Starting Immediate Treatment for HIV-1

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Slides of this presentation will be posted at
www.beyondaids.org/resources.html
www.academia.edu

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BEYOND AIDS

Objectives

- 1. The participant will be able to describe the importance of early initiation of treatment for HIV-1 infection, and how/why primary care providers can/should get involved

- 2. The participant will be able to prescribe (or assist) initial treatment of HIV positive adults and adolescents, utilizing currently-recommended antiretroviral medications, and will retain information on at least 1 combination

Treatment references

- Main sources for recommendations on initiation of ART (antiretroviral therapy)
  - DHHS Guidelines, ARVs (antiretrovirals) for adults/adolescents with HIV-1: U.S. Dept. Health and Human Services (not for pediatric or HIV-2)
    - Published by National Institutes of Health (NIH) on HIV.gov Website; latest is 01/20/2022 update https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/guidelines-adult-adolescent-arv.pdf
  - AAHIVM Fundamentals of HIV Medicine and Kaiser-Permanente Website for history and physical

Clinical case question, discuss at end

- In the course of your routine screening of patients, one test (4th generation, with confirmation) has come back positive for HIV-1. What should you do?
  - 1) Wait for the patient's next regular visit to discuss the result?
  - 2) Call the patient in right away? If so:
    - Tell him/her the result, provide post-test counseling, but hold treatment till the CD4 count is under 200?
    - Provide post-test counseling, order immediate blood tests and urge the patient to start treatment now?
    - Schedule a referral of patient to Infectious Diseases?

Primary care providers will be in position to start HIV treatment

- Routine screening recommended by US Preventive Services Task Force (2013), CDC (2006)
  - CA law: most primary care to offer if order blood tests
- About 13-14% of US HIV infections not yet diagnosed
- Primary care providers will occasionally get a positive result and need to do something about it
- Call patient in same day or ASAP: **start tests, meds**
  - Do not need to be an HIV expert to initiate therapy
- **See back** 2-6 wks to assess labs, drug tolerance
- **Options:** 1) continue HIV care in practice; 2) refer HIV care, retain primary care; 3) refer total care

Deciding whether to be the HIV provider and when to consult

- HIV can be simple to treat if
  - High CD4 cell count, asymptomatic, no complications
    - CD4 cell = T cell with CD4 receptor (a lymphocytic white blood cell critical t to immune system, and preferentially attacked by HIV)
  - No serious co-morbidities (mental, physical)
  - Patient tolerates, adheres to first drugs prescribed
- After 2-6 wk. f/u, see q 2-8 wks. till virus suppressed, then q 3-4 mos. for labs, refills, counseling; consults only when need help
- If CD4 count <200, called AIDS, more complex
  - Prophylaxis for opportunistic infections is indicated
  - Metabolic, neurocognitive, renal, cardiac, psych, other

Studies justifying early treatment

- In 2011, Cohen et al.: HIV infectiousness is reduced by **at least** 96% with suppressed (undetectable) viral load (VL) = virus in blood: "treatment as prevention"
  - http://www.nejm.org/doi/full/10.1056/NEJMoa1105243#t=article
- The START and TEMPRANO studies showed improved clinical outcomes with early antiretroviral treatment even at high CD4 levels
  - https://www.ncbi.nlm.nih.gov/pubmed/26192873, http://www.ncbi.nlm.nih.gov/pubmed/26193126
- Studies starting treatment on day of diagnosis show
  - More **rapid** achievement of viral suppression
  - Better **12-month** viral suppression, retention in care

Koenig S. et al., PLOS Medicine 2017; 14(7) (Haiti), Pilcher CD, JAIDS 2017, 744:44-51 (San Francisco), https://www.ncbi.nlm.nih.gov/pubmed/27434707

U.S. treatment guidelines since 2012: treat positives, right away

- 1996 Hattis, Jason (LLU PM) proposed that rapid treatment should reduce infectiousness
- 2001-2011 guidelines delayed treatment till CD4 count low, which could take years
- 2012 expanded treatment to anyone with HIV ("test and treat")
  - Be sure truly positive; have documentation of positive test
    - Errors and fictitious cases, esp. in mental patients
- 9/15: WHO endorsed "test and treat" globally

http://www.sajhivmed.org.za/index.php/hivmed/article/view/459/870

Exceptions to immediate treatment

- Patient refuses to start immediate treatment
- Patient in mental shock after first told of positive HIV test, not ready to accept or recall instructions
- Tuberculosis co-infection: HIV treatment can be delayed for up to 30 days after TB treatment start, especially if TB meningitis, CD4 count is <50, or miliary TB
  - Concern is possible IRIS (Immune Reconstitution Inflammatory Syndrome)

- "Elite controllers" (<1%): baseline VL undetectable
  - Clinical benefit of immediate treatment uncertain
  - Treat if CD4 drops, viremia, clinical progression *(HIV.gov 1/20/22)*

Baseline history/physical (AAHIVM, Kaiser)

- Special topics to discuss at first visit:
  - Reassurance about prognosis with treatment
  - Importance of immediate initiation of treatment
  - Basic information and Q and A about HIV/AIDS
- Chief complaint/health history:
  - Primary HIV or opportunistic infection symptoms: Fever, weight, chills, night sweats, fatigue, rash, GI, other acute?
  - Exposure risk or contact with HIV
- After lab results back, if CD4<200
  - More questions and exam regarding opportunistic inf's
- Review of systems:
  - Standard, including skin, HEENT, pulmonary, cardiac, hematolymphatic, GI, GU, neurological, musculoskeletal

Baseline history/physical (AAHIVM)

- Past history, social, etc.
  - Prior history of HIV dx, treatment?
  - TB, viral hepatitis history?
  - Medications, street drug use/opiates to treat?
  - Anxiety, depression, psychiatric history?
  - Immunization, allergy histories
- Physical exam: special attention to:
  - Skin
  - Eyes, mouth
  - Lymph nodes
  - Chest (cardio-pulmonary)
  - Abdomen
  - (Gynecological, Anorectal)

Baseline tests (just) before start treatment after HIV positive result

- **Viral load (VL)**: How many viral copies/ml blood by PCR?
  - Follow q2-8 wks till suppression, then q 3-4 mos. Find elite controllers. Abacavir only if <100,000, use Dovato only if <500,000
- **CD4 count**: How much immune function remains?
  - <200 ("AIDS" or Stage 3) calls for cotrimazole prophylaxis
  - Repeat 3 mos. then q 3-6 mos.; can get with viral load ~quarterly

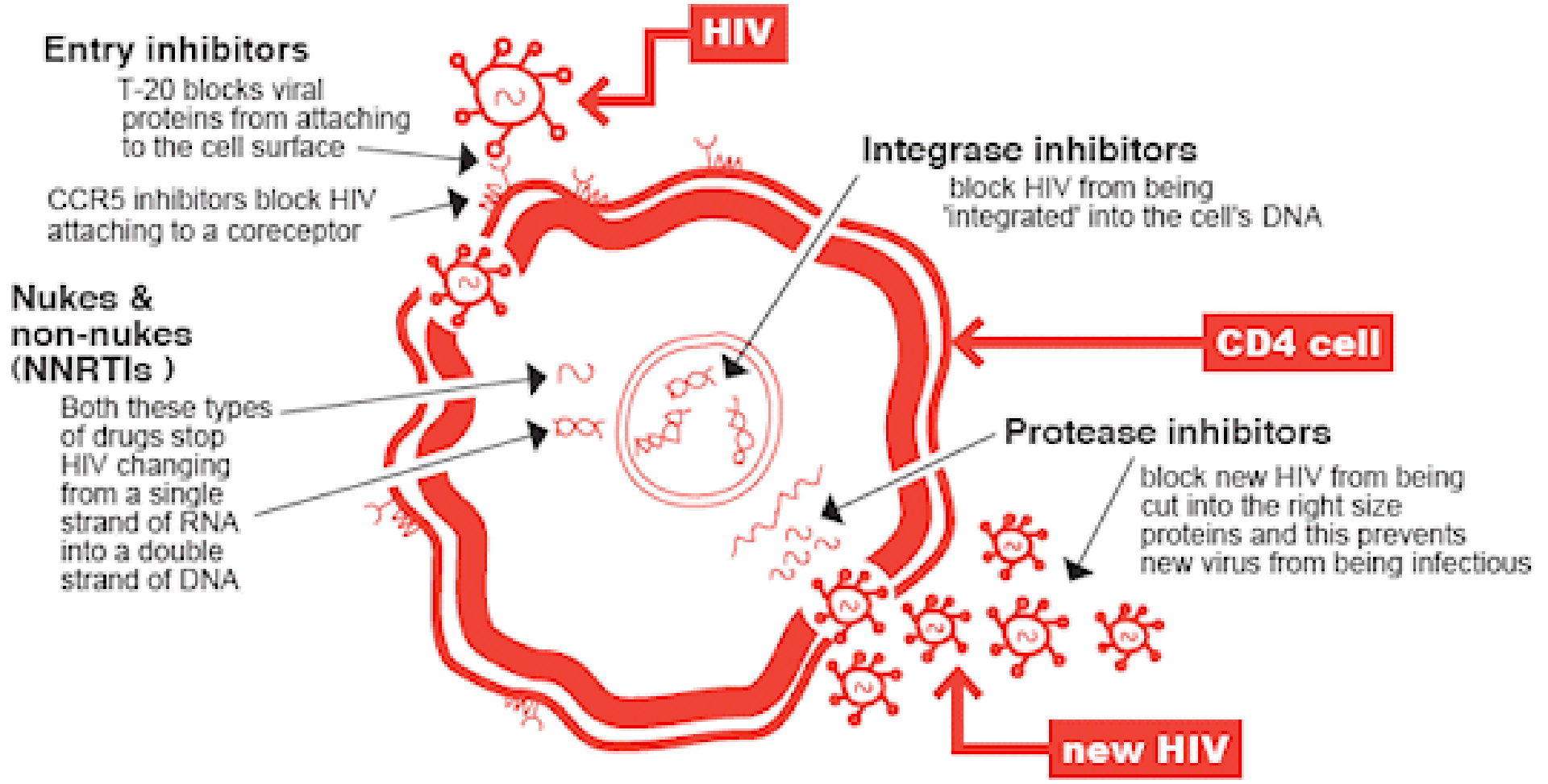
- **Genotype**: Detects mutations that characterize resistance
  - If select dolutegravir, bictegravir, or darunavir, no resistance expected, **no need to wait for genotype results before starting antiviral medication**
  - Genotype could detect mutations against other drugs in regimen, and useful if switch to other drugs later
  - If integrase inhibitor resistance testing suspected, include integrase gene
  - Repeat if virological failure (assuming patient believed to be adherent)
- **HBsAg:** If +, use drugs that treat both HIV and hep B
- **Anti-HCV:** Treat if +; some hep C drugs interact with some ARVs

More baseline tests (just) before start treatment after HIV positive result

- Also obtain these **(DHHS rec's those in bold)**
  - **Chemistry profile** (incl. **FBS**, **ALT**, **AST**, **bilirubin**, **creatinine**)
    - If creatinine elevated, avoid original form of tenofovir
    - Baseline creatinine needed if give dolutegravir, bictegravir, or cobicistat
      - Drugs inhibit secretion, elevation does not mean renal damage
  - **Lipid profile** (can be non-fasting; some HIV meds affect)
  - **CBC** (some meds could cause anemia; need baseline)
  - **Urinalysis** (for renal function and to rule out UTI)
  - Hemoglobin A-1c (insulin resistance from HIV, some meds)
  - STD screen (STDs increase HIV transmission) including RPR; chlamydia/GC: urine, also pharyngeal and anal for MSM
  - **Pregnancy test** if indicated

How 5 main classes of HIV antiretroviral drugs work

Combine 2; booster drugs can be considered as a 6th class



Original source (no longer unavailable): http://i-base.info/guides/starting/hiv-lifecycle

ARV drug classes utilized in initial regimens: "2 + 1" model

- The usual model since 1996: 2 NRTIs (nucleoside/tide reverse transcriptase inhibitors or "nukes") plus a 3rd drug from another class (exceptions discussed later)
  - A pair of NRTIs typically combined in a single pill, sometimes with third drug added
  - In first-line regimens for newly diagnosed patients, the third drug is selected from the integrase inhibitor or INSTI group (integrase strand transfer inhibitors)

The recommended "backbone" NRTIs for HIV-1: the tenofovirs

- **Tenofovir**, the most powerful NRTI, now comes in two forms
- **Tenofovir alafenamide (TAF)**: introduced 2015, used for HIV in combination pills with **emtricitabine (FTC)**, 25/200 mg: **Descovy**, >$1900/mo

- Safe and effective; blue tablet, take only 1/day
  - Also approved for pre-exposure prophylaxis (PrEP) except for cis-gender females (less vaginal protection than anal)
  - Need less than 1/10 the dosage of original tenofovir disoproxil (of which it is prodrug): 25 mg vs. 300 mg
  - Package insert permits use down to eGFR of 30 (vs. 60 for the older form of tenofovir, TDF)
  - Safe for both kidneys and bone
  - Adverse effect on lipids: LDL, TC, TG rise, but also HDL

The recommended "backbone" NRTIs for HIV-1: the tenofovirs, contd.

- Original form, **tenofovir disoproxil (TDF)**: In combo pills, best known in patented combination with **emtricitabine (FTC)**, another NRTI, 300/200 mg: original brand **Truvada**
- Both components now off patent, **over 10 generics available** at $1-3/tablet, (<5% of brand name cost)
- Also approved for pre-exposure prophylaxis (PrEP), all patients
- TDF also available combined with lamivudine (3TC), an NRTI similar to FTC, 300/300 mg: Cimduo and Temixys
- TDF may cause osteopenia and renal tubular proteinuria, may increase creatinine; TAF does not
- Still some advantages and exclusive uses for TDF:
  - TDF lowers LDL , total cholesterol, and TG, but also HDL; TAF does not lower lipids
  - **Tremendous cost savings with generics**

A dual benefit if patient tests pos. for hepatitis B (surface Antigen)

- Both forms of tenofovir, and both emtricitabine and lamivudine that are given with them, are active against hepatitis B
- Any standard 2-NRTI combination containing a tenofovir can therefore usually keep hepatitis B at bay
- However, beware when switching regimens: if one of these drugs is discontinued, there may be a reactivation of the hepatitis

An alternative "backbone" NRTIs for HIV-1, contd.: abacavir

- **Abacavir (ABC)**: Alternative to the tenofovirs, in combo with lamivudine (3TC) 600/300 mg: **Epzicom**
  - **Approved as part of a starting regimen**
  - **Generics available** so less expensive if used
  - **HLA B*5701 test must be done before considering abacavir**
    - **5-8% risk of severe hypersensitivity reaction if positive**
    - **Use only if HLA B*5701 negative,**
  - **VL<100,000**
  - Some studies suggest increased risk of myocardial infarctions, so **use only if low coronary risk**
  - Abacavir is not active against hepatitis B

3rd Drug: integrase inhibitors (INSTIs)

INSTI group favored to start: stable lipids; well-tolerated; more rapid viral suppression than Pis or NNRTIs

- **Bictegravir** (BIC) 50 mg in once/day combo pill with **TAF** and FTC, 50/25/200 mg: **Biktarvy**, almost no resistance, with or without food; complete regimen; approved by FDA 2/7/18; not sold separately

- (these are front and back views, only 1 pill)
- **Dolutegravir (DTG)** available alone, 50 mg: **Tivicay,** or in combo pill with abacavir and lamivudine: Triumeq;

- **Or with 2nd pill (TAF or TDF with emtricitabine)**
  - Once daily with or without food; small beige tablet
  - **Very low resistance**; fewer discontinuations than many other drugs
  - May raise creatinine levels without renal damage (inhibits secretion)
  - Earlier concerns about possible risk of neural tube defects resolved

Bictegravir, dolutegravir side effects

Weight gain (class effect for INSTIs) >3%

Bictarvy (side effects of all ingredients):

- GI: nausea, diarrhea
- Other: headache, upper respiratory tract infection
- Lactic acidosis; angioedema; nephrotoxity; depression
- Elevated CK, LFTs, bilirubin, amylase; neutropenia

Dolutegravir:

- Neuropsychiatric (more common than other INSTIs, and in women), 5% discontinuation
  - Insomnia (0-7%, early), depression (0-1%, delayed), headache (0-2%, early), fatigue (0-2%, early), suicidal ideation (0-2%, delayed)
- GI: Nausea (0-2%), Diarrhea (0-2%), early); hepatitis
- Delayed: Elevated transaminases, elevated glucose

Alternative integrase inhibitors

- Can be used in alternative starting regimens but not first choices:
- **Raltegravir (RAL),** longest experience; tolerated best; no combos; use with two NRTIs; some resistance; pregnancy-safe; with or without food; older drug but no generics available:
  - **Isentress HD** 1200 mg daily or Isentress 400 mg bid
- **Elvitegravir (EVG),** available only in combination tablets; this integrase inhibitor requires a booster (cobicistat is included), once daily complete regimens, taken with food:
  - **Genvoya**, including EVG 150/TAF 10/FTC 200/cobicistat 150 mg; or
  - Stribild, including EVG 150/TDF 300/FTC 200/cobicistat 150 mg

Alternative 3rd Drugs if 2 INSTIs not tolerated: 1) A protease Inhibitor (PI)

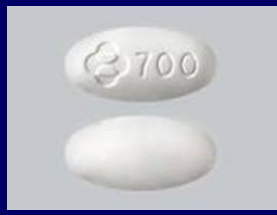
- **Darunavir** (DRV), 800 mg: **Prezista**

  - Inferior to dolutegravir or raltegravir in studies
  - Low resistance; start pending genotype results, 1/day
  - Combination with TAF, lamivudine, booster cobicistat: **Symtuza**; 1 tablet daily with food is total regimen

  - Or just boost with **cobicistat**, which is available combined with darunavir: Prezcobix, once daily, with food; avoid in pregnancy; can add **Descovy** for TAF and FTC, or cheaper generic TDF/FTC, 2 pills daily
  - Or boost with **ritonavir**, separately: Norvir or generic
    - Also a protease inhibitor, but used as booster in low dosage
    - Total regimen then requires 3 pills, all once-daily, with food

Alt. 3rd drugs, contd.: 2) An NNRTI

- **Doravirine (DOR),** 100 mg: Pifeltro



  - Newest drug of this class, take regardless of meals
  - With lamivudine, TDF (Delstrigo): One tablet, once daily; no combination with TAF available

  - Fewer CNS side effects, rashes than other NNRTIs, can use with acid-lowering drugs, good lipids
  - Less viral resistance , more resilient if mutations occur
    - Still active in presence of K103N, G190A mutations that confer resistance to other NNRTIs

- **Efavirenz (EFV)** 600 mg without food, in a single once/day combination pill (**Atripla**) with TDF, FTC;

  Inexpensive generic available; combos with TDF, lamivudine (Symfi, Symfi Lo): entirely generic but costly

  - High incidence of rash and neuropsychiatric side effects

Alt. 3rd drugs, contd.: 3) A cell entry/fusion inhibitor

- Varied drugs, reserved for multi-drug resistance
- Fostemsavir (Rokubia), oral 600 mg qd/bid
  - Prolongs QTc, increases ethinyl estradiol levels in contraceptives
- Enfuvirtide (Fuzeon) requires **twice daily SQ injections**; lots of local reactions
- Maraviroc (Selzentry; best brand name?) is a twice-daily tablet but only works if virus has tropism to enter cells through CCR5 receptor (which can change with mutations)
  - Test tropism before treating, retest if virological failure
  - Might also help memory loss, prevent dementia (research pending)
- Ibalizumab (Trogarzo), first biologic, requires biweekly **IV infusions**

Exceptions to "2 + 1" model: 1st licensed 2-drug regimens

- Dolutegravir plus only lamivudine: **Dovato** (appr. 4/8/19); 1/day; can be starting regimen if:
  - VL <500,000
  - Negative screening test for hepatitis B
  - Genotype results already available and no resistance to lamivudine

- Other 2-drug combo to consider, but not for starting regimen: two long-acting injectables in a kit, approved as Cabenuva (appr. 12/21/21)
  - Cabotegravir 400 mg (INSTI with injectable form)
  - Rilpivirine 600 mg (NNRTI with injectable form)
  - Start with pills of each for 28 days to test tolerance, then two injections at same visit, every month, or 900/600 mg q 2 mo.

Cost considerations in treatment

- Recommended regimens like Bictarvy have cash price of as high as $3,500/month if no insurance.
- Generic medication alternatives exist for uninsured patients, as little as $200/month, pending approval of Medicaid (Medi-Cal) or Affordable Care Act coverage, and/or referral to a Ryan White-grantee clinic for treatment:
  - Generic tenofovir disoproxil/emtricitabine (TDF/FTC), $49/mo., or
  - Generic abacavir/lamivudine (ABC/3TC); $85/mo., first confirm negative HLA B*5701 test and VL <100,000)
  - Combine one of these with Generic efavirenz 600 mg, $145/mo (separate pill, empty stomach)

Ongoing: Behavioral, preventive

- Discuss sexual practices, drug risks, housing, social/mental health
- Reinforce need for lifelong adherence to treatment
  - Educate, reassure re hopeful prognosis if do so
  - Outreach if miss appts.; urge return if side effects
- Motivational counseling on safe sex, no sharing injection "works," no plasma/blood donation
  - Emphasize condom use both to prevent transmission until VL persistently undetectable, and to protect from other dangerous STDs; offer to provide PrEP to partners
  - Urge to notify current/future partners of HIV status and get consent to have public health do contact tracing
- Offer referrals/consults or ask public health to assist:
  - Drug treatment, mental health, social services, housing

Keeping it simple (& safer with TAF)

- Remember a few starting drugs few can fault:
- **Biktarvy** (bictegravir, includes TAF/FTC)
  - Complete regimen in one tablet daily

  OR: Tivicay (dolutegravir, DTG) 1 tab (50 mg) daily, integrase inhibitor with almost no resistance, **plus**
- **Descovy** (tenovofir alefenamide/emtricitabine, TAF/FTC), 1 tab (25/200 mg) daily, only 1 dosage form; safest combo of two NRTIs; **or much cheaper generic TDF/emtricitabine** if renal function OK
- ADVANTAGES OF THESE REGIMENS:
  - Food or not; usually well-tolerated
  - Very little resistance; start immediately, no need to wait for lab results

Summary: Starting HIV treatment for adults and adolescents

- Almost all HIV-infected patients should be **rapidly offered ART; primary care providers can do**
  - Improves clinical outcomes; prevents transmission
- Draw blood before start treatment (DHHS recs in bold)
  - **Test at least viral load (VL), CD4 count, genotype,** (pre-Tx baselines essential), **hepatitis B surface antigen hepatitis C antibody**
    - Detect pre-existing drug resistance mutations
    - Detect special or contra-indications for certain drugs
    - Determine how advanced HIV is, which influences treatment
  - **Chemistry (incl. creatinine, FBS), lipids, CBC,** A-1c, **UA**
  - Also suggested: STD screen incl. RPR, urine chlamydia/GC (and pharyngeal, anal swabs for MSM)
  - **Pregnancy test** if indicated

Summary, concluded

- Start treatment: General principle is to use 3 **drugs**:
  - **Biktarvy =** bictegravir available in new 3-drug combo (with TAF, FTC), 1 pill/day, no food restrictions; total regimen
  - Or combine **Tivicay = dolutegravir (DTG),** 50 mg; hardly any resistance, no food restrictions
  - Plus one of recommended combinations of 2-NRTIs;

    Descovy = tenofovir alafenamide/emtricitabine (TAF/FTC), 25/300 mg, has safety advantages
  - Lowest cost alternatives for uninsured patients
    - Generic tenofovir/emtricitabine (TDF/FTC) or generic abacavir/lamivudine (ABC/3TC; test HLA B*5701), combined with generic efavirenz 600 mg (separate pill, empty stomach)
  - Assess at 2-6 weeks, decide to refer or follow
  - Report case to PH; behavioral and preventive measures

Reprise of clinical case question

- In the course of your routine screening of patients, one test (4th generation, with confirmation) has come back positive for HIV-1. What should you do?
  - 1) Wait for the patient's next regular visit to discuss the result? No
  - 2) Call the patient in right away? Yes If so:
    - Tell him/her the result, provide post-test counseling, but hold treatment till the CD4 count is under 200? No
    - Provide post-test counseling, order immediate blood tests and urge the patient to start treatment now? Yes
    - Schedule a referral of patient to Infectious Diseases? No