GENERAL HIV MANAGEMENT

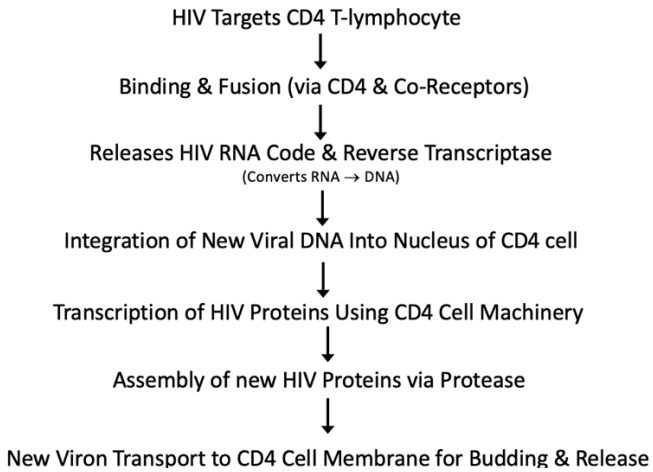
Background

- Human Immunodeficiency Virus (HIV) continues to be a global health issue that has claimed the lives of approximately 40 million people.
- In 2022, an estimated 39 million people were living with HIV.
  - Although there is still no cure, antiretroviral therapy (ART) for the treatment of HIV has continued to improve since the start of combination therapy in 1996 and has made HIV a manageable comorbidity with a life expectancy similar to those without HIV.
  - HIV attacks the body's immune system by targeting white blood cells, which weakens the immune system and makes patients more prone to illness.

Pathophysiology

- HIV is a single-stranded RNA (ssRNA) retrovirus that attaches to and enters host CD4+ lymphocytes, where it uses reverse transcription to form DNA (from ssRNA).
- This newly formed DNA then migrates to the host cell nucleus and integrates into the chromosome.
- Viral proteins and DNA are subsequently packaged by viral proteases into a budding virion, where a mature virus is formed and able to infect other cells.
- As the virus replicates using CD4 lymphocytes, the available circulating concentration falls at an accelerating rate as it approaches an absolute value of 200 cells/mm^3.
- Acquired Immune Deficiency Syndrome (AIDS) occurs when the CD4 count falls below 200 cells/mm^3 or an AIDS-defining illness is diagnosed.

HIV Life Cycle



Risk Factors

- Blood transfusion
- Needle-sharing during injection drug use or from a needle-stick
- Sexual intercourse, with receptive anal intercourse having the highest risk
- Infants during pregnancy, delivery, or breastfeeding with an untreated mother

Clinical Presentation

- Patients with HIV progress through 3 main clinical stages and may present in any one of these. (See Table 1)
  - If patients are not identified or go untreated, the infection will progress to the next stage and eventually lead to other opportunistic infections and/or death.

- **Note:** The stages listed below are not the same as the Fiebig Laboratory Stages for HIV-1 infection, which is a stage classification based on the number of days after infection and when various laboratory tests reflect positive results consistent with early infection.

Table 1.

MAIN CLINICAL STAGES OF HIV INFECTION High-Yield Med Reviews	
Stage	**Description**
Acute Infection	▪ First 2-4 weeks after HIV infection ▪ Flu-like symptoms (fever, lymphadenopathy, headache, sore throat, rash (pruritic papular eruption), fatigue, and muscle aches) ▪ Large amounts of viral production
Clinical Latency	▪ HIV is reproducing at lower levels but is active. ▪ Duration of approximately 10 years without treatment – Decades with treatment
Acquired Immunodeficiency Syndrome (AIDS)	▪ Usually have CD4 counts < 200 ▪ Survival of approximately 3 years without treatment ▪ Increased risk of opportunistic infections and some cancers

- The initial presentation of HIV may be with one of the numerous AIDS-defining illnesses, including *Pneumocystis jiroveci* pneumonia, esophageal candidiasis, extrapulmonary cryptococcus, cytomegalovirus (CMV) retinitis, herpes simplex virus (HSV) esophagitis or chronic ulcers, Kaposi sarcoma, lymphoma, toxoplasmosis, microsporidiosis, Mycobacterium avium complex infection, HIV-related encephalopathy, Salmonella bacteremia, pulmonary tuberculosis (TB) or disseminated TB.

Primary Work-Up & Evaluation

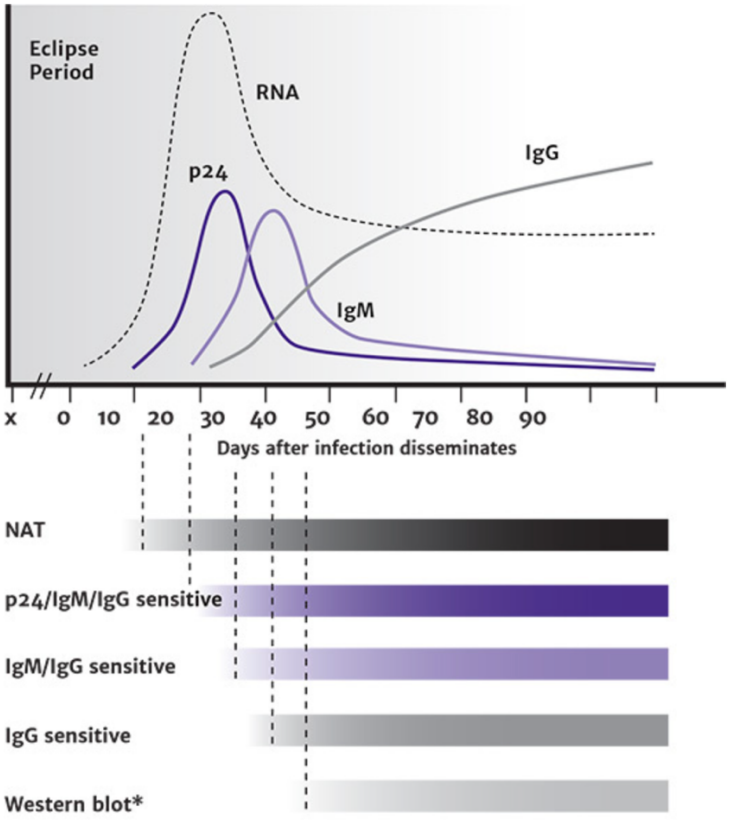
- Vital Signs: Temp (for new infections), BP, weight, height, and/or BMI as some medications can cause weight gain
- Labs:
  - Everyone between the ages of 13 to 64 should get tested for HIV at least once and more often if they engage in certain risks (consider risk factors).
  - HIV-specific labs: HIV antigen/antibody testing, genotypic resistance testing, HIV viral load, CD4 cell count and %
    - Viral load and CD4 demonstrate an inverse relationship and assist in monitoring HIV infection and ART response.
      - High viral load with low CD4 count: greater potential for virus transmission and HIV-related illness
      - Low or undetectable viral load with high CD4 count: lower potential for virus transmission and HIV-related illness
  - Other labs: complete blood count (CBC) with differential, comprehensive metabolic panel (CMP), urinalysis (UA), blood glucose, A1c, lipid profile
    - CBC with differential can identify potential opportunistic infections and adverse effects of treatment (need baseline) and give information about current disease.
    - A1c and lipids should be monitored because ART can potentially exacerbate diabetes and dyslipidemia.
    - UA can identify potential complications from therapy, as well as the CMP.
  - Screening for coinfections: gonorrhea, toxoplasma IgG, chlamydia, trichomoniasis, syphilis, TB, and hepatitis serologies (A, B, and C), varicella virus serology, and measles titer
    - STDs are common co-infections due to concomitant risky behaviors.
    - Varicella and measles titers are needed to determine immunity.
  - Medication specific: HLA-B*5701 (for abacavir use), viral tropism (for CCR5 antagonist), glucose-6-phosphate dehydrogenase (i.e., dapsone)

- Other:
  - Pap smear and pregnancy test for women
    - Assess pregnancy status to determine therapy and potential risk for the infant.
    - Pap smear may identify co-infection.

Diagnostic Criteria

- The laboratory tests that confirm the diagnosis can be influenced by the from actual infection within the eclipse period. The classic distribution of biomarkers has been classically outlined by the CDC (Figure 1).
- **Step 1:**
  - HIV antigen/antibody combination immunoassay
    - Known as a 4th generation test that detects HIV sooner
    - Detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen.
- **Step 2:**
  - If Step 1 is positive, differentiate between HIV-1 and HIV-2 using an HIV-1/HIV-2 antibody differentiation immunoassay
    - If there is a non-reactive or indeterminant result, an HIV-1 Nucleic Acid Amplification Test (NAT) test should be performed (HIV viral load test).
    - If Step 2 is positive or the NAT result is positive, then the diagnosis of HIV is confirmed.
- Other:
  - HIV self-tests are now available but should be confirmed using the above-mentioned steps.

Figure 1.



* Western blot is no longer used for HIV.

Primary Treatments (1st Line)

- **Primary Treatment Goals**
  - Suppress plasma HIV RNA (a.k.a., the "an undetectable viral load")
    - Undetectable within the first 12-24 weeks
  - Restore and maintain immunologic function
  - Decrease HIV-associated morbidity and mortality
  - Prolong the duration and quality of survival
  - Prevent HIV transmission
    - N Engl J Med. 2001;365(6):493-505.

Accelerate Your Knowledge

- ✓ *Treatment of choice for HIV typically contains an INSTI and 2 NRTIs, with bictegravir/emtricitabine/tenofovir alafenamide (AF) being the most common.*
- ✓ *Most patients without HIV resistance can take 1 tablet a day.*
- ✓ *Life expectancy can be similar to patients without HIV, assuming medication compliance and follow-up.*

- **Pharmacologic Treatments**
  - All patients diagnosed with HIV should be offered ART due to the clinical benefits, even in patients with baseline CD4 cell counts > 500 cells/mm^3.
  - The ART regimen chosen initially and over time is not only influenced by the guidelines but should also consider several patient-specific factors when choosing a regimen that aligns with the predictors of success to achieve viral suppression or HIV RNA undetectable levels.
    - Factors given consideration when choosing an ART regimen (not limited to these)
      - Patient's known drug-related allergies
      - Patient's HIV genotype
      - Presence of patient-specific genetic polymorphism (e.g., HLA-B*5701 if using abacavir)
      - Presence of other comorbidities (e.g., hepatitis B & C, diabetes, dyslipidemia, CKD)
      - Pregnancy status
      - Risk for medication side effects and/or drug interactions
      - Pill burden of the regimen in the context of all the patient's medications
      - Socioeconomic status and/or access to healthcare resources
  - **Basic Backbone of an ART Regimen:**
    - Viral suppression with ART to goals typically includes a total of 3 active medications from two or more drug classes (Table 2).

Table 2.

ANTIRETROVIRAL DRUG CLASSES IN HIV High-Yield Med Reviews	
Primary Drug Classes	**Main Agents**
NNRTI	Doravirine, efavirenz, etravirine, nevirapine, rilpivirine
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)	Abacavir, emtricitabine, lamivudine, tenofovir alafenamide, tenofovir disoproxil fumarate, zidovudine
Protease Inhibitor (PI) **+/-** **Boosting Agents**	Atazanavir, darunavir, fosamprenavir, nelfinavir, tipranavir, lopinavir (only available in combination with ritonavir) Always administered with a PI Cobicistat, ritonavir (also considered a PI but at higher doses)
INSTIs	Bictegravir (not available as single tablet), cabotegravir (tablet and IM), dolutegravir, elvitegravir (always boosted with cobicistat, not available as single tablet), raltegravir
Adjuvant Drug Class	**Main Agents Added to Primary ART Regimens**
Entry Inhibitors	Ibalizumab (IV), fostemsavir, maraviroc, enfuvirtide (SUBQ)
Capsid Inhibitor	Lenacapavir

- Note: Two of the 3 active drugs in the high-potency ART regimen represent nucleoside reverse transcriptase inhibitors (NRTIs).
  - The 3rd agent represents one of the other drug classes and should never be another NRTI (i.e., an all-NRTI regimen is never recommended).
    - If the 3rd agent is a PI, it is usually with another agent (e.g., cobicistat or ritonavir) to create a desired drug interaction to pharmacologically "boost" the concentrations of the PI.
      - Regimens with this combination are referred to as "Boosted PI" regimens.
  - Numerous single-tablet ART regimens are now available.
  - There is some data to support the use of a 2-drug regimen with dolutegravir + lamivudine, but it is less common (Table 3).

- **First-line Initial Regimens (INSTI-based regimens are preferred in most cases):**
  - Long-acting cabotegravir (CAB-LA) for pre-exposure prophylaxis (PrEP) can remain in the body for up to 4 years, and INSTI resistance can occur, so the initial ART regimens should consider this (Table 3).

Table 3.

INITIAL ANTIRETROVIRAL REGIMENS FOR HIV INFECTION **High-Yield Med Reviews**	
***NO* Prior Use of Long-Acting Cabotegravir (CAB-LA) for Pre-Exposure Prophylaxis (PrEP)**	
Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)	▪ 1 tablet regimen dosed once daily
Abacavir/dolutegravir/lamivudine (Triumeq)	▪ 1 tablet regimen dosed once daily ▪ Avoid in known or unknown hepatitis B infection ▪ Only used in HLA-B*5701 negative patients
Dolutegravir (Tivicay) + (Emtricitabine + tenofovir alafenamide (Descovy)) **Dolutegravir (Tivicay) + (Emtricitabine + tenofovir disoproxil fumarate (Truvada))** **Dolutegravir (Tivicay) + (Lamivudine + tenofovir disoproxil fumarate (Cimduo))**	▪ 2 tablets dosed once daily ▪ Note exception: Dolutegravir may sometimes require twice daily dosing due to drug interactions or INSTI-resistance. ▪ Emtricitabine + tenofovir alafenamide (Descovy) tends to be more common.
Dolutegravir/lamivudine (Dovato)	▪ Avoid in patients with HIV RNA > 500,000 copies/mL, HBV coinfection, or when ART is used before HIV genotypic testing is available.
Known or Suspected Prior Use of CAB-LA for PrEP	
Boosted darunavir + tenofovir alafenamide (AF) or disoproxil fumarate (DF) + lamivudine	▪ This regimen is recommended if started prior to INSTI genotypic resistance testing has resulted.

- **Special Considerations:**
  - Tenofovir comes in two formulations, alafenamide (AF) and disoproxil fumarate (DF).
  - Emtricitabine and lamivudine are often considered interchangeable, and the regimens mentioned below with these two agents are based on the combination of tablets available.
  - Abacavir should only be used if the HLA-B*5701 test is negative.

- Other regimens considered to represent high-potency ART (Table 4)

Table 4.

OTHER INITIAL ANTIRETROVIAL REGIMENS FOR HIV INFECTION	
ART Regimens	**Individual Agents in ART Regimen**
INSTI plus 2 NRTIs	▪ Elvitegravir with cobicistat/tenofovir/emtricitabine ▪ Raltegravir/tenofovir/emtricitabine or lamivudine
Boosted PI plus 2 NRTIs	▪ Darunavir with cobicistat or ritonavir/abacavir/lamivudine ▪ Darunavir with cobicistat or ritonavir/tenofovir/emtricitabine ▪ Atazanavir with cobicistat or ritonavir/tenofovir/emtricitabine
NNRTI plus 2 NRTIs	▪ Doravirine/tenofovir/emtricitabine ▪ Efavirenz/tenofovir/emtricitabine ▪ Rilpivirine/tenofovir/emtricitabine - if HIV RNA < 100,000 copies/mL and CD4 count > 200 cells/mm^3

Alternative Treatments (2nd Line)

- **Pharmacologic Treatments**
  - **Single-agent combination ART regimens:**
    - Atripla (efavirenz, emtricitabine, tenofovir disoproxil fumarate)
    - Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide)
    - Complera (emtricitabine, rilpivirine, tenofovir disoproxil fumarate)
    - Delstrigo (doravirine, lamivudine, and tenofovir disoproxil fumarate)
    - Dovato (dolutegravir and lamivudine)
    - Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide)
    - Juluca (dolutegravir, rilpivirine)
    - Odefsey (emtricitabine, rilpivirine, tenofovir alafenamide)
    - Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)
    - Symtuza (darunavir, cobicistat, emtricitabine, tenofovir alafenamide)
    - Triumeq (abacavir, dolutegravir, lamivudine)
    - Cabenuva (cabotegravir, rilpivirine) - long-acting injectable regimen
  - **Combination tablets used in addition to other HIV medications:**
    - Cimduo/Temixys (lamivudine and tenofovir disoproxil fumarate)
    - Combivir (lamivudine and zidovudine)
    - Descovy (emtricitabine and tenofovir alafenamide)
    - Epzicom (abacavir and lamivudine)
    - Evotaz (atazanavir with cobicistat)
    - Prezcobix (darunavir and cobicistat)
    - Symfi (efavirenz, lamivudine, tenofovir disoproxil fumarate)
    - Trizivir (abacavir, lamivudine, zidovudine)
    - Truvada (emtricitabine and tenofovir disoproxil fumarate)

High-Yield Clinical Knowledge

- **Predictors of Therapy Success in Treatment-Naïve Patients**
  - Undetectable viral loads within 12-24 weeks
  - Use of high-potency ART
  - Good compliance with medications
  - Low baseline viral loads
  - Higher baseline CD4 counts, especially > 200 cells/mm^3
  - Rapid reduction in viral load with ART initiation

- J Infect Dis. 2012;205(1):87-96; Clin Infect Dis. 2012;55(12):1690-97; Science. 1996;272:1167-70; JAMA. 1998;279(1):35-40; AIDS. 1999;13(13):1717:1726.

- **Notable Drug Interactions**
  - Acid-reducing agents can decrease concentrations of atazanavir and rilpivirine, which require gastric acid for absorption.
  - Polyvalent cations such as calcium and magnesium can bind to INSTIs and reduce absorption.
  - Many ART regimens are impacted by the induction or inhibition of CYP450 or the efflux transporter p-glycoprotein, as the drugs are substrates and/or inhibitors or inducers (NNRTIs and PIs), especially protease inhibitors (strong inhibitors).
- **Common Adverse Effects**
  - **The difficulty with some antiretroviral drugs is their side effect profile. This is especially true for older agents. (Table 5)**

Table 5.

ANTIRETROVIRAL ADVERSE DRUG EFFECTS BY DRUG CLASS	
DRUG CLASS	**ADVERSE EFFECTS**
INSTIs	▪ Weight gain
NNRTIs	▪ Commonly associated with GI intolerances and skin rashes. Rashes can range from mild and self-limiting to toxic epidermal necrolysis (TEN). ▪ Efavirenz is associated with neuropsychiatric events which is why it is taken at bedtime. Note: this SE is worsened when taking with a high-fat meal that causes increased absorption.
NRTI	▪ Tenofovir DF is associated with bone loss and renal toxicity (tenofovir AF is often preferred). ▪ Abacavir can cause hypersensitivity reactions (contraindicated if HLA-B*5701 is positive).
Protease Inhibitors	▪ All agents are strong inhibitors of CYP3A4 and usually P-gp, which can result in clinically relevant drug interactions. ▪ Commonly associated with GI intolerance (diarrhea), central fat redistribution (buffalo hump plus peripheral fat wasting), hyperlipidemia, hyperglycemia and risk of diabetes, and PR and QT prolongation. ▪ Adverse effect profile typically makes them second-line therapy, unless a patient has HIV resistance.

- **Monitoring**
  - CD4 count and HIV viral load
    - Determine disease burden and/or ART effectiveness.
  - BMP, CBC, A1c, and lipid profile
    - Assess for common complications of HIV, AIDs, or drug therapies.
- **Patient Education**
  - ART should be taken daily to decrease the risk of selecting for resistance and ensure viral suppression.
  - Numerous ART regimens are now available, so an alternative therapy can likely be identified in the event of intolerability or adverse effects.
  - A physician should be notified before starting any new medications due to the risk of drug interactions.
- **Clinical Pearls**
  - **Common Regimens and Variations**
    - Most patients without resistance will be on a single-tablet combination regimen for the management of HIV.
      - Most regimens will contain 2 NRTIs and an INSTI.
    - If they are on more than one tablet, it is typically due to resistance or patient preference.

- Entry Inhibitors are typically only seen in patients with complex HIV resistance.
- **Boosting Agents**
  - Protease inhibitors can benefit from their common hepatic oxidation pathway by causing a pharmacokinetically predictable inhibition of their metabolism using the CYP3A4 inhibitors cobicistat or ritonavir.
    - Therefore, when ritonavir is used as a boosting agent, it must not be included in the count of "active" antiretroviral agents.
  - Although cobicistat and ritonavir are interchangeable boosting agents, their impact on CYP enzymes differs, making it important to assess drug interactions before changing therapies.
- **Long-acting ART Options**
  - Cabotegravir/rilpivirine is a long-acting injectable complete ART regimen given every 1 to 2 months that can be used in patients with viral suppression on a stable oral regimen who prefer to not take a daily medication.
- **HBV/HIV Coinfection**
  - In patients with HBV/HIV coinfection, an ART regimen with 2 active hepatitis B medications should be included.
  - Agents with activity are emtricitabine or lamivudine and tenofovir AF and DF.
- **Immune Reconstitution Inflammatory Syndrome (IRIS)**
  - Inflammatory response that may occur with initial HIV treatment in response to an indolent or residual opportunistic infection or activation of an autoimmune disorder.
    - Occurs typically within the first 6 months of treatment with ART.
    - May increase resistance, increase progression to AIDS, and decrease quality of life.
- **Pneumocystis Pneumonia Prophylaxis**
  - Patients with HIV with a CD4 count of < 200 cells/mm^3 will typically also be on one double-strength tablet of trimethoprim-sulfamethoxazole (Bactrim DS) daily for *Pneumocystis* pneumonia prophylaxis.
- **Dyslipidemia Management in HIV**
  - Statin therapy is now recommended in patients with HIV at risk for atherosclerotic cardiovascular disease based on the REPRIEVE study.
    - Demonstrated a 35% decreased risk in major events in patients on pitavastatin versus placebo.
    - N Engl J Med. 2023;389:687-699.
  - Patients with HIV are at a higher risk of cardiovascular disease and cancer despite ART.
- **Preexposure Prophylaxis (PrEP)**
  - PrEP for HIV prevention is recommended to reduce the risk of sexual HIV acquisition in certain patient populations.
  - First-Line Recommendations
    - Tenofovir DF and emtricitabine (Truvada) daily
    - Tenofovir AF and emtricitabine (Descovy) daily
    - Cabotegravir injection every 2 months
    - These regimens are NOT for HIV treatment but for prevention.

- **Special Population Considerations**
  - **Pediatrics**
    - Diagnosis: Virologic assays (HIV RNA or HIV DNA NATs) that directly detect HIV are used instead of HIV antibody and HIV antigen/antibody tests in infants and children <18 months with perinatal and postnatal exposure.
    - Primary Treatments (First-Line):
      - ART should be initiated in all infants and children.
      - The treatment of choice is two NNRTIs plus one INSTI, NNRTI, or boosted PI.
      - The regimen options are based on age and weight at treatment initiation.
        - < 2 years old: regimens typically contain abacavir plus emtricitabine or lamivudine with raltegravir, lopinavir/ritonavir, or dolutegravir based on age
        - ≥ 2 years old: can take regimens similar to those preferred in adults (tenofovir AF/emtricitabine/bictegravir)

- Monitoring: similar to adults and should occur at least every 3 to 4 months.
- ART for newborns with perinatal HIV exposure:
  - Newborns at low risk should receive a 2-week zidovudine ART regimen for prophylaxis.
  - Newborns at high risk should have a 3-drug regimen given from birth for 2-6 weeks, and if the duration is less than 6 weeks, zidovudine alone should be continued to complete a total of 6 weeks.

- **Pregnancy**
  - Women pregnant with HIV have an additional goal to maintain their viral load below the limit of detection to reduce the risk of transmission to the fetus.
  - Primary Treatments (First-Line):
    - Two NRTIs (abacavir plus lamivudine or tenofovir DF plus emtricitabine) AND either a PI with ritonavir (atazanavir or darunavir) OR an INSTI (dolutegravir or raltegravir).
    - Abacavir/lamivudine/dolutegravir (Triumeq) allows for a single tablet regimen.
  - A scheduled cesarean delivery at 38 weeks is recommended to minimize the risk of transmission if HIV RNA is > 1,000 copies/mL or unknown at the time of delivery.
    - Intrapartum intravenous zidovudine is also recommended in this scenario.
- **Chronic Kidney Disease**
  - Many NRTIs, such as tenofovir DF or AF, emtricitabine, and lamivudine, require dose adjustments in the setting of renal dysfunction.
  - This often requires splitting a combination tablet into individual medications to accommodate the dose change or switching to an alternative regimen unaffected by renal dysfunction.

High-Yield Core Evidence

- **SMART Study**
  - Patients with a CD4 count of > 350 cells/mm^3 were randomized to continuous ART or episodic use (initiated after the CD4 count dropped to < 250 cells/mm^3 and continued until > 350 cells/mm^3).
  - The study was conducted on the premise that despite its mortality reduction, ART's health benefits were limited by adverse effects.
    - Now, ART adverse effects are significantly reduced compared to the historic regimens that included older generation protease inhibitors.
  - Study showed that continuous ART decreased the risk of opportunistic disease or death from any cause and also showed a decrease in major cardiovascular, renal, and hepatic disease.
  - Suggested that despite the relative cardiovascular risk of ART, the risk of untreated HIV causing inflammation and leading to cardiovascular disease and other comorbidities was greater.
  - N Engl J Med. 2006;355(22):2283-2296.
- **START Study**
  - Patients with CD4 cell counts > 500 cells/mm^3 were randomized to receive antiretrovirals immediately or only after their CD4 count dropped to 350 or they developed a clinical condition requiring therapy.
  - This study demonstrated that patients with CD4 counts > 500 benefited from immediate initiation based on a lower primary composite end point of AIDS-related event, serious non-AIDS-related event, or death from any cause.
  - N Engl J Med. 2015;373(9):795-807.
- **HIV.gov Guidelines**
  - Guidelines are updated every 6 months and are federally approved HIV practice guidelines.
  - https://clinicalinfo.hiv.gov/en/guidelines

HIGH-YIELD BOARD EXAM ESSENTIALS

- **PATHO:** HIV attaches and enters host CD4+ lymphocytes, where it uses reverse transcription to form DNA. This DNA migrates to the host cell nucleus and integrates into the host chromosome. Viral proteins and DNA are packaged by viral proteases into a budding virion, in which a mature virus is formed and able to infect other cells.
- **CLASSIC PRESENTATION:** One of the numerous AIDS-defining illnesses, or fever, fatigue, pharyngitis, a pruritic papular eruption of HIV, headache, and lymphadenopathy
- **CLASSIC FINDINGS:** Positive HIV antigen/antibody combination immunoassay followed by a positive HIV-1/HIV-2 antibody differentiation immunoassay
- **TREATMENT:**
  - First-line regimens include bictegravir/emtricitabine/tenofovir AF, abacavir/dolutegravir/lamivudine, and dolutegravir/emtricitabine/tenofovir AF