Leah Canellakis, Molly Isaac, Kathryn Masetti

Student Case Study #2: Helping Harold with HAART
BC362, Medical Biochemistry

Case Background:

Harold, a 28-year-old man from New York City, went to the doctor complaining of flu-like symptoms, including fever, night sweats, fatigue, swollen lymph nodes, and significant weight loss. He admitted to inconsistent condom use, and his ex-partner recently informed him of their positive HIV status. A rapid HIV antibody test for Harold returned positive.

To further assess his condition, the doctor ordered several lab tests, including a Complete Blood Count (CBC), a viral load test, CD4+ T-cell count, hemoglobin (Hb), and platelet count. Based on these results, Harold was diagnosed with HIV (Human Immunodeficiency Virus), and the doctor determined that the most effective treatment would be HAART (Highly Active Antiretroviral Therapy), a combination of three drugs that inhibit key enzymes essential for HIV replication.

Clinical Findings:

Table 1. Lab test results for Harold upon admission and after three months of treatment with HAART.

	Upon admission	**After Treatment (3 months later)**	**Normal Values**
White Blood Cells	3500 cells/μL	5000 cells/μL	4500-11,000 cells/μL
CD4+ T-cells	300 cells/mm^3	550 cells/mm^3	500-1500 cells/mm^3
Hemoglobin (Hb)	12.1 g/dL	13.1 g/dL	13.5-16.5 g/dL
Platelets	100,000 cells/μL	200,000 cells/μL	150,000-450,000 cells/μL
Viral Load (VL)	100,000 copies/mL	<50 copies/mL	0 copies/mL (undetectable)

Vocabulary:

CD4+ T cells, Viral Load, HAART, Integrase Inhibitor (INSTIs), NRTIs/NNRTIs, PIs

Biochemistry:

HIV (Human Immunodeficiency Virus) is a retrovirus that primarily targets CD4+ T lymphocytes, leading to progressive immune suppression. Without treatment, HIV can advance to AIDs (Acquired Immunodeficiency Syndrome). HIV relies on three crucial enzymes for replication and production of new viral particles: reverse transcriptase, integrase, and protease. **Reverse transcriptase** converts the virus's RNA into DNA, and **integrase** inserts this viral DNA into the host cell's genome. After the viral genetic material is replicated, producing large polyprotein precursors, **protease** cleaves these polyproteins into smaller, functional viral proteins, which then combine with viral RNA to form new infectious virus particles.

HAART (Highly Active Antiretroviral Therapy) is a combination therapy that targets these enzymes at multiple points in the viral life cycle. **Reverse Transcriptase Inhibitors (RTIs)** block the reverse transcriptase enzyme from producing viral DNA and include two types: Nucleoside/Nucleotide RTIs (NRTIs) and Non-Nucleoside RTIs (NNRTIs). NRTIs act as fake building blocks (nucleosides) that are inserted into viral DNA, causing chain termination and preventing the virus from completing DNA synthesis. NNRTIs bind directly to reverse transcriptase and block its ability to convert viral RNA to DNA. **Protease Inhibitors (PIs)** prevent the protease enzyme from cleaving the polyproteins, stopping proper viral assembly and maturation, which results in non-infectious viral particles. **Integrase Strand Transfer Inhibitors (INSTIs)** block integrase, preventing viral DNA from integrating into the host DNA and stopping the production of new virus particles.

Analysis:

1) **Why is HAART administered as a combination therapy rather than a single drug?**
    - Consider where in the HIV life cycle each drug acts.

2) **What is notable about Harold's lab results?**
    - What does his initial CD4+ count indicate about his immune system?
    - How does the observed decrease in viral load relate to the recovery of CD4+ T cell count and overall health?

3) The **HIV protease inhibitor** works by binding to the active site of the protease enzyme.
    - What type of inhibition is this (competitive, uncompetitive, or non-competitive)?
    - Based on the Lineweaver-Burk plots below, which one best represents the mechanism of the protease inhibitor, and why?

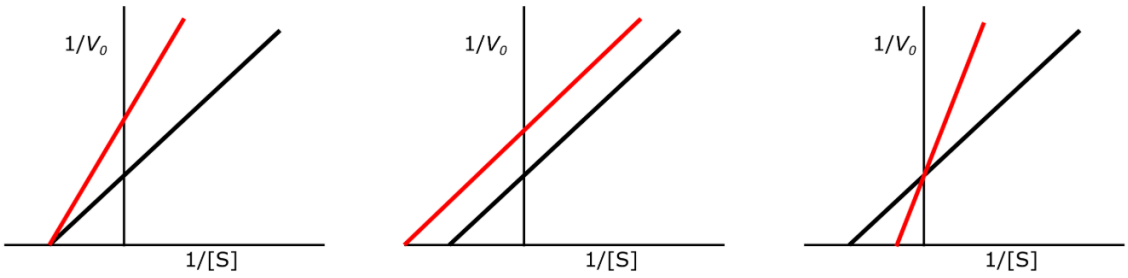

Figure 1: Example Lineweaver-Burk plots showing competitive, uncompetitive, and non-competitive enzyme inhibition, both with and without inhibitor.

References:

1. "Protease Inhibitors (HIV)." *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]*., U.S. National Library of Medicine, 1 Sept. 2017, www.ncbi.nlm.nih.gov/books/NBK548893/.
2. "Getting Tested for HIV." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, www.cdc.gov/hiv/testing/index.html#:~:text=Antibody%20tests%20can%20usually%20detect,to%2033%20days%20after%20exposure.
3. *Laboratory Testing for Initial Assessment and Monitoring of People with HIV | NIH*, clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/tests-initial-assessment-follow-up.
4. "HIV Replication Cycle." *National Institute of Allergy and Infectious Diseases*, U.S. Department of Health and Human Services, www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle.
5. *Khan Academy*, Khan Academy, www.khanacademy.org/test-prep/mcat/biomolecules/enzyme-kinetics/a/enzyme-inhibition-and-kinetics-graphs. Accessed 7 Oct. 2025.

Leah Canellakis, Molly Isaac, Kathryn Masetti

Answer Key

Vocabulary:

- **CD4+ T cells**: A type of white blood cell targeted by HIV.
- **Viral Load**: The amount of HIV RNA in the blood; used to monitor treatment success.
- **HAART**: Combination therapy that targets multiple stages of the HIV life cycle.
- **Integrase Inhibitor**: A drug that blocks integration of viral DNA into the host genome.
- **NRTIs/NNRTIs**: Nucleoside/non-nucleoside reverse transcriptase inhibitors.
- **PIs**: Protease inhibitors that block HIV protease.

Analysis:

1) HAART is administered as a combination of drugs because a single drug may not be sufficient to stop the virus from replicating. The combination of the three makes it more likely to be successful. HIV can quickly develop mutations, making it resistant to one drug, but it is less likely to become resistant to all three drugs at once. By targeting different stages of the HIV life cycle, the combination therapy increases the chances of successfully suppressing the virus.

2) Harold's initial CD4+ T cell count is very low, indicating that his immune system is compromised. A decrease in viral load means there are fewer HIV particles to target the CD4+ T cells, allowing their numbers to recover to a normal level. The increase in CD4+ T cells is associated with improved immune function and overall health for Harold.

3) HIV protease inhibitors are competitive because they bind to the active site of the enzyme. In this type of inhibition, the y-intercept (1/Vmax) remains the same as the uninhibited reaction, while the x-intercept (-1/Km) shifts closer to zero, reflecting the enzyme's decrease in affinity for the substrate. Protease inhibitors block HIV protease from cleaving large viral polyproteins, preventing proper viral assembly. Most HIV protease inhibitors are selective, reversible, and competitive, effectively reducing the production of infectious virus particles.
    - **Disclaimer**: The answer above stating that the HIV protease inhibitor acts as a competitive inhibitor relies on knowing that the inhibitor is reversible. An irreversible inhibitor, like a "Trojan horse," could also bind at the active site.