

BLOOD BULLETIN

Individual Donor Risk Assessment and Blood Safety

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KEY POINTS

- HIV risk is related to behaviors, not gender and sexual orientation. New FDA guidance recognizes this by replacing time-based deferral predicated on gender and sexual orientation with an individual risk assessment applied to all donors.
- Blood safety is the paramount goal and is supported by data systems established to allow continuous monitoring of transfusion safety when the new FDA guidance is implemented.
- The performance characteristics of current donor assays and donor data from the US, UK and Canada suggest the blanket deferral of men having sex with men (MSM) may be replaced with a uniform individual donor assessment without compromising the safety of the US blood supply.
- Implementing FDA's donor suitability recommendations in the highly regulated environment of current Good Manufacturing Practices is complex and blood centers may require several months for completion.

I. HISTORICAL CONTEXT FOR THE MSM DEFERRAL

The deferral of MSM from blood donation began before identification of HIV as the cause of AIDS. When transfusion transmission was recognized, epidemiologic studies in the developed world had demonstrated disproportionate risk associated with MSM. This led to the MSM deferral that, absent sensitive and specific *in vitro* testing, was effective in reducing the collection of potentially infectious donations¹. The discovery of HIV allowed development of diagnostic and donor screening tests that currently detect new infections within ≤ 10 days after exposure.

70% of incident infections in the US are still among the $< 5\%$ of the male population who identify as MSM. This disproportion made MSM an operationally simple screening criterion in donor rooms². However, more sophisticated analysis of HIV infections over time demonstrates that self-identification as MSM functions as a

proxy for other behaviors that include multiple recent sexual partners, recent new partners, and condomless anal sex. A long history of advocacy, starting in the LGBTQ+ community, expanding to the international blood community, major medical associations, and legislators recognizes that risk is associated with behaviors, not gender or sexual preference. This is the scientific basis for permitting MSM at minimal risk of infection to donate while also addressing these behavioral risks in the general population³.

During debates about the MSM deferral, blood collectors and regulators (FDA in the US) have prioritized blood safety as the paramount goal. They require systems to generate valid, peer-reviewed, evidence to demonstrate that proposed changes do not compromise safety of the blood supply. FDA, HHS and the blood community have achieved this by implementing the Transfusion-Transmitted Infections Monitoring System (TTIMS), which collects test results and demographics for over 50%

of US blood collections. According to TTIMS estimates, the residual risk for HIV, HBV, and HCV in the US blood supply is estimated to be less than 1-2:1,000,000 after reducing the permanent MSM deferral to one year^{4,5}. Data from TTIMS regarding the MSM deferral reduction to three months are pending. However, the system will continue to be in place as the old deferral is replaced by the individual donor behavioral assessments recommended in FDA guidance⁶. Data from the UK and Canada, where HIV epidemiology is very similar to that in the US, suggest that replacing the MSM deferral with individual donor assessments not only maintains safety but also has the potential to increase the supply of safe blood⁶. It is worth noting that the observed rate of Transfusion-Transmitted Infections (TTIs) has significantly decreased, with the last TTI due to HIV in the US reported in 2008, despite tens of millions of blood components having been transfused since⁷.

II. THE PROCESS OF REGULATORY CHANGE

The Center for Biologics Evaluation and Research (CBER), operating through its Office of Blood Research and Review (OBRR) at FDA, is responsible for regulating biological products for human use, including human blood and blood components. To ensure effective engagement with the regulated community and the public, CBER/OBRR utilizes advisory committees and workshops. The agency develops policies by incorporating input from experts, the public and the regulated industry, particularly professionals specializing in donor management, HIV and infectious diseases and transfusion medicine. These valuable resources have been utilized extensively over several years to address the matter of the MSM deferral.

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III. BLOOD SAFETY

Blood collectors and regulators are dedicated to ensuring the utmost safety of blood products. Significant progress has been made in understanding and addressing TTIs leading to historically low levels of residual risk in the US. Improved testing techniques, particularly molecular assays, have played a crucial role in nearly eliminating the risk of HIV, HBV, and HCV, providing substantial safety margins as we consider revisions in donor screening policies. The test-negative window period when false negative screening can occur is now ≤10 days, making the FDA 3-month deferrals for targeted behaviors highly conservative.

UK, Australia, and Canada have seen no significant changes following subsequent incremental decreases in the MSM deferral⁸⁻¹¹. TTIMS data reveals that residual risks of HIV, HCV and HIV per million donations remained unchanged in the two non-overlapping 15-month periods after the 2015 deferral modification to one year⁴.

Extensive literature provides substantial evidence of associations between general HIV incidence and factors such as new and/or multiple sex partners and anal sex, regardless of donor sexual orientation. In the context of blood donors, the ENGAGE study demonstrated strong predictive values for injection drug use, having more than two anal sex partners, and engaging in new anal sex partnerships¹². These

findings align with those from the UK FAIR review⁴. The ADVANCE study (a preprint at this writing), supported by FDA, the Office of the Assistant Secretary for Health and the blood community, has identified a specific subgroup of low-risk HIV-negative MSM who can be identified through the use of questions outlined in the new guidance¹³. The donor assessment outlined in the new guidance applies to all donors, regardless of sex or gender⁶. The purpose of these questions is to identify donors who may be at risk for TTI by inquiring about new sex partners, multiple sex partners and anal sex three months preceding donation without considering gender or sexual orientation. The Blood DROPS study aimed to assess the motivating factors and level of compliance with deferral. Out of 3,185 donors surveyed, only 2.6% donated blood after engaging in male-male sex¹³. This study, along with others, indicates a low level of non-compliance with eligibility criteria, which is taken into account when estimating the current residual risk^{14,15}. Additional data from the ADVANCE study are forthcoming and will provide further insights.

It is important to note that the use of antiretroviral drugs in pre- and post-exposure prophylaxis (PrEP and PEP) can delay seroconversion and suppress viral nucleic acid levels below the detection limit of available tests, leading to potential false negative results. Recent evidence has shown that PrEP or PEP

can delay both molecular and serologic assay positivity resulting in false negative tests¹⁶. Donors who have taken these medications by mouth are deferred three months from their last dose, while those who have received the medication via injection are deferred for two years due to the prolonged persistence of parenteral prophylactic drugs.

IV. INDIVIDUAL RISK ASSESSMENT ALGORITHM

The guidance requires these actions to replace the current 3-month MSM deferral⁶.

1. Defer for 3 months from the most recent sexual contact, an individual who has had a new sexual partner in the past 3 months **and** who has had anal sex in the past 3 months.
2. Defer for 3 months from the most recent sexual contact, an individual who has had more than one sexual partner in the past 3 months **and** who has had anal sex in the past 3 months.
3. Defer for 3 months from the most recent dose, an individual who has taken any medication by mouth (oral) to prevent HIV infection (i.e., antiretroviral PrEP or PEP).
4. Defer for two years from the most recent injection, an individual who has received any medication by injection to prevent HIV infection (e.g., long-acting antiretroviral PrEP or PEP).

Questions concerning HIV diagnoses, therapeutic antiretrovirals, blood exposures, injection drug use, sexually transmitted bacterial infections and remunerated sex remain in the donor questionnaire. A deferred donor may be eligible to donate after the 3-month period provided they meet all other eligibility criteria.

WEIGHTED RESIDUAL RISK/DONATION FOR INFECTION IN ALL DONORS IN NON-OVERLAPPING POST-CHANGE 15-MONTH INTERVALS IN TTIMS⁴

	Pre-change to a one-year MSM deferral	Post-change interval 1	Post-change interval 2
HIV	1:1,151,127	1:1,337,943	1:1,606,972
HCV	1:2,019,521	1:1,387,247	1:1,980,534
HBV	1:1,162,271	1:1,022,267	1:989,841

V. CONTINUED HEMOVIGILANCE

Continuous surveillance efforts are necessary to track and document the longer-term impact on rates of HIV and other infectious disease markers, ensuring that they remain at low levels. Using TIMMS and other available methods, FDA will maintain surveillance of the safety of the blood supply following implementation of individual risk-based donor eligibility questions.^{4,6} By leveraging this large data set, blood establishments can proactively identify potential risks and take necessary measures to minimize TTI risks. Furthermore, the blood supply will be continuously monitored to assess the impact of changes in donor eligibility criteria. ■

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