Recommendations to Reduce the Risk of Transmission of Human Immunodeficiency Virus (HIV) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Draft Guidance for Industry

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I. INTRODUCTION

We, FDA or Agency, are issuing this guidance to assist you, establishments making donor eligibility determinations,[1] in understanding the requirements in Title 21 Code of Federal Regulations, part 1271, subpart C (21 CFR part 1271, subpart C). The regulations under 21 CFR part 1271, subpart C set out requirements for determining donor eligibility, including donor screening and testing, for donors of human cells, tissues, or cellular or tissue-based products (HCT/Ps).[2]

This guidance applies to human cells and tissues recovered on or after May 25, 2005, the effective date of the regulations contained in 21 CFR part 1271, subpart C, and provides recommendations to reduce the risk of transmission of human immunodeficiency virus (HIV) by HCT/Ps. This guidance updates information regarding HIV risk included in the guidance entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry," dated August 2007 (August 2007 HCT/P DE Guidance), by revising recommendations for: 1) donor screening that includes reducing certain time-based risk factors and conditions; 2) assessing every HCT/P donor for HIV risk using the same individual risk-based questions regardless of sex; and 3) use of an FDA-licensed donor screening test that includes detection of anti-HIV-1 group O and removing the recommendation to screen HCT/P donors for HIV-1 group O risk.

In addition, as described further below, we recommend establishments determine to be ineligible any potential HCT/P donors taking medications to treat or prevent HIV infection (e.g., antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP), and post-exposure prophylaxis (PEP)). FDA-approved antiretroviral drugs are safe and effective and can reduce the HIV viral

[1] See 21 CFR 1271.50.

[2] HCT/Ps are defined in 21 CFR 1271.3(d) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."

load of individuals to undetectable levels as determined by nucleic acid tests (NAT). However, these antiretroviral drugs do not fully eliminate the virus from the body, and donated HCT/Ps from individuals infected with HIV taking ART can potentially still transmit HIV to a recipient. Further, the use of PrEP and PEP may delay detection of HIV by currently licensed screening tests, potentially resulting in false negative results.

When finalized, this guidance will provide specific recommendations for HCT/P donor testing and screening for risk associated with HIV infection and supersede information regarding HIV risk in the August 2007 HCT/P DE Guidance.

In general, 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's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HIV is a retrovirus that is a major global public health problem (Refs. 1-3). In 2022, an estimated 1.3 million new cases of HIV were diagnosed, and an estimated 39 million people were infected with HIV worldwide (Ref. 1). At the end of 2022, the Centers for Disease Control and Prevention (CDC) estimated approximately 1.1 million people 13 years of age and older were living with diagnosed HIV infection in the United States (U.S.) and six territories and freely associated states (Ref. 4). In addition, it was estimated that 158,300 people 13 years of age and older had HIV infections that had not been diagnosed (Ref. 5).

There are two types of HIV (Refs. 2-3, 6). HIV, type 1 (i.e., HIV-1) accounts for the majority of HIV infections that occur globally and has 40 to 60% amino acid homology with HIV, type 2 (i.e., HIV-2) (Ref. 6). Within HIV-1 are different groups (i.e., groups M, N, and O). HIV-1 group O is common in Africa (Ref. 6), but there have been a few cases of HIV-1 group O reported outside of Africa. HIV-2 is less prevalent than HIV-1 but remains an important cause of disease in certain regions of the world where it is endemic (Refs. 2-3, 7). HIV-2 occurs primarily in West Africa, but an increasing number of cases have been recognized in the U.S., Europe, and India (Refs. 2-3, 7).

The clinical features of primary acute HIV infection, also referred to as acute retroviral syndrome, can be variable and many patients are asymptomatic or have limited symptoms (Ref. 6). Newly infected patients with HIV who are asymptomatic or who have non-specific symptoms may not seek medical attention (Ref. 6). The most common clinical manifestations and physical findings in acute HIV infection are fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, diarrhea, weight loss, and headache (Refs. 8-13). Neurologic manifestations (neuritis, encephalitis, meningitis, paresis, paresthesia, vertigo), keratitis, oral ulcers, and opportunistic infections have also been reported (Refs. 8-13). Untreated chronic infection can

lead to Acquired Immunodeficiency Syndrome (AIDS) and if left untreated, HIV/AIDS can be associated with high morbidity and mortality (Refs. 1-6).

III. DISCUSSION

In the Federal Register of May 25, 2004 (69 FR 29786), FDA issued a final rule entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" (21 CFR part 1271, subpart C), which took effect on May 25, 2005. In this final rule, FDA identified HIV-1 and HIV-2 as relevant communicable disease agents or diseases (RCDADs) under 21 CFR 1271.3(r)(1). Thus, for donors of HCT/Ps recovered on or after May 25, 2005, screening and testing for HIV-1 and HIV-2 is required (21 CFR 1271.75(a)(1)(i) and 1271.85(a)(1-2)). Specific tests for HIV and donor screening for specific risk factors and conditions associated with HIV infection, have been recommended for HCT/P donors in order to adequately and appropriately reduce risk of transmission. Specific recommendations for donor testing and screening for risk associated with HIV were issued in the August 2007 HCT/P DE Guidance.

A. Risk of Transmission

There is a risk of transmission of HIV by HCT/Ps. This is supported by reported cases of HIV transmission via transfusion of blood products, by organ transplantation, and from the use of HCT/Ps. Although HIV was initially identified in the early 1980's in men who have sex with men (MSM) and associated with male-to-male sexual contact, it was soon identified that HIV could be transmitted in other ways, including by transfusion of blood products, infusion of clotting factor concentrates to individuals with hemophilia, percutaneous and mucosal exposure to infectious blood or body fluids, intravenous drug use, sharing or using non-sterilized needles or syringes, sexual contact with any infected person, and maternal to child transmission (vertical transmission and breast milk) (Refs. 2, 7-32). HIV has also been transmitted through transplantation of infected organs (Refs. 33-40) and through use of contaminated human cells or tissues (Refs. 35-36, 41-50). Although the prevalence rate of HIV in U.S. tissue donors has been estimated to be lower than in the general population, the estimated probability of undetected viremia at the time of donation is higher among tissue donors than among first-time blood donors (Ref. 51).

1. Potential for Transmission of HIV by Blood Products and Solid Organs

HIV can be transmitted by blood and blood products and solid organs (Refs. 2, 7-40). Thousands of recipients of blood and blood components for transfusion and recipients of plasma-derived clotting factors became infected with HIV before the causative virus was identified and before the first screening tests for HIV were approved by FDA in 1985 (Refs. 20, 22, 25, 52-54).

Since blood establishments implemented FDA-approved donor screening tests, including sensitive tests for detecting HIV antibody, antigen, and nucleic acids,

there has been a dramatic reduction in the transmission of HIV-1 by human blood and blood components (Ref. 55). Sources of remaining risk for HIV-1 transmission include:

- marker-negative "window period" donations made during the period that the donor is infected with the virus, but neither the virus nor antibodies to the virus are detectable by current tests;
- donors infected with genetic and immunovariant viral strains;
- persistent antibody-negative (immunosilent) carriers; and
- laboratory errors.

The window period, including the "eclipse period" attributable to NAT, has improved with each new class of HIV tests (Ref. 56).

Use of donor educational material, specific deferral questions, and advances in HIV donor testing (e.g., HIV antibody assays, p24 antigen/antibody combination assays, and NAT) have reduced the risk of HIV transmission from blood transfusion from about 1 in 2500 units prior to HIV testing to a current estimated residual risk of about 1 in 1.47 million transfusions (Refs. 25, 57-60). NAT window periods have been estimated to be an average of 11–15 days for HIV donor screening tests (Refs. 54-55, 61), which highlights the importance of donor screening.

Additionally, although confidence with testing did not address whether donors are given highly active antiretroviral therapy, data presented at the June 2001 Blood Products Advisory Committee (BPAC) meeting where donor re-entry algorithms were discussed demonstrated with sufficient confidence that negative test results can rule out HIV-1 infection after at least 8 weeks have passed from the time of a presumed false positive test result (Ref. 62), and this period has been supported recently by studies of HIV incidence and residual risk in U.S. blood donors (Refs. 25, 63-66).

Beginning in September 1985, FDA recommended that blood establishments indefinitely defer male donors who have had sex with another male, even one time, since 1977, because of the strong clustering of AIDS and the subsequent discovery of high rates of HIV infection among MSM (Ref. 15). FDA subsequently concluded that the available evidence supported a change from the indefinite deferral for MSM, and in December 2015, recommended a 12-month deferral for MSM.

In 2014, FDA launched the Transfusion Transmissible Infections Monitoring System (TTIMS), a program implemented in the U.S. in order to facilitate monitoring blood safety, particularly in the context of changes in blood collection policy and practice. Following implementation of the 12-month blood donor deferral policy in December 2015 for MSM, four years of data from TTIMS indicated there had been no increase in risk to the blood supply from the policy

change. Additionally, other countries, including the United Kingdom and Canada moved to a 3-month deferral period for MSM, after which, there were no reports from these countries suggesting safety concerns following the implementation of this change. Thereafter, FDA reduced the recommended blood donor deferral period to 3 months for MSM, through recommendations published in guidance in April 2020 (Ref. 25).

In addition to shortening the recommended deferral period for MSM in 2020, FDA concurrently evaluated the available scientific evidence that could support modification of several other blood donor deferrals related to risk for HIV. Based on the experience in the United Kingdom and Canada, along with the detection characteristics of the NAT noted above, in April 2020, FDA also revised the recommended deferrals for individuals who exchange sex for money or drugs or engage in non-prescription injection drug use from indefinite to 3-month deferrals. In addition, for similar reasons, the recommended 12-month deferral for other risk factors, including contact with another person's blood, receipt of a blood transfusion or a recent tattoo or piercing, was revised to 3 months.

FDA subsequently helped facilitate and fund the ADVANCE (Assessing Donor Variability And New Concepts in Eligibility) study, a pilot study intended to evaluate individual risk assessment strategies as an alternative to time-based deferrals for MSM (Ref. 67). The ADVANCE study examined a number of HIV risk factors, such as anal sex and rates of HIV infection among MSM study participants. In addition, the ADVANCE study determined the rates of PrEP and PEP use among MSM study participants (Refs. 67-68).

FDA also recognized that other countries with similar HIV epidemiology as the U.S. revised their donor eligibility criteria for MSM, based on risk assessments performed in these countries. Notably, the United Kingdom in 2021 and Canada in 2022 introduced a new approach for donor questioning based on individual risk factors (Refs. 69-73). The approach is based on surveillance, epidemiology, and risk assessments that demonstrate that new or multiple sexual partners, and for those with new or multiple partners, anal sex, are the most significant risk factors that increase the likelihood of HIV infection (Refs. 17, 69-73). The United Kingdom and Canada have adopted an individual risk-based approach that asks all presenting blood donors (regardless of sex), if they have had a new sexual partner or more than one sexual partner in the last 3 months, and if so, they are asked if they had anal sex (Refs. 71, 74). Individuals who report having a new sexual partner and anal sex or having more than one sexual partner and anal sex in the last three months are deferred from blood donation. To date, the United Kingdom and Canada have not reported safety concerns following the implementation of this individual risk-based deferral policy.

Subsequently, FDA concluded that implementing an individual risk-based approach will maintain the safety of the blood supply, and in May 2023, FDA

issued guidance that recommends (1) eliminating the blood donor screening questions specific to MSM and women who have sex with MSM; and (2) assessing blood donor eligibility using the same individual risk-based questions relevant to HIV risk for every donor regardless of sex. FDA also recommended deferral of any individual taking medications to treat or prevent HIV infection (e.g., ART, PrEP, and PEP) (Ref. 25).

Other federal agencies have also reconsidered the transmission risk of HIV through solid organs. When quantifying risk of transmission of an undetected HIV infection from an organ donor with an HIV risk factor, the probability has been estimated to be fewer than one per 1 million when the donor was additionally screened by testing using a NAT for HIV at least 14 days after the donor's most recent exposure (Ref. 61). In addition, in the setting where donor testing may not detect a recent infection, Public Health Service guidelines for assessing solid organ donors and monitoring transplant recipients for risk of HIV (as well as hepatitis B virus (HBV), and hepatitis C virus (HCV)) infection have evolved (Ref. 54). An evidence-based process was used to update guidelines that included developing key questions to evaluate behavioral and non-behavioral risk factors associated with transmission of these viruses, and an exhaustive literature review was undertaken where they were categorized according to strength and data quality, and evidence was graded. Organ donor screening guidelines were revised to identify donors at risk for acquiring a recent HIV, HBV, or HCV infection (Ref. 105).

2. Potential for Transmission of HIV by HCT/Ps

HIV has been reported to be transmitted by HCT/Ps such as fresh bone, frozen tendon, and skin allografts (Refs. 35-36, 41-50). HIV has also been isolated from tears, retina, cornea, aqueous humor, iris, and conjunctiva (Refs. 37, 75-82).

As noted above, advances in HIV donor testing (e.g., HIV antibody assays, HIV antigen/antibody combination assays, and HIV NATs) have reduced the "window period" when HIV RNA, HIV antigen and/or HIV antibody are not detectable by screening tests (Refs. 54-55, 61).

Formal studies and collection of data specific to HCT/P donors are lacking, however, many of the studies used to support blood donor deferral recommendations (e.g., ADVANCE study, risk assessments) are relevant beyond blood donation. These studies considered certain risk factors associated with donors acquiring HIV, and the same risk factors associated with acquiring HIV are relevant to screening not only blood donors but also donors of HCT/Ps. In addition, the evidence-based process used to update organ donor screening guidelines that evaluated behavioral and non-behavioral risk factors associated with transmission of HIV, HBV, or HCV, for which a number of risk factors overlap, provides substantial support to identify donors at risk for acquiring a

recent infection. Having a recent infection is relevant to risk of transmission presented by HCT/P donors in addition to organ donors. Given these data, experience with a 3-month blood donor deferral in other countries, and the uniform use of HIV NAT for testing HCT/P donors (which can detect HIV well within a 3-month period following initial infection), the Agency concludes, at this time, that a change to a recommended 3-month risk period as detailed below is scientifically supported for certain risk factors and conditions associated with HIV for donors of HCT/Ps (Ref. 54, 105).

Additionally, based on our review of the available science, adequacy of available test methods, studies used to evaluate risk behaviors, and experiences with updated blood donor screening questions, FDA also recommends eliminating the HCT/P donor screening questions specific to MSM and women who have sex with MSM and, instead, recommends assessing every HCT/P donor for HIV risk using the same individual risk-based questions relevant to HIV risk regardless of sex.

B. Severity of Effect

HIV disease is associated with a risk for development of neurologic complications including Guillain-Barré syndrome, encephalitis, meningitis, paresis, HIV-associated neurocognitive disorder, and HIV-associated dementia (Refs. 6, 8-13, 83-84). There is also a risk of developing malignancies (e.g., primary CNS lymphoma, Burkitt's lymphoma, Kaposi's sarcoma) and opportunistic infections (Ref. 6). Untreated chronic infection can lead to AIDS and, if left untreated, HIV/AIDS can be associated with high morbidity and mortality (Refs. 1-6).

C. Availability of Appropriate Screening and/or Testing Measures

As described above, appropriate donor screening measures have been developed for HIV and specific details are listed below for screening a donor for clinical and physical evidence, and risk factors and conditions to reduce the risk of transmission of HIV.

FDA-licensed donor screening tests to detect antibodies to HIV-1, including detection of HIV-1 group O, and HIV-2 (anti-HIV I/O/II), and to detect HIV-1 and HIV-2 viral nucleic acid (using NAT), are available for screening living and cadaveric (non-heart-beating) donors of HCT/Ps. Some NATs are multiplex assays that can simultaneously detect HIV, HBV, and HCV in a single blood specimen. An FDA-licensed HIV antigen-antibody combination test is also available for testing HCT/P donors.

The addition of NAT to screen HCT/P donors significantly reduces the risk of transmission of HIV (Refs. 51, 85-87). The probability of detecting HIV viremia at the time of tissue donation has been estimated to be 1 in 55,000 and the probability of detecting donor viremia is estimated to be reduced to 1 in 173,000 when individual HIV NAT is used (Ref. 51).

However, antiretroviral medications to prevent sexual transmission of HIV, or for treatment of HIV infection (i.e., PrEP, PEP, or ART), can affect HIV test results. FDA-approved antiretroviral drugs can reduce the HIV viral load of individuals to undetectable levels as determined by conventional testing; however, these antiretroviral drugs do not fully eliminate the virus from the body (Refs. 88-94). Therefore, the addition of appropriate screening measures to identify use of antiretroviral drugs to treat or prevent HIV infection is recommended.

IV. RECOMMENDATIONS

A. Screening a Donor for Risk Factors and Conditions of HIV Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records (21 CFR 1271.3(s)) and ask questions about the donor's medical history and relevant conditions and behavioral risks, including risk factors for RCDADs (21 CFR 1271.75(a)).

The list below provides risk factors and conditions for which we recommend screening in order to reduce the risk of transmission of HIV infection. Except as noted in this section, and in accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for HIV. The following conditions or behaviors should be considered risk factors for HIV:

1. Persons who have ever had a positive or reactive screening test for HIV (Refs. 88-91).

2. Persons who have engaged in non-prescription injection drug use in the preceding 3 months, including intravenous, intramuscular, or subcutaneous injections (Refs. 25-26, 54, 95-125).

3. Persons who have had sex[3] in exchange for money or drugs or other payment[4] in the preceding 3 months (Refs. 25, 27, 54, 105, 126-131).

4. Persons who have had sexual contact in the preceding 3 months with any individual who has ever had a positive test for HIV infection (Refs. 4, 25, 54, 95-113, 132).

5. Persons who have had sexual contact in the preceding 3 months with any individual who has exchanged sex for money, drugs or other payment. If there is any uncertainty about when their sexual partner exchanged sex for

[3] Throughout this guidance, unless specified as "anal sex," the term "sex" or "sexual contact" refers to vaginal, anal, or oral sex, regardless of whether a condom or other protection is used.
[4] https://www.unaids.org/sites/default/files/media_asset/2024-terminology-guidelines_en.pdf

money, drugs or other payment, the person is ineligible for 3 months (Refs. 4, 25, 54, 95-113, 132).

6. Persons who have had sexual contact in the preceding 3 months with any individual who has engaged in non-prescription injection drug use. If there is any uncertainty about when their sexual partner engaged in non-prescription injection drug use, the person is ineligible for 3 months (Refs. 4, 25, 54).

7. Persons who have had a new sexual partner[5] in the preceding 3 months **and** have had anal sex in the preceding three months (Refs. 4, 25, 54, 95-113, 132).

   Note: An anonymous semen donor who reports this behavior may be eligible provided that the semen donation is kept in quarantine and the results from initial and requisite retesting of the donor are negative (or non-reactive) and no other risk factor for an RCDAD is identified.[6] If a directed semen donor reports this behavior, you may elect to perform the quarantine and retesting steps described for an anonymous semen donor. If such steps are taken, the directed semen donor may be eligible provided that the results from initial testing and retesting of the donor are negative (or non-reactive) and no other risk factor for any RCDAD is identified.

8. Persons who have had more than one sexual partner[7] in the preceding 3 months **and** have had anal sex in the preceding three months (Refs. 4, 25, 54, 95-113, 132).

   Note: An anonymous semen donor who reports this behavior may be eligible provided that the semen donation is kept in quarantine and the results from initial and requisite retesting of the donor are negative (or non-reactive) and no other risk factor for an RCDAD is identified.[8] If a directed semen donor reports this behavior, you may elect to perform the quarantine and retesting steps described for an anonymous semen donor. If such steps are taken, the directed semen donor may be eligible provided that the results from initial testing and retesting of the donor are negative (or non-reactive) and no other risk factor for any RCDAD is identified.

[5] For the purposes of this guidance, the following examples would be considered having sex with a new partner: having sex with someone for the first time; or having had sex with someone in a relationship that ended in the past and having sex again with that person in the last 3 months.

[6] In accordance with 21 CFR 1271.60(a), you must quarantine semen from anonymous donors until the retesting required under § 1271.85(d) is complete. In accordance with 21 CFR 1271.85(d), at least 6 months after the date of donation of semen from anonymous donors, you must collect a new specimen from the donor and test it for evidence of infection due to the communicable disease agents for which testing is required under paragraphs (a), (b), and (c) of 1271.85(d).

[7] See footnote 5.

[8] See footnote 6.

9. Persons who have ever taken any medication to treat HIV infection (i.e., ART) (Refs. 25, 89, 91-94, 133-136).

10. Persons who have taken any medication by mouth (oral) in the preceding 3 months to prevent HIV infection (i.e., antiviral PrEP or PEP) (Refs. 25, 91-94, 134-137).

11. Persons who have received any medication by injection in the preceding 2 years to prevent HIV infection (e.g., long-acting antiviral PrEP or PEP) (Refs. 25, 134, 138).

12. Persons who have been exposed in the preceding 3 months to known or suspected HIV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane (Refs. 25, 54, 95, 105).

13. Persons who have been in lock up, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 3 months (Refs. 54, 105, 151-154).

14. Persons who have undergone tattooing, ear piercing or body piercing in the preceding 3 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used. A person may be eligible, for example, if a tattoo was applied by a state regulated entity with sterile needles and non-reused ink, or if ear or body piercing was done using single-use equipment (Refs. 25, 154-158).

15. Children 1 month of age or younger who were born to a mother with, or at risk for, an HIV infection; see risk factors above (Refs. 30-32, 139-150).

16. Children breastfed in the preceding 6 months by a mother with, or at risk for, an HIV infection; see risk factors above (Refs. 30-32, 139-150).

We do not recommend deferral of a donor who is a child born to a mother with or at risk for HIV infection if the child is over 1 month of age and has not been breast-fed within the preceding 6 months, provided that all of the child's HIV tests, physical examination, and medical records do not indicate evidence of HIV infection (Refs. 54, 95, 105, 139-150).

Infant donors may receive human breast milk from a source other than the birth mother. Although there is no specific requirement under 21 CFR part 1271 for screening a third-party human breast milk donor, this information, if available, would be considered relevant medical records and must be considered in the final

determination as to whether the infant is an eligible donor. The medical director or other responsible person making the donor eligibility determination should consider the information obtained during the donor medical history interview, including information regarding use of human breast milk from a third-party, and determine whether the information obtained increases the risk of transmission of relevant communicable diseases including HIV.

B. Screening a Donor for Clinical Evidence of HIV Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases (21 CFR 1271.75). In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who exhibits clinical evidence of HIV (Refs. 2-3, 6-7, 10-12, 23-24). Examples of clinical evidence of HIV may include:

- A prior positive or reactive screening test for HIV;
- Unexplained weight loss;
- Unexplained night sweats;
- Unexplained generalized rash;
- Blue or purple spots on or under the skin or mucous membranes typical of Kaposi's sarcoma;
- Generalized lymphadenopathy (swollen lymph nodes) for longer than one month;
- Unexplained temperature of >100.5°F (38.06°C) for more than 10 days;
- Unexplained persistent cough or shortness of breath;
- Opportunistic infections;
- Unexplained persistent diarrhea; and/or
- Unexplained persistent white spots or unusual blemishes in the mouth.

C. Screening a Donor for Physical Evidence of HIV Infection

Relevant medical records (21 CFR 1271.3(s)) include the report of the physical assessment of a cadaveric donor (21 CFR 1271.3(o)) or the physical examination of a living donor.

Some of the following observations are not physical evidence of HIV, but rather are indications of high-risk behavior associated with the disease and would increase the donor's relevant communicable disease risk. Unless an exception identified in 21 CFR 1271.90(a) applies, in accordance with 21 CFR 1271.75(d)(1), you must determine to be ineligible any potential donor who has risk factors for or clinical evidence of HIV. The following are examples of physical evidence of HIV or high-risk behavior associated with HIV:

1. Physical evidence for risk of sexually transmitted diseases and infections, such as perianal lesions, genital ulcerative disease, herpes simplex, mpox,

or chancroid (when making a donor eligibility determination, you should consider these findings in light of other information obtained about the donor) (Refs. 2, 4, 10-12, 17, 159, 166).

2. Physical evidence of non-prescription injection drug use such as needle tracks; your examination should include examination of tattoos, which might be covering needle tracks (Refs. 2, 4, 15-17, 105, 154-158).

3. Physical evidence of recent tattooing, ear piercing, or body piercing. Persons who have undergone tattooing, ear piercing, or body piercing in the preceding 3 months, in which sterile procedures were not used (e.g., contaminated instruments and or/ink were used), or instruments that had not been sterilized between uses were used. A person may be eligible, for example, if a tattoo was applied by a state regulated entity with sterile needles and non-reused ink, or if ear or body piercing was done using single-use equipment (Refs. 25, 154-158).

4. Generalized lymphadenopathy (Refs. 10-12).

5. Unexplained oral thrush (Refs. 4, 6, 10-12).

6. Blue or purple spots consistent with Kaposi's sarcoma (Refs. 6, 160-165).

7. Unexplained generalized rash or fever (Refs. 10-12).

D. Testing a Donor for Evidence of HIV Infection

You must test all donors of HCT/Ps for HIV-1 and HIV-2 as required under 21 CFR 1271.85(a), unless an exception under 21 CFR 1271.90(a) applies, and you must use appropriate FDA-licensed, approved, or cleared screening tests in accordance with the manufacturer's instructions, as required in 21 CFR 1271.80(c).[9]

The following donor screening tests adequately and appropriately reduce the risk of transmission of HIV. Our recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge:

1. For HIV-1: An FDA-licensed donor screening test either for anti-HIV-1 (including group O) or a combination test for anti-HIV-1 (including group O) and anti-HIV-2 (Refs. 167) and an FDA-licensed donor screening NAT for HIV-1, or a combination (multiplex) NAT (Refs. 51, 55, 85-87); and

[9] The following CBER website includes a list of FDA-licensed, approved, or cleared donor screening tests (including manufacturers and tradenames): https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable.

2. For HIV-2: An FDA-licensed donor screening test either for anti-HIV-2 or a combination test for anti-HIV-1 (including group O) and anti-HIV-2 (Ref. 167).

3. An FDA-licensed HIV antigen/HIV 1/O/2 antibody combination assay can be used for the simultaneous qualitative detection of HIV p24 antigen and antibodies to HIV-1 (including group O) and HIV-2. Such a licensed donor screening test should be used in combination with an HIV-1 NAT to adequately and appropriately test an HCT/P donor for HIV-1 and HIV-2.

Any HCT/P donor whose specimen tests negative (or non-reactive) for all assays (i.e., anti-HIV-1 (including group O), anti-HIV-2, or a combination test for those disease agents; and HIV-1 NAT) is considered to be negative (or non-reactive) when making a donor eligibility determination. Note that a negative (or non-reactive) test does not necessarily mean that a donor is eligible; donor screening also applies as described above.

Any HCT/P donor whose specimen tests positive (or reactive) using any of the assays (i.e., anti-HIV-1 (including group O), anti-HIV-2, a combination test for those disease agents, or HIV-1 NAT) is considered ineligible (21 CFR 1271.80(d)(1)).

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