

MTN-025 (HOPE) Operational Guidance #2: Additional Information on Residual Drug Results and Counseling

This document provides additional information on the interpretation of residual drug results at a participant and a site level. See also HOPE Operational Guidance document #1.

Using an algorithm based on ASPIRE data that adjusts for the actual or estimated length of time the participant had access to the ring, the residual drug levels are categorized into groups based on estimated use of the ring. Results are provided in 4 categories represented by a number on a scale: 0, 1, 2, 3; where “0” reflects probable low or no use/no HIV protection and “3” reflects probable high use/high HIV protection.

In HOPE, we are continuing to study the dapivirine ring. Thus, we cannot say yet with absolute certainty what level of drug release is necessary to achieve HIV protection. We know that the ring cannot provide protection if it is not used, and that protection is highest when used all the time. We also know the ring is not 100% effective. Information from ASPIRE indicates that when the ring is used most of the time, protection from HIV-1 infection could be 75% or higher, and when used all the time, protection could be over 90%. It is important to recognize that sometimes women may not use the ring all the time but still get good levels of protection, specifically if they use it when most at risk. For example – if they are not having sex during periods of ring non-use, but are using the ring consistently during times of the month when they do have sex, they will be reducing their risk of HIV-1 infection. As such, the residual drug feedback can be used to open a conversation about this with the participant, but counseling sessions should emphasize the importance of the participant’s reported experience and regard her as the most reliable source of this information.

Residual drug testing provides an *estimate* of ring use and is not 100% accurate. All quantitative laboratory tests have small levels of variability. The allowed variability for this specific test may result in misclassifying individual used rings – for example, a woman who used the ring the entire month may receive a value of a “2.” It is important to recognize this variability and uncertainty when providing individual ring residual drug results, and to counsel participants appropriately. Ultimately, only the participant knows how and when she used the ring throughout each month.

Importantly, when we consider multiple measurements over time (i.e. sequential rings for an individual participant) or residual drug results on average (i.e. at a site level)—the measurement error present on individual test results reduces, and our ability to interpret these results improves.

At a site level, sites should pay close attention to the number of rings in the “0” category, and aim to reduce this proportion by as much as possible over time.

- Based on results from ASPIRE and other studies of this ring, a result in the “0” category means that ring was used very little, or more likely not at all. Therefore, a high proportion of results in the “0” category may speak to many participants accepting a ring and then not using it, and a need for strengthening education and counseling about CHOICE, and how HOPE is different than ASPIRE. It is more beneficial to the study for a participant who does not intend to use the ring to feel free to decline taking it, than to feel pressure to accept a ring she will not or cannot use.
- Results in the categories of 1-3 indicate that drug was released from the ring. In ASPIRE, on average, higher levels of drug release were associated with higher levels of HIV protection. At a site level, the goal should be to shift the proportion of results falling into these categories “up the scale.”
- For an individual participant, Importantly, depending on how and when she used the ring, any of these results 1-3 could represent achieving adequate protection from HIV-1 based on her needs and circumstances.

Additional guidance on interpretation of each residual drug result at a participant level is provided below.

Participant Level Residual Drug Interpretation	
FOR ALL LEVELS	<ul style="list-style-type: none"> • The ring offers no protection if it is not used. Protection from HIV is highest when the ring is used all the time. • Residual drug level testing is not perfect. It should be recognized that individual results may reflect variability in the tests (in other words, it is possible for the participant to receive results that are not reflective of her actual use). <u>Remember, only the participant knows what her actual use of the ring was.</u> • Regardless of what the participant’s test results show, if she knows she used the ring consistently, especially during periods of potential exposure to HIV-1, then her protection from HIV-1 was likely high. • Consistent use of the ring throughout the month is best practice for reducing HIV-1 risk, as we don’t know how long after insertion of the ring it takes to achieve full protection, nor how long the drug remains after removal of the ring at levels that would provide protection.
Level 0	<ul style="list-style-type: none"> • Results indicate that very little to no drug was released from the ring. • Little or no drug release suggest little or no protection from the ring if the participant was sexually active throughout the month. • These results may reflect using the ring very little, or not at all. • Participants with several ring results in this category (i.e. more than one) should be counseled about choice and whether the ring is the best fit for her HIV prevention plan. • Participants should be aware that if they do not intend to use the ring, it is best not to take it—taking the ring without an intention or ability to use it provides no benefits to her, and can negatively impact the overall results of the study and the future of HIV-1 prevention work for women in Africa.
Level 1	<ul style="list-style-type: none"> • Results indicate that a little to some drug was released from the ring. • This level of drug release indicates some protection from the ring, but how much may depend on her sexual activity and when the ring was used. • These results may reflect low to moderate use, or that the ring was removed for some periods of time. • Challenges with ring use should be explored, but participant should also be reassured that if she knows she used the ring consistently when she was sexually active then her protection from HIV-1 was likely high.
Level 2	<ul style="list-style-type: none"> • Results indicate that some drug was released from the ring. • This level of drug release indicates some protection from the ring, but how much may depend on her sexual activity and when the ring was used. • These results likely reflect moderate to high use, or that the ring was removed occasionally. • Challenges with ring use should be explored, but participant should also be reassured that if she knows she used the ring consistently when she was sexually active, then her protection from HIV was likely high.
Level 3	<ul style="list-style-type: none"> • Results indicate that a high amount of drug was released from the ring. • These results also indicate good protection from the ring throughout the month. • These results likely reflect high use, or that the ring was use most of the time. • Participants should still be asked about her experiences and any challenges to ring use that she may have had and discuss plans to maintain success with her risk reduction plan.