  OR

- NAT-non-reactive for HIV-1 (or HIV-1 NAT not performed) and anti-HIV-1 or -2 or anti-HIV-1/2 test RR (regardless of WB or IFA result) and HIV-1 p24 EIA RR (regardless of Neutralization test result).

1. FDA has accepted a method or process for reentry of deferred donors in the following three groups (see Figure 5 and Table 5):

   - **Group I**: Donors who were HIV-1 NAT-reactive (i.e., reactive on a Discriminatory NAT for HIV-1 or on a Single Virus NAT for HIV-1 or a Multiplex NAT that detects and discriminates HIV) and seronegative. This includes donors previously deferred because of reactive test results on an investigational HIV-1 NAT. The HIV-1 p24 antigen EIA may not have been performed if it was replaced by an approved NAT that was validated to replace the HIV-1 p24 antigen test.

NOTE: If the original donor sample that was NAT-reactive was negative on the Discriminatory NAT for HIV-1 or on the Single Virus NAT for HIV-1 but was reactive on the Discriminatory NAT for HCV or on the Single Virus NAT for HCV, you may attempt to reenter the donor according to the recommendations in section V.B. (see Figure 6 and Table 6). If the original donor sample that was NAT-reactive was reactive on both of the Discriminatory NATs for HIV-1 and HCV or on both of the Single Virus NATs for HIV-1 and HCV, or reactive for both HIV-1 and HCV on the Multiplex test that detects and discriminates HIV and HCV, you may attempt to reenter the donor according to the recommendations in both sections V.A and V.B (see Figures 5 and 6, and Tables 5 and 6).

- **Group II:** Donors who were NAT-non-reactive (or NAT was not performed) and who were RR on a screening test for HIV-1 or -2 or HIV-1 and -2 or HIV-1/2 antibody, with an HIV-1 WB or IFA that was indeterminate (viral bands may be present), unreadable, negative, or was not performed. If an HIV-1 IFA was performed to resolve an indeterminate or unreadable HIV-1 WB, the IFA result must not have been positive. This group includes donors previously deferred because of RR HIV-1 or HIV-2 (or combination HIV-1/2) serologic test results prior to the initiation of testing by NAT.

  These donors may be eligible for reentry only if:
  - the HIV-1 p24 antigen EIA (if performed) was negative, and
  - if a second, different, licensed HIV-2 test performed on the index donation was negative, or, if the second HIV-2 test was RR, an investigational HIV-2 supplemental test (if performed) was not positive. Performance of an investigational HIV-2 supplemental test (if available) is optional at the present time. Currently, we have not approved a supplemental test for HIV-2. If a supplemental test for HIV-2 is licensed in the future, that test must be performed in accordance with 21 CFR 610.40(e), and the result of the supplemental test for HIV-2 must not be positive for the donor to be eligible for reentry.

- **Group III:** Donors who were NAT-non-reactive (or NAT was not performed) and who were negative on a screening test for HIV-1 and -2 or HIV-1/2 antibody, but who were RR on an HIV-1 p24 antigen EIA with an indeterminate (that is, a non-neutralized or an invalid) or a positive result on the Neutralization test, even on more than one occasion.

2. To reenter a donor who meets FDA eligibility criteria (i.e., the donor is otherwise eligible to donate again), we recommend that you do the following (see Figure 5 and Table 5):

    a. At least 8 weeks after the original donation obtain a new sample from the donor (no donation is made at this time) and perform follow-up testing using:

        (1) A licensed ID-NAT for HIV-1 (e.g., a Discriminatory NAT for HIV-1 or a Single Virus NAT for HIV-1).

        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 or Multiplex NAT that detects and discriminates HIV) 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).

        AND

        (2) A licensed anti-HIV-1/2 test.

        If the original donor sample was RR on the anti-HIV-1 or 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 or 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 Group O.

        NOTE: For purposes of donor counseling, you may choose to test the deferred donor with an HIV-1 ID-NAT and an anti-HIV-1/2 test at any time prior to the end of this 8-week waiting period after the original donation. However, if an HIV-1 ID-NAT is reactive prior to the end of this 8-week waiting period, the donor would not be eligible for reentry and we recommend that you defer the donor permanently. If an anti-HIV-1/2 test is RR prior to the end of this 8-week waiting period, and a licensed supplemental test for antibodies to HIV-1 (e.g., WB or IFA), if performed, is not positive, you may take another follow-up sample from the donor for testing by both HIV-1 ID-NAT and an anti-HIV-1/2 test after another 8-week waiting period has passed.

b. Evaluate the results of the follow-up testing on the donor's new sample as follows:

(1) If the ID-NAT is reactive and the anti-HIV-1/2 test is RR, we recommend that you defer the donor permanently.

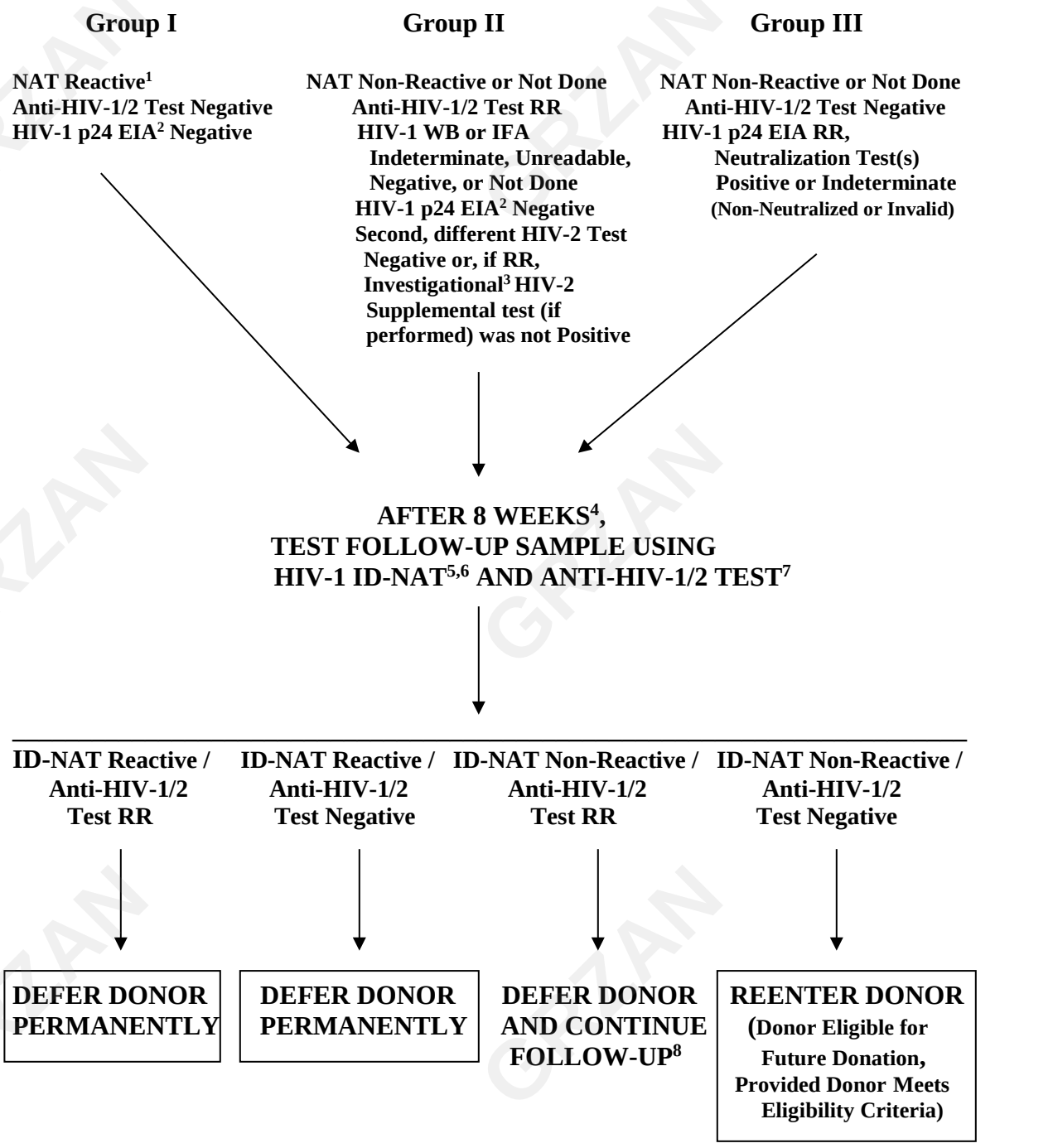
(2) If the ID-NAT is reactive and the anti-HIV-1/2 test is negative, we recommend that you defer the donor permanently.

(3) If the ID-NAT is non-reactive and the anti-HIV-1/2 test is RR, you may reconsider the donor for reentry by conducting additional follow-up testing after a second waiting period of 8 weeks.

(4) When there is a persistent anti-HIV-1/2 RR result, you may wish to further test the donor's new sample using a licensed supplemental test for antibodies to HIV-1 such as a WB or IFA. If the WB or IFA test result is indeterminate, unreadable, or negative, you may reconsider the donor for reentry by conducting follow-up testing after one or more additional waiting period of 8 weeks. If the WB or IFA test result is positive, we recommend that you defer the donor permanently.

(5) If the ID-NAT is non-reactive and the anti-HIV-1/2 test is negative, you may reenter the donor (i.e., the donor is eligible to donate in the future, provided the donor meets all donor eligibility criteria).

FIGURE 5. Reentry for Donors Deferred Because of Reactive HIV-1/2 Test Results



Footnotes for FIGURE 5.

[1] Reactive for HIV-1 (i.e., a Discriminatory NAT for HIV-1 or on a Single Virus NAT for HIV-1 or a Multiplex NAT that detects and discriminates HIV)
[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 must be performed in accordance with 21 CFR 610.40(e) 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 or the Multiplex NAT that detects and discriminates HIV) 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.

TABLE 5. Reentry for Donors Deferred Because of Reactive HIV-1/2 Test Results

If:	*Then:*	*After that if:*	*Then:*
Group I: **NAT Reactive[1]** **Anti-HIV-1/2 Test Negative** **HIV-1 p24 EIA[2] Negative** **OR** **Group II:** **NAT Non-Reactive or Not Done** **Anti-HIV-1/2 Test RR** **HIV-1 WB or IFA Indeterminate, Unreadable, Negative, or Not Done** **HIV-1 p24 EIA[2] Negative** **Second, different HIV-2 Test Negative, or if RR, Investigational[3] HIV-2 Supplemental test (if performed) was not Positive** **OR** **Group III:** **NAT Non-Reactive or Not Done** **Anti-HIV-1/2 Test Negative** **HIV-1 p24 EIA RR, Neut. Test(s) Positive or Indeterminate (Non-Neutralized or Invalid)**	**After 8 weeks[4], test follow-up sample using HIV-1 ID-NAT[5,6] and Anti-HIV-1/2 Test[7]**	**ID-NAT Reactive/ Anti-HIV-1/2 Test RR**	**Defer donor permanently**
		ID-NAT Reactive/ Anti-HIV-1/2 Test Negative	**Defer donor permanently**
		ID-NAT Non-Reactive/ Anti-HIV-1/2 Test RR	**Defer donor and continue follow-up[8]**
		ID-NAT Non-Reactive/ Anti-HIV-1/2 Test Negative	**REENTER DONOR (Donor eligible for future donation, provided donor meets eligibility criteria)**

Footnotes for TABLE 5.

[1] Reactive for HIV-1 (i.e., on a Discriminatory NAT for HIV-1 or on a Single Virus NAT for HIV-1 or the Multiplex NAT that detects and discriminates HIV).
[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 must be performed in accordance with 21 CFR 610.40(e) 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 or the Multiplex NAT that detects and discriminates HIV) 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.

B. Reentry for Donors Deferred Because of Reactive HCV Test Results

Currently, FDA has not found acceptable a process for reentry of deferred donors with the following HCV test results:

- NAT-reactive for HCV (e.g., a Discriminatory NAT after a reactive Multiplex NAT or by a separate NAT for HCV RNA) and anti-HCV test RR (regardless of historical HCV RIBA result)

  OR

- NAT-non-reactive for HCV (or HCV NAT not performed) and anti-HCV test RR and historical HCV RIBA positive

1. FDA has accepted a method or process for reentry of deferred donors in the following two groups (see Figure 6 and Table 6):

   - **Group A:** Donors who were HCV NAT-reactive (e.g., reactive on a Discriminatory NAT for HCV or on a Single Virus NAT for HCV) and seronegative. This includes donors previously deferred because of reactive test results on an investigational HCV NAT.

NOTE: If the original donor sample that was NAT-reactive was negative on the Discriminatory NAT for HCV or on the Single Virus NAT for HCV but was reactive on the Discriminatory NAT for HIV-1 or on the Single Virus NAT for HIV-1, you may attempt to reenter the donor according to the recommendations in section V.A. (see Figure 5 and Table 5). If the original donor sample that was NAT-reactive was reactive on both of the Discriminatory NATs for HIV-1 and HCV or on both of the Single Virus NATs for HIV-1 and HCV or for both HIV-1 and HCV on the Multiplex test that detects and discriminates HIV and HCV, you may attempt to reenter the donor according to the recommendations in both sections V.A and V.B (see Figures 5 and 6 and Tables 5 and 6).

- **Group B:** Donors who were NAT-non-reactive (or NAT was not performed) and who were RR on a screening test for HCV antibody.[5] This group includes donors who were RR on a second, different licensed screening test for HCV antibody if it was used in further testing of the index donation in accordance with 21 CFR 610.40(e).

2. To reenter a donor who meets FDA eligibility criteria (i.e., the donor is otherwise eligible to donate again), we recommend that you do the following (see Figure 6 and Table 6):

a. At least 6 months after the original donation obtain a new sample from the donor (no donation is made at this time) and perform follow-up testing using:

(1) A licensed ID-NAT for HCV (e.g., a Discriminatory NAT for HCV or a Single Virus NAT for HCV)

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 or the Multiplex NAT that detects and discriminates 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.

AND

(2) Two different, licensed anti-HCV screening tests.

If the original donor sample was RR on the anti-HCV test (Group B donors), we recommend that you use the same anti-HCV test that was performed on the original donor sample or a more sensitive version (i.e.,

[5] This group includes deferred donors with an historical HCV RIBA that was indeterminate, negative or was not performed.

HCV EIA version 3.0 or later) as one of the two licensed-anti HCV screening tests to test this follow-up sample.

NOTE: For purposes of donor counseling and to detect possible HCV viremia, you may also choose to test the deferred donor with an HCV ID-NAT and two different, licensed anti-HCV screening tests at any time prior to the completion of the 6-month period after the original donation. However, if an HCV ID-NAT is reactive prior to the end of this 6-month period, the donor would not be eligible for reentry and we recommend that you defer the donor permanently. If an anti-HCV test is RR prior to the end of this 6-month waiting period, you may take one more follow-up sample from the donor after a waiting period of at least 6 months for testing by HCV ID-NAT and two different, licensed anti-HCV screening tests. If an anti-HCV test is still RR on a second follow-up sample at any time after the original donation, we recommend that you defer the donor permanently.

b. Evaluate the results of the follow-up testing on the donor's new sample as follows:

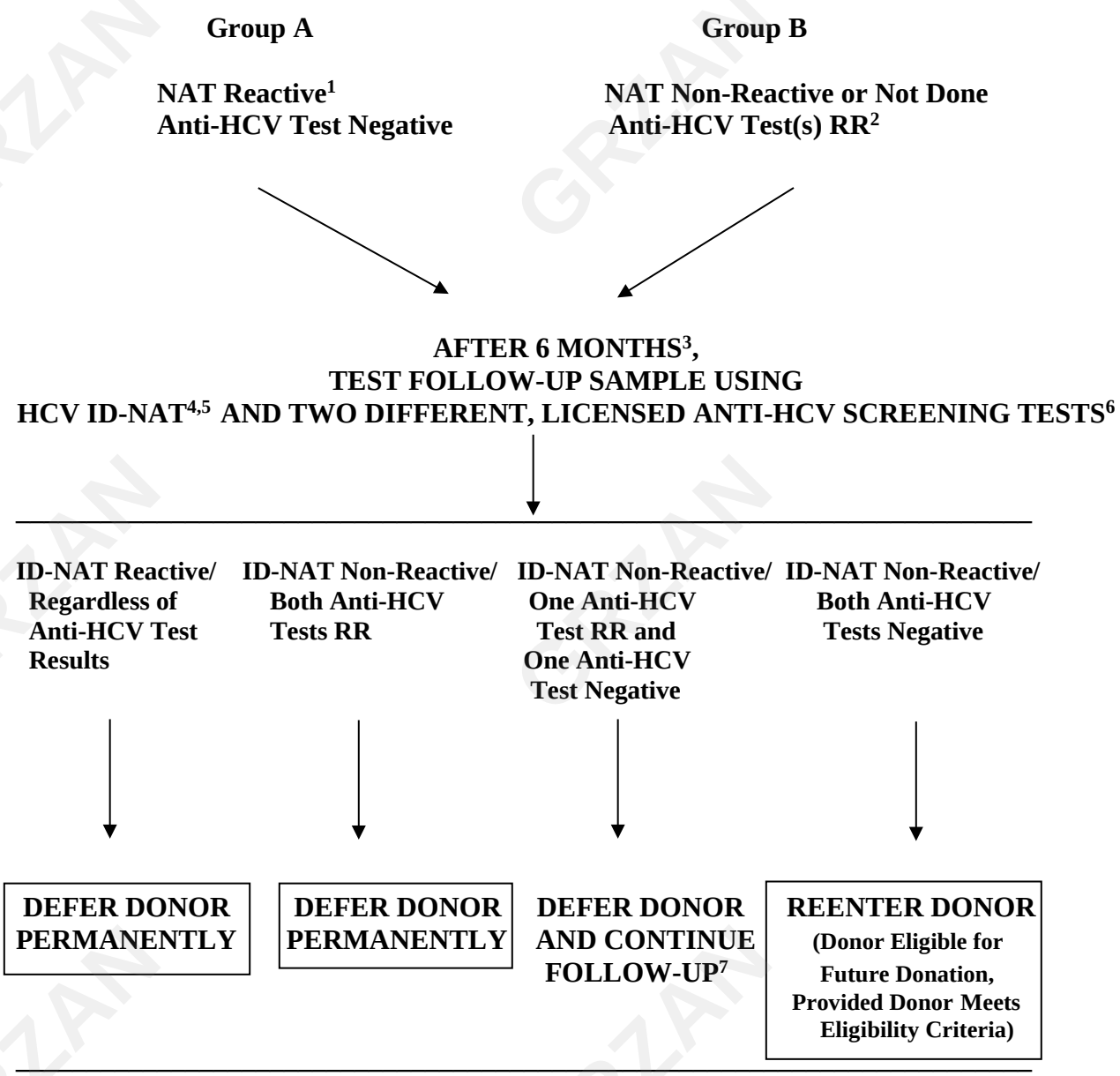
(1) If the ID-NAT is reactive regardless of anti-HCV test results, we recommend that you defer the donor permanently.

(2) If the ID-NAT is non-reactive and both of the anti-HCV tests are RR, we recommend that you defer the donor permanently.

(3) If the ID-NAT is non-reactive and only one anti-HCV test is RR, you may reconsider the donor for reentry by testing a follow-up sample after one more waiting period of at least 6 months**.** If an anti-HCV test is still RR on a second follow-up sample at any time after the original donation, we recommend that you defer the donor permanently.

(4) If the ID-NAT is non-reactive and both anti-HCV tests are negative, you may reenter the donor (i.e., the donor is eligible to donate in the future, provided the donor meets all donor eligibility criteria).

FIGURE 6. Reentry for Donors Deferred Because of Reactive HCV Test Results



Footnotes for FIGURE 6.

[1] Reactive on a Discriminatory NAT for HCV or on a Single Virus NAT for HCV or on a Multiplex NAT that detects and discriminates HCV.
[2] Group B includes deferred donors with an historical HCV RIBA that was indeterminate, negative or was not performed. Donors can be RR in a second, different licensed screening test for HCV antibody if it was used for further testing of the index donation.
[3] HCV ID-NAT, if performed prior to 6 months, must be negative for the donor to be eligible for reentry.
[4] 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).
[5] 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 or the Multiplex NAT that detects and discriminates 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.
[6] If the original donor sample was RR on the anti-HCV test (Group B donors) we recommend that you use the same anti-HCV test that was run on the original donor sample or a more sensitive version (i.e., HCV EIA version 3.0 or later) as one of the two licensed-anti HCV screening tests to test this follow-up sample.
[7] You may reconsider the donor for reentry by testing a follow-up sample after one more waiting period of at least 6 months using an HCV ID NAT and two different, licensed anti-HCV screening tests. If an anti-HCV test is still RR on a second follow-up sample at any time after the original donation, we recommend that you defer the donor permanently.

TABLE 6. Reentry for Donors Deferred Because of Reactive HCV Test Results

If:	*Then:*	*After that if:*	*Then:*
Group A: **NAT Reactive[1]** **Anti-HCV Test Negative** **OR** **Group B:** **NAT Non-Reactive or Not Done** **Anti-HCV Test(s) RR[2]**	**After 6 months[3], test follow-up sample using HCV ID-NAT[4,5] and two different licensed Anti-HCV Screening Tests[6]**	**ID-NAT Reactive/ Regardless of Anti-HCV Test Results**	**Defer donor permanently**
		ID NAT Non-Reactive/ Both Anti-HCV Tests RR	**Defer donor permanently**
		ID-NAT Non-Reactive/ One Anti-HCV Test RR and One Anti-HCV Test Negative	**Defer donor and continue follow-up[7]**
		ID-NAT Non-Reactive/ Both Anti-HCV Test Negative	**REENTER DONOR (Donor eligible for future donation, provided donor meets eligibility criteria)**

[1] Reactive on a Discriminatory NAT for HCV or on a Single Virus NAT for HCV or on a Multiplex NAT that detects and discriminates HCV.

[2] Group B includes deferred donors with an historical HCV RIBA that was indeterminate, negative or was not performed. Donors can be RR in a second, different licensed screening test for HCV antibody if it was used for further testing of the index donation.

[3.]HCV ID-NAT, if performed prior to 6 months, must be negative for the donor to be eligible for reentry.

[4] 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).

[5.] 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 or the Multiplex NAT that detects and discriminates 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.

[6] If the original donor sample was RR on the anti-HCV test (Group B donors), we recommend that you use the same anti-HCV test that was run on the original donor sample or a more sensitive version (i.e., HCV EIA version 3.0 or later) as one of the two licensed-anti HCV screening tests to test this follow-up sample.

[7] You may reconsider the donor for reentry by testing a follow-up sample after one more waiting period of at least 6 months using an HCV ID NAT and two different, licensed anti-HCV screening tests. If an anti-HCV test is still RR on a second follow-up sample at any time after the original donation, we recommend that you defer the donor permanently.

VI. REFERENCES

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