Changes to baseline definition and Inclusion criteria in RESPOND:

Based on practical and analytical experiences from the preceding years of the RESPOND study, as well as changes made to HIV treatment guidelines since the initiation of RESPOND, changes to both the RESPOND baseline definition and eligibility criteria for inclusion. The inclusion criteria and baseline definition can be seen below.

The inclusion criteria as follows:

1. HIV-1 positive
2. Individuals ≥18 years of age at RESPOND_Baseline
3. Must have a CD4 count and HIV viral load measurement available within the 12 months before to RESPOND_Baseline or within three months after baseline
4. Have at least one clinical visit >1 January 2012
5. Individuals that have not started INSTIs before 1 January 2012,
6. Individuals that have not started INSTIs before inclusion in the local cohort

The RESPOND baseline definition as follows:

The latest date of starting an integrase inhibitor (INSTI), local cohort enrolment, or 1 January 2012.

- Inclusion criteria:

In accordance with the RESPOND Governance V 6.0, 2020, Individuals who initiated integrase strand transfer inhibitor (INSTI)-based antiretroviral treatment before local cohort enrolment were excluded. The criterion was formulated for safety reasons to ensure RESPOND prospectively captured all key data for individuals initiating INSTIs. However, since RESPOND was initiated in 2017, collecting data back to 2012, INSTIs has internationally become an integrated part of recommended 1st line and switch treatment for HIV.[1–3] Thus, continuing to only include INSTI-naïve individuals onwards into RESPOND may pose a risk of introducing selection bias. In addition, RESPOND now has considerable follow-up time with INSTI-exposed individuals.

Moreover, no INSTI-naïve individuals have ever been excluded based on prior exposure to other drugs. Therefore, removing the exclusion criterion related to INSTI exposure will ensure an equal comparison between antiretroviral classes within RESPOND. Following the same rationale, we suggest that INSTI exposure before 2012 is no longer considered an exclusion criterion.

Changing the inclusion criteria to disregard participants' INSTI status will further significantly ease the administrative processes for both the RESPOND secretariat and participating cohorts when including new participants.

To monitor any potential impact this change may have on future analyses, we further suggest that all coming analyses perform a sensitivity analysis, including only individuals who initiated/switched to any new ART during follow-up.

Collectively, the inclusion criteria for future enrolments would be:

1. HIV-1 positive
2. Individuals ≥18 years of age at RESPOND_Baseline (see below)
3. Must have a CD4 count and HIV viral load measurement available within the 12 months before RESPOND_Baseline or within three months after baseline
4. Have at least one clinical visit >1 January 2012

- RESPOND baseline definition:

Changes to baseline definition and Inclusion criteria in RESPOND:

After analyses of the RESPOND dataset, it became evident that a RESPOND baseline definition including INSTI initiation, could artificially increase the incidence rates of clinical events for those on INSTIs compared to those on non-INSTIs. In short, including INSTI start in the baseline definition, causes the baseline for those initiating INSTIs to be later compared to those initiating a non-INSTI, as the baseline for those starting a non-INSTI is not related to initiation of a specific ART-class, but rather defined as the latest of cohort enrolment and 2012, causing an unequal basis for comparison. This issue was previously described in *Analysis plan for RESPOND projects assessing clinical events and INSTI exposure, May 2021* (attached to email).

Therefore, as already used in all RESPOND analyses considering clinical outcomes to date, to formalise, that the date of INSTI initiation should not be part of the baseline definition. The default baseline should rather be defined as: The latest of local cohort enrolment or 1 January 2012 for all participants regardless of ART exposure.

However, the specific baseline for any individual analysis may vary depending on the type of analysis planned and which exact comparisons are intended, as assessed by the main statistician involved in the project with a rational provided in the statistical analysis plan.

e.g., The prior RESPOND baseline, including INSTI start, may be preferred to avoid immortal time bias when analysing mortality outcomes.

References:

1. Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society-USA Panel. *Jama*. 2023;329(1):63-84. doi:10.1001/jama.2022.22246
2. Waters L, Vice-chair AW. BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022. *HIV Med*. 2022;23(October):3-115. doi:10.1111/hiv.13446
3. EACS Guidelines version 11.1, October 2022. doi:10.1097/DCR.0000000000002594