Introductory Summary of Ragon Meeting ATI Recommendations and Examples of ART Restart Criteria

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Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting

- Published in The Lancet HIV, March 15, 2019. Meeting took place at the Ragon Institute of MGH, MIT and Harvard on July 9, 2018.
- https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(19)30052-9/fulltext (free with registration)
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6688772/ (open access via PMC, available April 1, 2020)

Recommendations for analytical antiretroviral treatment interruptions in HIV research trials—report of a consensus meeting

- **Inclusion criteria**
  - Stable CD4 counts ≥500 cells per μL*
  - HIV RNA undetectable on stable ART†
  - Otherwise healthy individuals without major comorbidities
    - ***Baseline CD4 counts of ≥350 cells per μL might be considered.**
    - †Based on FDA-approved HIV RNA quantification assay.

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- **Key exclusion criteria**
  - Active or chronic hepatitis B virus infection, with detectable hepatitis B surface antigen, hepatitis B virus DNA, or both
  - Active hepatitis C virus infection, with detectable virus RNA
  - Active Mycobacterium tuberculous infection
  - History of systemic cancers, such as Kaposi's sarcoma and lymphoma, or other virus-associated malignancies
  - History of HIV-associated dementia or progressive multifocal leukoencephalopathy
  - Resistance to two or more classes of antiretroviral drugs
  - History of cardiovascular event or at high risk of an event (eg, atherosclerotic cardiovascular disease score >15%)

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- **Key exclusion criteria**
  - History of AIDS-defining illness according to CDC criteria **(time dependent?)**
  - **History of CD4 nadir <200 cells per µL during chronic stages of infection (some favored <350, some suggested a nadir <200 might be acceptable if a long time in the past)**
  - Women who are pregnant or breastfeeding
  - Advanced non-alcoholic fatty liver and advanced nonalcoholic steatohepatitis
  - HIV-related kidney disease or moderate-to-severe decrease in estimated glomerular filtration rate
  - Children younger than 2 years of age when the ATI is planned

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- **Monitoring**
  - HIV RNA monitoring weekly for 12 weeks, then every other week
  - CD4 count monitoring every two weeks
  - Monitoring of clinical symptoms, in particular in people who started ART during the hyperacute HIV phase
  - Monitoring of participants' psychosocial experiences

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- **ART restart criteria**
  - If requested by the participant or their HIV health-care provider
  - If participant becomes pregnant
  - If ART is deemed medically necessary for non-HIV related causes
  - Symptomatic HIV disease
  - Confirmed absolute CD4 value <350 cells per μL or CD4% <15%
  - **HIV RNA ≥1000 copies per mL for 4 weeks**
  - **Absolute HIV RNA >100,000 copies per mL***
    - *** "There was a general consensus that anyone who reaches confirmed HIV RNA of more than 100,000 copies in time-to-rebound studies should restart ART immediately, regardless of duration. If the endpoint, however, is viral setpoint, high viral peaks, even of more than 100,000 copies, might need to be tolerated for several weeks."**

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- **Reducing risk of HIV transmission to sexual partners**
  - Offer pre-exposure prophylaxis and HIV testing referral information that trial participants can provide to their sexual partners

Examples of ART restart criteria in current or recent trials

- Two viral loads (VL) >50 or stage B or C AIDS-defining events or any serious non-AIDS clinical event at least potentially related to ATI
- Two VL >200 and/or CD4 T cell count <350
- Two VL >400, CD4 <400, HIV-related clinical event
- Two VL >1000 at least 1 week apart, two CD4 <350 at least 2 weeks apart, CD4 decline >50%, CDC B, C progression, pregnancy, acute retroviral syndrome (ARS)
- Sustained VL >1000, >30% decline in CD4 or count <350, HIV-related symptoms

Examples of ART restart criteria in current or recent trials

- Two VL >1000, single VL >10,000, VL rise ≥0.5 log10copies/mL/day, CD4 <350 or decline >50%, CDC B, C progression, pregnancy, ARS
- VL >50,000 for ≥4 weeks, >30% decline in CD4 or count <350, ARS
- Two VL >75,000 at least one month apart or CD4 <350 or HIV-related symptoms
- VL ≥100,000, CD4 ≤350, evidence of disease progression
- Sustained VL >100,000 or CD4 <350 or less than 50% of baseline