Low-Level Viremia

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Case

A 60-year-old man with HIV (last CD4 478 cells/mm^3, HIV RNA 80 copies/mL) and multiple medical problems is seen for routine follow-up. He has been taking TAF/FTC + DTG + MVC + r/DRV BID since 2016.

- Most Recent Genotype
  - NRTI: M184V, M41L, T215Y
  - NNRTI: K103N, Y181C, H221Y
  - PI: I84V
  - INSTI: none

M184V – resistance to ABC, 3TC, and FTC
M41L, T215Y (TAMs) – resistance to ABC and Tenofovir
K103N – resistance to EFV and NVP
Y181C – resistance to EFV, NVP, ETR, and RPV
H221Y – some resistance to all NNRTIs
I84V – low-level resistance to DRV

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Adherence ROS

Dosing	When was the last time you missed a dose? In the past week/month, how many doses did you miss?
Logistical	What is your system for taking pills/how do you take your ART? Do you take it with food? Do you take all the pills together?
DDI	Beyond your medication list, what OTC meds do you take? Do you take any vitamins or supplements?
Existential	How do you feel about your ART? What issues or annoyances do you have with your ART?

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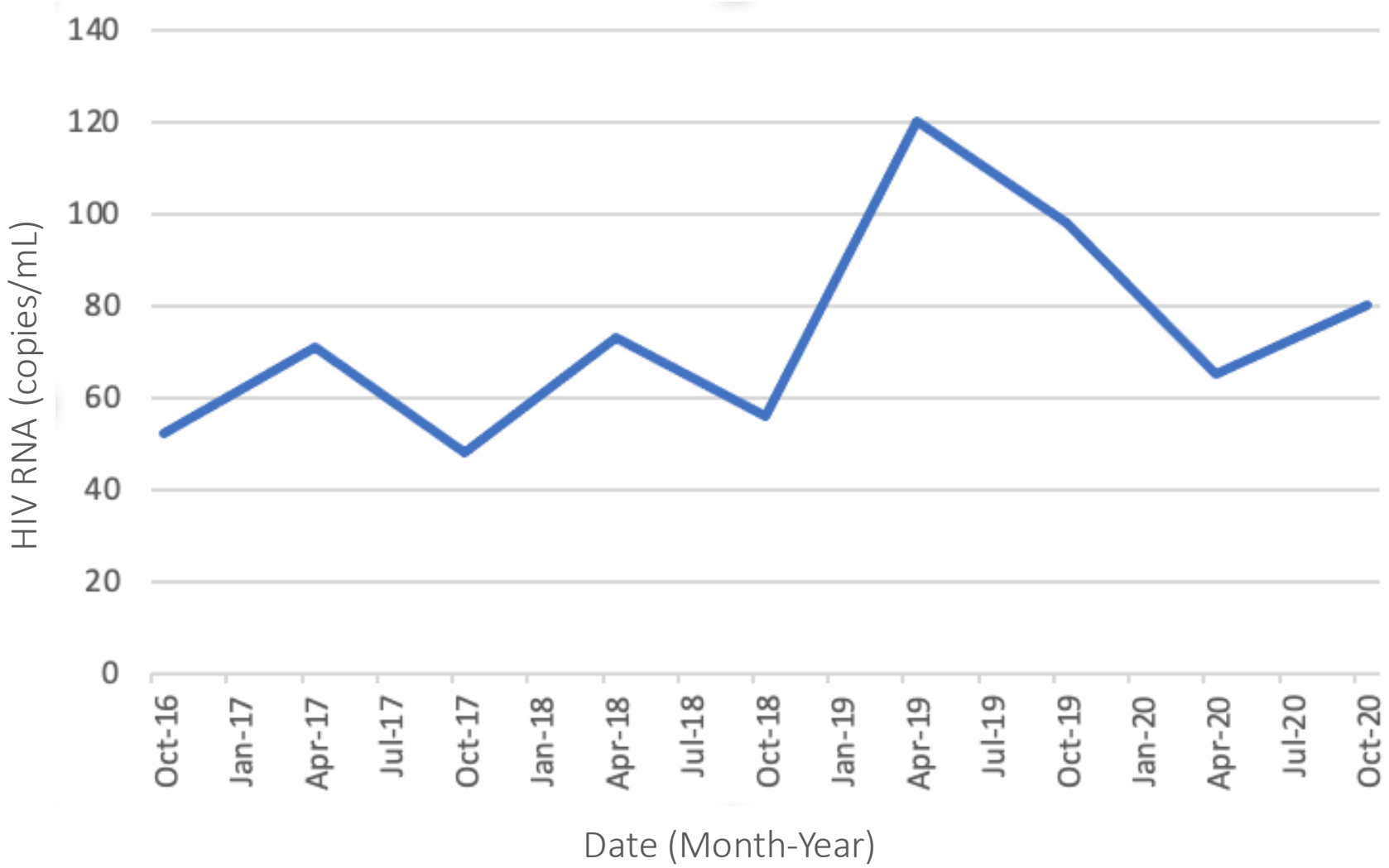
Case: HIV RNA Levels



ARS

What would you do with his ART in the setting of his low-level viremia?

A. Continue current regimen (TAF/FTC + DTG + MVC + r/DRV BID)

B. Add fostemsavir

C. Double the dolutegravir dose

D. Add doravirine

Terms Related to Virologic Response

Incomplete Virologic Response	Failure to suppress HIV RNA to undetectable after 24 weeks of an ARV regimen
Virologic Blip	After achieving virologic suppression, a single detectable HIV RNA level (usually < 200 copies/mL), followed by a return to suppression
Virologic Rebound	Confirmed HIV RNA level ≥ 200 copies/mL after achieving virologic suppression on ART
Low-Level Viremia	Persistent HIV RNA levels above the level of detection for the assay but often < 200 copies/mL (i.e. usually 50-199 copies/mL)

Low-Level Viremia

- Possible etiologies include suboptimal adherence, drug interactions, drug-food interactions, early virologic failure, or none of the above

- Low-level viremia (LLV) is rare
  - In a cohort of 1485 PWH from Taiwan switched to DTG or BIC, between 2016 and 2021, incidence ranged from 1.2-1.7%[1]

- Persistent low-level viremia in the setting of excellent adherence to a potent ARV regimen is felt to be due to replication-incompetent HIV being released from a latent reservoir or persistent replication

1-Chen GJ, Int J Antimicrob Agents, 2022.

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Data about Low-Level Viremia is Mostly Conflicting

- LLV and mortality
  - Some data show no association between LLV and increased mortality[1]
  - LLV was associated with increased mortality (aHR 2.2, CI 1.3-3.8)[2]

- LLV and virologic failure
  - LLV was associated with virologic failure (aHR 1.83, CI 1.1-3.04)[3]
  - In Taiwan cohort, no increased risk of virologic failure in those with LLV while on DTG or BIC[4]
  - In European cohort, LLV was associated with virologic failure (aHR 2.2, CI 1.6-3.0)[5]
    - In a sub-analysis of those on INSTI-based initial regimen, LLV was not associated with virologic failure (aHR 1.0, CI 0.2-4.3)

1-Ryscavage P, AAC, 2014. 2-Elvstam O, CID, 2020. 3-Fleming J, AIDS, 2019. 4-Chen GJ, Int J Antimicrob Agents, 2022. 5-Elvstam O, CID, 2022.

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Low-Level Viremia and its Impact on Drug Resistance?

- In the European cohort (Elvstam O et al.), mutations are commented upon, however, this is in reference to those with HIV RNA 200-999 copies/mL[1]
- In a Chilean cohort of 16 PWH on INSTI-based regimens with HIV RNA 22-175 copies/mL with analysis of proviral DNA, while some RAMs were found on proviral DNA, no baseline genotypic data was available, thus unclear if these were transmitted or new RAMs[2]

Most studies have shown a low risk of virologic resistance in persons with persistently detectable HIV RNA levels < 200 copies/mL

1-Elvstam O, CID, 2022. 2-Villalobos C, J Clin Virol, 2020.

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Undetectable = Untransmittable (U=U)

- An individual with an undetectable HIV VL cannot transmit HIV to their sexual partners

STUDY	FINDINGS	HIV RNA (copies/mL)
HPTN-052	96% reduction in infections among heterosexual couples when the partner with HIV started ART[1]	<400
PARTNER-1	Of 58K condomless sex acts in 888 serodiscordant couples (40% MSM), no new HIV infections phylogenetically linked[2]	<200
PARTNER-2	972 serodiscordant coupled MSM had 76,088 acts of condomless anal sex, no HIV infections phylogenetically linked within couples[3]	<200

1-Cohen NEJM 2016, 2-Rodger JAMA 2016, 3-Rodger Lancet 2019

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Guideline Recommendations Regarding-Low Level Viremia

DHHS Guidelines

Patients with low-level viremia do not typically require a change in treatment (AII). Although there is no consensus on how to manage these patients, the risk that drug resistance will emerge is believed to be relatively low. Therefore, these patients should continue their current regimens and have HIV RNA checked every 3 months. (AIII)

IAS-USA Guidelines

For patients with intermittent or persistent low-level viremia between 50 - 200 copies/mL, assessments for ART adherence, tolerability, and toxic effects are recommended (CI), but changing ART regimens is not recommended unless ART toxicity or intolerability are identified (AIII).

1-DHHS ART Guidelines, Accessed January 2023. 2-Gandhi RT, JAMA, 2022.

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Additional Comments on Management of Low-Level Viremia

- Do not double the dose of a medication or add another medication[1].
- Do not stop ART.
- Assess adherence, ask exactly how the patient takes medications, and assess drug interactions, food requirements, and absorption.
- If on an ART regimen with a low-barrier to resistance, update ART. Otherwise, changing or intensifying ART is not recommended.
- Can consider obtaining DRV level.

1-Gandhi RT, PLOS Medicine, 2010.

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Low Level Viremia: Key Points

1. Low-level viremia is defined as persistent HIV RNA levels above the level of detection for the assay but below 200 copies/mL.
2. Assess adherence, ask how the patient takes medications, and assess drug interactions, food requirements, and absorption.
3. LLV may or may not increase risk of virologic failure and/or mortality.
4. If on an ART regimen with a low barrier to resistance, update ART. Otherwise, changing or intensifying ART is not recommended.

Dr. Paul Sax writes, "regardless, the absolute risk [of failure] is still quite low, especially if adherence is good. And [patients] do not appear to be slowly developing resistance to their regimens."[1]

1-Sax P, NEJM Journal Watch, 2017.

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