HCV Response Nomenclature: *The Issues*

1. Endpoints: Level of HCV RNA detection utilized (LLOQ vs. LLOD) varies from study to study, and according to assay and viral genotype. This makes study to study comparisons difficult and confuses casual readers. A goal would be consistent reporting.

2. Categorizing treatment response: Terms utilized to define on-treatment response (e.g. RVR, cEVR, pEVR, eRVR, vRVR) are becoming cumbersome and confusing as new DAAs move through the system.

3. Categorization of prior treatment response: As DAAs enter the clinical arena, terms such as “nonresponse” and “relapse” will take on multiple meanings

HCV Response Nomenclature

- Endpoints: LLOQ vs. LLOD
  - Recommendation: report both values at each critical time period in future studies
    - *The current recommendation to require reporting of both LLOQ and LLOD is based on trying to address an urgent, short term need to provide guidance as the first DAAs potentially move from clinical research to clinical practice.*
    - *Assay improvements over time and the possibility of having LLOD approach LLOQ will obviate the need for reporting both values, allowing for more streamlined efficacy evaluation of virologic endpoints in clinical trials.*

HCV Response Nomenclature

- Categorizing treatment response: RVR, EVR, pEVR, cEVR,..
  - Recommendation: Create a standardized way of reporting viral response at each time period
    - Viremia Undetected @ week 4= **W4U**
    - Viremia Detected @ week 8= **W8D**
  - Further designation by cut-off LLOQ / LLOD:
    - Viremia Undetected @ week 4 by LLOD= **W4Ud** (old RVR)
    - Viremia Undetected @ week 8 by LLOQ= **W8Uq**
  - For most therapies, this will be sufficient, but
  - May add designation for lead-in response, e.g.:
    - Viremia undetected at week 8 by LLOD after lead-in: **W8Ud (b4)**

HCV Response Nomenclature

- Categorizing treatment response:
  - Viremia detected: VD Log decline from baseline:
    - Week 4 with one log decline (>1, but <2): **W4D [-1]**
    - Week 4 with less than one log decline: **W4D [<1]**
    - Week 12 with less than 2 log decline: **W12D [1]** *or* **W12D[<2]**
    - Week 8 with lead-in with 2 log decline: **W8D(b4)[-2]**

Factors considered:

1. Future critical time points may change to include “days”, so VR4 could mean both “RVR” or “day 4 VR”, etc., hence “W4” instead of “VR4”
2. Delineating LLOQ and LLOD increases complexity but improves utility
3. Incorporating the P/R lead-in further increases complexity
4. This is a “work in progress”……

HCV Response Nomenclature

- Categorization based upon previous treatment:

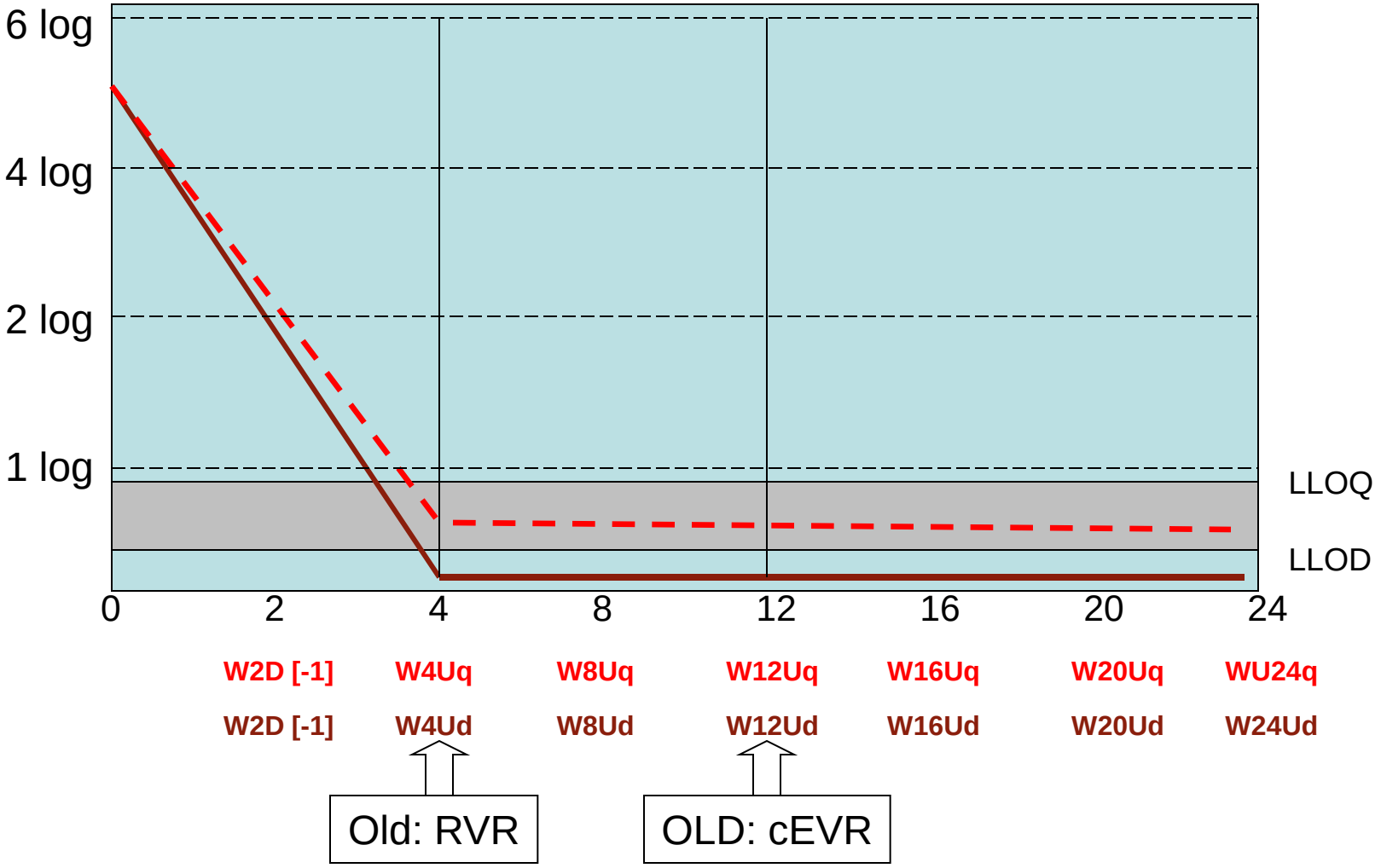
1) **Naïve**: Patients who have never been treated with any type of HCV medication.

2) **Treatment experienced**: Patients who received prior treatment(s) e.g. pegylated interferon and ribavirin; pegylated interferon, ribavirin and DAA, etc. and did not clear virus. These treatment(s) should be identified for each category of treatment experienced patients (e.g. PI-experienced patients).

   a) *Relapser: Patients in whom HCV RNA decreased and remained below the limit of detection during a prior treatment, but became detectable after end of treatment. The number of weeks a person was treated should be specified.*

   b) *Breakthrough: Patients in whom HCV RNA decreased during prior treatment and remained below the limit of detection, but rebounded and became detectable before treatment completion.*

Scenario 1a
Without lead-in



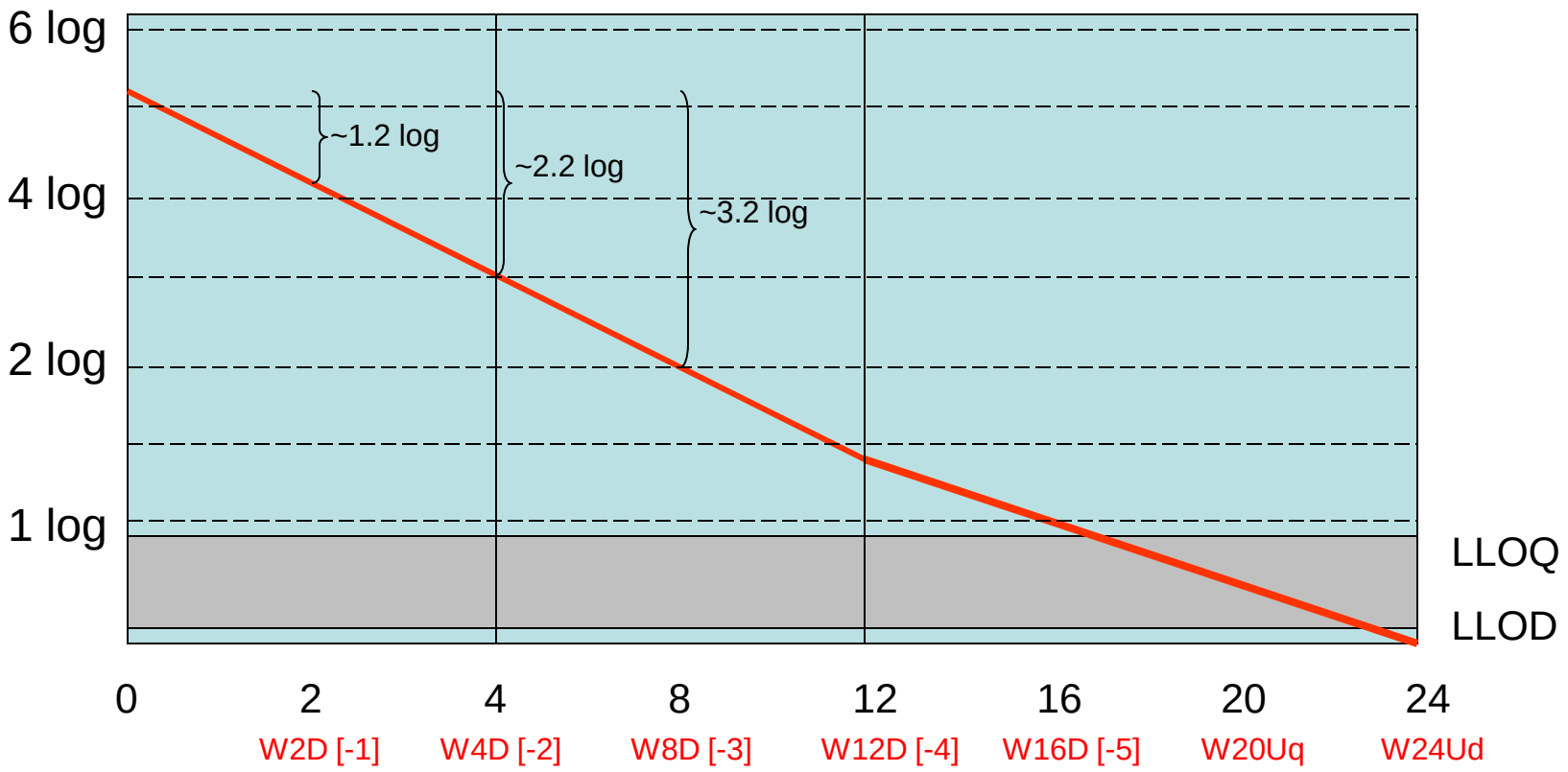
Scenario 1b
With lead-in

W2D(b0)[-1] W4D (b0)[-2] W8Uq [b4] W12Uq [b8] W16Uq [b12] W20Uq [b16] W24Uq [b20]

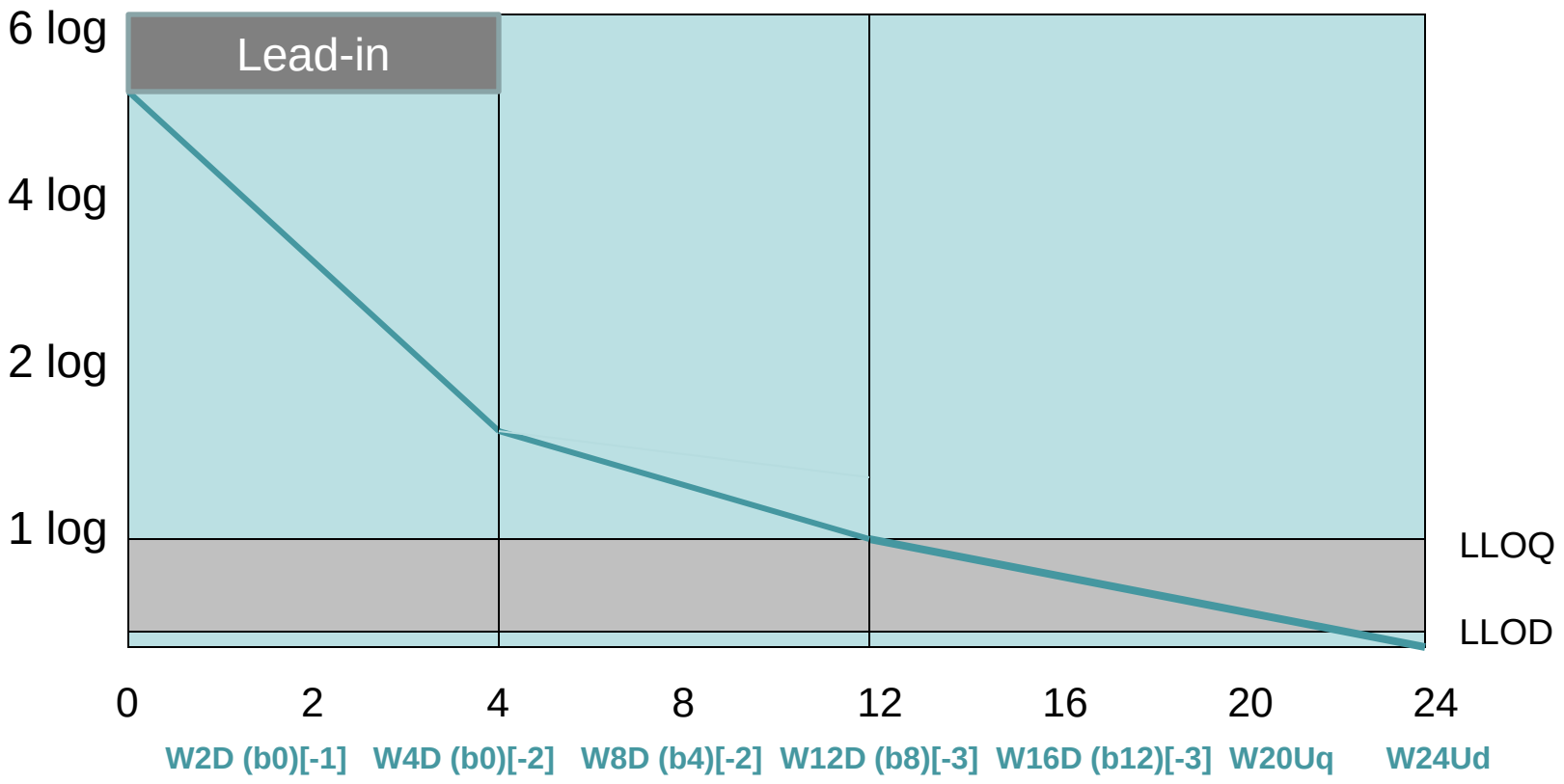
W2D (b0)[-1] W4D (b0)[-2] W8Ud [b4] W12Ud [b8] W16Ud [b12] W20Ud [b16] W24Ud [b20]

Old: RVR

Scenario 2a: Without lead-in



Scenario 2b: With lead-in



Scenario 3:
With or Without lead-in