Reply to the Food and Drug Administration Request for Comments

Blood Donor Deferral Policy for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products
[Docket No. FDA-2016-N-1502]

Working Group on Blood Donation
December 2016

1. Introduction

In December 2015, the FDA published "Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products; Guidance for Industry" [1]. In this document, the agency updated its recommendations concerning blood donor deferral periods, changing the recommendation from a lifetime deferral for men who have sex with men (MSM) to a deferral of 12 months since the last sexual contact with another man.

The FDA's updated recommendation is scientifically justified by, among other things, (i) the fact that an HIV infection acquired at least one year earlier should be readily detected by the blood-screening tests routinely performed on donated blood samples before they are released for use, and (ii) the observation that Australia's decision to revise its policy from lifetime deferral to 12-month deferral for MSM led to no detected change in the safety of the blood supply.

In July 2016, the FDA sought public input [Docket No. FDA-2016-N-1502] concerning whether it would be scientifically justified to again update its recommendations to (i) employ a deferral period shorter than 12 months for MSM and/or (ii) base deferral of MSM on individualized risk assessment. The agency also asked for input about how best to design a potential study to evaluate the feasibility and effectiveness of such approaches.

A fundamental issue with a 12-month deferral policy is that the vast majority of MSM excluded under this policy pose no increased risk of HIV transmission through blood donation compared to current blood donors. **The increased risk is concentrated only in the very small proportion of MSM who have acquired an HIV infection so recently that it will not be readily detected** by the extremely sensitive HIV-screening tests performed on all blood samples.

Excluding a large group to avoid increased risks posed by a small subset of individuals raises several potential concerns:

(i) It unnecessarily decreases the number of blood donors;

(ii) It discriminates against the individuals who pose no increased risk, barring them from participating in an important civic activity;

(iii) It could conceivably **increase** the risk to the blood supply, because some individuals may refuse to comply with a policy that is seen to cast too wide a net.

It is thus important to examine whether there are more precise ways to identify the small set of individuals who actually pose an increased risk of carrying undetected HIV.

In June 2016, the Broad Institute of Harvard and MIT formed a Blood Donation Working Group—engaging 49 physicians, scientists and other staff members—to consider such questions. (Working Group Members are listed in Appendix 1.) In this document, the Blood Donation Working Group provides input in response to the FDA's July 2016 request.

The document seeks to lay out a **framework** for revised recommendations that incorporate individualized risk assessment. Appendices 2, 3 and 4 summarize relevant background information and discuss some recommendations in greater detail.

For concreteness in the exposition below, we make specific quantitative choices—for example, about lengths of waiting periods and sample sizes—that are grounded in the scientific literature. However, it is our intention that these quantities should be carefully evaluated and optimized by the FDA based on the latest and most complete scientific evidence, including confidential information available to the agency.

2. Risk under recent policy[1]

We begin by considering the risk of HIV transmission from accepted blood donors over the past decade. Understanding this issue provides a framework for considering changes to current policy.

The 14 million units of blood donated each year in the U.S. are subjected to highly sensitive testing procedures to detect the presence of HIV infection. These tests include Nucleic Acid Testing (NAT), which looks for the presence of viral nucleic acid, and Antibody Testing, which looks for evidence of an immune reaction against the virus [3, 4]. The tests are able to detect infection with extremely high reliability—**with the exception of extremely recently acquired infection.**

The time following HIV infection can be divided into three relevant periods:

(i) A very short "pre-viremia" period, from when HIV enters the body and resides in mucosa to when it is first present in blood. During this period, HIV cannot be transmitted via blood donation [5].

(ii) A "window" period, from when HIV is present in blood to when the virus has replicated to a level detectable in a blood sample by NAT. Blood screening is typically performed in mini-pools of 16 samples (MP-NAT), resulting in a window period estimated at ~9 days. For greater sensitivity, screening can be performed on individual donors (ID-NAT), resulting in a shorter window period estimated at ~5-6 days [6].

(iii) A "detectable" period thereafter, when HIV can be readily detected in blood. The accuracy of detection is at least 99.8% and is likely to be considerably higher, in the vicinity of ~99.99% [7, 8].

Each year, ~400 units of HIV-infected blood are collected from accepted donors and identified by the screening process [3]. These donations do not enter the U.S. blood supply. **The only significant risk to the blood supply comes from units of blood collected during the window period—when blood carries HIV at levels below current detection limits**. The number of infected blood units donated in the window period is unknown but it has been estimated at ~10.2 per year, based on the number of detectable infected samples annually and the length of the window period [9, 10].

The estimated number of "window-period units" is much higher than the number of known transfusion-transmitted HIV cases. In 2002, the FDA licensed NAT testing for commercial sale

[1] See Appendix 2 for more detailed background information.

and issued draft guidance on the use of NAT to reduce the risk of HIV transmission. Since 2003, there has been only a single known case of HIV transmission through blood transfusion, from a donation made in 2008.

If ~10 window-period units are in fact donated each year, the probability *P* that a window-period unit gives rise to a **known** new case of HIV is thus very low. Focusing on the 10-year period from 2003-2012 (to allow time for cases to have come to light), the data imply that P is ~1% (upper 95% confidence limit of ~5%). The current value of P may well be lower because increasing sensitivity of NAT over time may have shortened the window period.

Possible reasons why window-period units have not resulted in known HIV transmissions include: (i) viral levels are relatively low during the window period [5, 11, 12]; (ii) most blood products are subjected to leukodepletion—that is, removal of white blood cells, which can significantly reduce viral loads by eliminating cell-associated virus [13]; (iii) the majority of blood products go into people who survive for less than a year (accident victims, cancer patients, the elderly) [14]; and (iv) cases may go undetected or unreported for other reasons.

Summary: The 14 million units of blood donated each year are subjected to highly sensitive screening for HIV, leading to the detection and removal of ~400 HIV-infected units per year. A small number of infected units are likely donated each year during the window period, before detection becomes completely reliable (estimated at ~10 per year). However, these presumed infected units have given rise to only one **known** case of HIV since 2003—indicating that the probability of a window-period unit giving rise to a known transmission is very low (point estimate of ~1%, upper 95% confidence limit of ~5%).

3. Risk due to MSM donors in the complete absence of risk assessment[2]

We now consider the risk associated with donations by MSM donors (compared to current donors) in the complete absence of risk assessment This discussion largely follows the approach laid out in Yang et al. (2016) [9].

Approximately 24% of HIV infections in the U.S. each year occur in individuals who report **only heterosexual behavior** and no injection drug use, corresponding to ~12,100 infections per year [9]. Based on this number, the length of the window period, and the assumption that HIV infected individuals within this group donate at the same rate as others (that is, assuming no increased self-deferral in this group based on perceived risk), the model of Yang et al. predicts ~12.5 units of HIV-infected blood would be donated annually during the window period [9]. This is close to the 10.2 units inferred based on the number of infected units actually detected.

Approximately 67% of HIV infections in the U.S. each year occur in MSM who report no injection drug use, corresponding to ~29,800 infections per year [15, 16]. The number of incident infections in MSM is thus ~2.5-fold greater than the number in non-MSM (men and women) [2]. Given the estimated size of the MSM population, the incidence rate is ~63-fold higher than in

[2] See Appendix 2 for more detailed background information.

non-MSM [2].[3] However, this risk is not uniformly distributed but rather concentrated in a subset of the MSM population.

It follows that if all MSM simply donated blood at the same rate as the rest of the population (that is, with no deferral policy and no self-deferral based on perceived risk), the number of window-period units would increase proportionally. Specifically, the estimated 10.2 window-period units per year would increase by an additional ~30.8 to a total of ~41 window-period units per year, corresponding to a ~4-fold increase. It is difficult to assess the impact of such an increase because the number of known infections resulting from blood transfusion is so low. Using the estimate P = 1% discussed above, **this might translate into 3 additional known transmissions per decade.**

Notably, the estimates above are based on the assumption of no self-deferral based on perceived risk. In fact, recent research suggests a self-deferral rate of ~75% [3]. Under this assumption, the number of additional window-period units attributable to MSM would be only ~8 per year (vs. ~30.8), corresponding to a 1.8-fold increase [9]. Using the estimate P = 1% discussed above, **this might translate into 0.8 additional known transmissions per decade.**

Summary: If MSM were to donate at the same rate as the rest of the population (that is, with no deferral policy and no self-deferral based on perceived risk), the **total** number of new known transfusion-transmitted HIV infections might increase by ~4-fold—or ~3 additional transmissions per decade. Assuming a self-deferral rate of 75% (consistent with a recent study [3]), the total number of new known HIV infections might increase by 1.8-fold—or ~0.8 additional transmissions per decade.

4. Strategies to identify low-risk MSM donors

While the absolute numbers cited above are extremely low, it is nonetheless desirable to avoid **any** significant increase in the risk of transmission per unit of blood. A logical approach to accomplish this goal is to identify MSM who, at the time of donation, have a very low likelihood of being in the window period—which is the only period in which blood may be infectious but escape detection by routine screening. The issue then is to develop strategies for identifying low-risk MSM donors and **validate** that they achieve the desired decrease in risk.

To illustrate the benefits of individualized risk assessment, we consider a quantitative example.[4] The HIV incidence among MSM has been reported to be 63-fold higher than among currently eligible donors [2]. Suppose that a group of low-risk MSM (defined according to specific criteria) has only 6.3-fold higher incidence—corresponding to a 10-fold reduction in risk. Based on the estimated proportion of MSM in the overall population[5], allowing donations by this group would result in only ~1.9 additional window-period units per year above the current base

[3] Average of Rate Ratio relative to Other Men (67-fold) and Women (58-fold) in Table 4 of [2].
[4] The FDA should review and revise the estimates below, based on the best available data and its judgments concerning acceptable risk.
[5] The proportion of males who reported MSM behavior within the past year was estimated at 2.9%, corresponding to ~1.5% of the overall population [2]. To be conservative, we will use an estimate of 3%.

of ~10.2 (i.e., an increase of <20%). Given the estimated value of P = 1%, this would translate to only **~2 additional known cases per century.**

Below, we discuss several strategies for identifying low-risk MSM and approaches to validation. We use the term "infection-to-detection" (ITD) period to refer to the span from initial infection to the point at which HIV reaches detectable levels in blood—that is, the union of the pre-viremia and window periods.

A) Long deferral period

The traditional approach has been to recommend long-term deferral of MSM—either under the previous policy of lifetime deferral or the current policy of a 12-month deferral since last sexual contact with another man. This approach certainly eliminates excess risk because the deferral period far exceeds the ITD period. However, the deferral period is **so long** that it essentially bars any sexually active MSM from donating blood. As discussed above, this approach raises substantial concerns.

B) No sexual activity during a waiting period tied to the ITD period

A 12-month deferral period is clearly much longer than necessary. Comparably low risk could be achieved if an MSM donor has refrained from sexual activity, and is therefore not at risk of exposure to HIV through that route, for a period that is highly likely to exceed the ITD period.

The ITD period is estimated to have a mean of ~10 days. Studies indicate that the ITD period exceeds 15 days in only ~10% of cases, and exceeds 27 days in only ~1% of cases [17, 18].[6]

Expected impact: Short deferral period

Based on this information about the length of the ITD period, the impact of a short deferral period is expected to be as follows:

- A 15-day deferral period should provide 10-fold reduction in risk, corresponding to the level discussed above (~1.9 additional window units per year, or ~2 additional known cases per century).
- A 30-day deferral period should provide 100-fold reduction in risk, which would result in an estimated risk that is **lower** than for current donors.

While the appropriate deferral period should be determined by the FDA, we will refer to a "2-3 week period". Such a period is sufficiently short that it might be better described as a "waiting period" to allow any recent HIV infection to become detectable.

[6] A study in 2015 measured the proportion of individuals who developed a positive HIV-antibody test at various time periods after infection [17]; the HIV-NAT test can detect infections about 15 days earlier. A smaller study in 2000 directly measured the proportion of individuals who developed a positive HIV-NAT test; it similarly found that only ~10% of individuals show a window period exceeding 15 days [18].

The effectiveness of this strategy depends on the assumptions that, in the considerable majority of cases, (i) the waiting period is indeed long enough to exceed the ITD period and (ii) donors' responses concerning lack of sexual contact during the waiting period are accurate. We note that existing deferral policies rely on the accuracy of donor responses to the donor questionnaire.

C) Low-risk sexual contact during a waiting period tied to the ITD period[7]

The preceding time-based deferral strategy would likely result in an extremely low risk of HIV transmission by blood transfusion. However, it would continue to exclude many sexually active MSM from donating. It could still be viewed as unnecessarily restrictive or discriminatory because it assumes that any kind of sexual activity by any MSM donor is a significant risk factor for recent HIV infection, contrary to epidemiological evidence. **Individualized risk assessment would help address these issues through a more precise definition of low-risk behavior.**

Unprotected anal intercourse with a partner whose HIV status is positive or unknown poses the highest risk of HIV transmission [19-21]. However, behaviors such as avoiding anal intercourse, consistent and proper use of condoms during anal intercourse, limiting the number of sexual partners, or being in a sexually monogamous relationship with an HIV-negative partner, can greatly reduce the risk of acquiring HIV [22-26]. Behavioral surveys suggest a large fraction of MSM adhere to such safe practices [27-29].

Individualized risk assessment would **allow blood donation by MSM who have engaged in only low-risk behaviors over the preceding ~2-3 weeks.** The precise definition for low-risk MSM should be determined by the FDA but possible criteria might include individuals who report that, during the waiting period, they had:

(i) No sexual contact (discussed above); **or**

(ii) Sexual contact only in a relationship with a partner who tested HIV-negative within a defined recent period (e.g., within the past 6 months); **or**

(iii) Sexual contact only in a relationship with a partner who tested HIV-negative within a defined recent period **and** who the donor believes has been sexually monogamous with him since testing HIV-negative; **or**

(iv) Exclusively condom-protected intercourse with a defined small number of partners who are not known to be HIV-positive.

We note that similar criteria are already used to identify MSM at low or high risk of HIV for recruitment to HIV-vaccine clinical trials, and by clinicians evaluating patients for testing and prevention [25]. Other correlates of elevated risk for HIV infection, such as recent diagnosis of a sexually-transmitted infection or drug use, might also be used for risk classification [22-25].

[7] See Appendix 3 for detailed discussion of the rationale, supporting evidence and possible implementation.

Expected impact: Sexual contact only in a relationship with an HIV-negative partner

For concreteness, we will assume that the partner tested HIV-negative within the past 6 months.

Criterion (ii) would be expected to dramatically reduce the risk of infection **regardless of whether the partner has been sexually monogamous with the donor**, as follows:

- A donor who has had sexual contact with only a single partner for the past 2-3 weeks could only be in the window period if that partner is infected with HIV.
- Because the partner tested HIV-negative no more than 6 months ago, the partner must have become infected within the past 6 months.
- The incidence of HIV infection for MSM over a 6-month period is ~24-fold lower than overall HIV prevalence among MSM [2].
- Thus, if an MSM donor has had sex only with a partner who tested HIV-negative six months ago, the chance that he has been exposed to HIV and could be in the window period is expected to be **at least ~24-fold lower** than the chance for a random MSM. It follows that the incidence rate for such donors is expected to be **no more than ~2.6-fold higher than for donors under current policy.**

Criterion (iii) adds the donor's belief that his partner has been sexually monogamous with him since testing HIV-negative:

- **If this belief is accurate, there is essentially no risk** that the donor is in the window period.
- **Even if it is only mostly accurate, the criterion will substantially reduce the risk** beyond the ~24-fold reduction cited above.

With respect to criterion (iv), the approach is premised on the facts that infection is highly unlikely through any act other than unprotected anal intercourse [20] and that condoms provide a very high degree of protection **per-act**. Moreover, **self-reported** consistent condom use by MSM who had **known HIV-positive** sex partners was shown to decrease the risk of HIV infection **over several years** by ~70% [22]. Thus, the risk of HIV infection during a **2-3 week period** is likely to be very low with consistent condom use, and more so when limiting the number of partners. The FDA should consider how best to define this criterion.

The effectiveness of the criteria above depends on the assumptions that (i) engaging in only low-risk behaviors during the preceding ~2-3 week period greatly reduces the risk of recent HIV infection, and (ii) donors' reports are reasonably accurate.

Adopting **a short waiting period would likely increase the accuracy** of self-reporting, as it is easier to remember events over a period of a few weeks than over a year. Donors are also **more likely to truthfully answer questions on short-term behavior tied to HIV transmission** rather than on immutable group labels [30-32]. Moreover, **computer-assisted self-assessment has been shown to yield more accurate reporting** of high risk behavior as compared to face-to-face interviews, and could be more broadly applied [33].

The FDA should also consider whether it would be useful to pose some or all of the behavioral questions to **all** donors, even if the criteria for deferral would differ among groups based on their associated risk factors.

Summary: Several strategies are available that are likely to provide similar safety to the 12-month deferral period. These include accepting donations from MSM who report (i) no sexual activity or (ii) only low-risk sexual activity during a short waiting period tied to the ITD period (~2-3 weeks).

5. Studies to validate strategies to identify low-risk MSM donors

We now discuss study designs to validate that donors classified as low-risk by strategies such as those presented above are indeed unlikely to be in the window period of infection at the time of donation. The highest priority in study design and allocation of resources should be adequately testing the efficacy of classification **for MSM donors**.[8]

A study might be designed as follows:

(i) Subjects would be administered an appropriate questionnaire[9] to determine whether they should be classified as low-risk or high-risk for recent infection;

(ii) The subjects would provide an initial blood sample at the time of questionnaire administration, a portion of which would be subjected to HIV testing by NAT;

(iii) The same subjects would provide a second blood sample for HIV testing by NAT approximately one month later;[10]

(iv) The two HIV tests would be compared to identify the (very small number of) subjects who had converted from NAT-negative to NAT-positive;

(v) For these subjects, the remaining portion of the initial sample would be subjected to extremely sensitive genomic analysis[11] to determine whether any HIV genomes were present in the blood—that is, whether the individual was actually in the ITD period as opposed to having acquired HIV subsequent to the initial sample.

The study could be achieved without incurring the costs and complications of blood quarantine in the setting of actual donation. On the other hand, the protective effect of self-deferral by individuals who perceive themselves at high risk might not apply outside this setting.

[8] The FDA should consider whether to also collect data on a non-MSM control group, as opposed to simply comparing the results on MSM to well-established rates for first-time blood donors. A non-MSM group could also be useful for testing a behavioral questionnaire for all donors.

[9] Wording of questions and accompanying explanatory text should be tested on a small scale to validate donors' understanding, comfort and likely compliance [34]. As noted above, computer-based questionnaires may be preferable.

[10] Having subjects return after one month provides a conservative approach to testing the proposed 2-3 week waiting period, as it is expected to provide extremely high confidence (99%) that any recent infection would be detected and can be compared to the risk classification.

[11] Ideally, the entire sample would be subjected to an assay with near-single-molecule sensitivity, such as digital droplet PCR or ultra-deep sequencing (see Appendix 4 for available methods).

An important aspect of study design will be ensuring that MSM subjects in the study are representative of the U.S. MSM potential donor population, taking into account the need to return for follow-up one month after initial testing.

Based on reported incidence rates [2], the expected number of individuals who will become HIV positive within a given month is

- ~0.9 per 100,000 among donors under recent policy; and
- ~56 per 100,000 among unselected MSM.

A successful strategy for identifying **low-risk** MSM should result in a substantially lower rate than for unselected MSM.

The FDA should decide on the appropriate sample size to estimate the rate for low-risk MSM with sufficient accuracy. Given the target rates of interest discussed above (for example, ~10-fold lower than for unselected MSM), a sample size in the range of 30,000-60,000 low-risk MSM is likely required to establish, with reasonable confidence, an **upper bound** on the rate of window-period donations.

Summary: It is feasible to validate the effectiveness of strategies to identify low-risk MSM donors.

6. Increasing the sensitivity of NAT[12]

Finally, we note that a complementary approach to decrease the number of window-period donations is to shorten the window period by increasing the sensitivity of NAT testing. For example, the FDA should consider whether it would be feasible and desirable for samples from low-risk MSM to be tested by the more sensitive ID-NAT protocol, at least initially.

In addition, the FDA should encourage the continued development of more sensitive NAT testing. With advances in molecular biology, it is likely to become possible to routinely detect HIV at levels approaching 1 copy per ml. Such sensitivity, on a routine basis, could dramatically shorten the window-period for **all** donors, resulting in even lower risk of HIV transmission than under current policy and possibly decreased reliance on classifying donors based on self-reported behavioral risk.

7. Recommendations

Recommendation 1. Based on a review of current scientific evidence, the FDA should consider revising its guidelines concerning blood donation to:

(i) Shorten the deferral period for all MSM from 1 year to approximately 2-3 weeks; and

(ii) Accept donations without deferral from low-risk MSM who meet specific behavior-based criteria.

To evaluate such a revision, the FDA should conduct a study to validate that these criteria would carry low risk to the blood supply.

[12] See Appendix 4 for details on available methods.

Recommendation 2. The FDA should encourage the development of even more sensitive NAT testing to reduce the risk of window-period transmissions from all donors.

We believe these changes will serve both the continued safety of the U.S. blood supply and the fairness of the blood donation policy.

8. References

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