**When to start HIV antiretrovirals**

**In a nutshell:** HIV treatment is recommended for everyone. Assess and support patient readiness and ability to adhere to a chosen regimen.

- Recommended for All! CD4 <350 (AI), CD4 ≤ 500 (AII) and >500 (BIII)
- regardless of CD4 count in the setting of: pregnancy (AI), AIDS (AI), HIV-assoc nephropathy (AII), HBV coinfection (AIII), at risk of transmitting to partners (heterosexual partners AI, all other partners AIII), age >50 (BIII)
- offer to those with acute or early HIV infection (BII)

**IAS guidelines:** [IAS July 2014; JAMA 312, Gunthard, et. al.]
- recommended for asymptomatic patients with CD4≤500 (Ala) and asymptomatic patients with CD4>500 (BII)
- at any CD4: opportunistic illnesses (Ala), pregnant women (Ala), chronic hep B (Alla) or hep C coinfxn (CIII), age >60 yo (BIIa), HIV nephropathy (Alla), acute HIV (BIII)

**WHO guidelines:** CD4 ≤ 500, WHO clinical stage 3 or 4, TB, hep B, HIV- partner [WHO June 2013; http://www.who.int/hiv/pub/arv/en/]

**Controversies: early vs. deferred treatment**

**Arguments for early treatment:**
- better CD4 gain/retention; fewer OIs, cardiovascular, renal and liver comorbidities; lower rates of AIDS; better response to HBV vaccines, reduction of HIV transmission, a public health benefit [SMART, Kitahata, NA-ACCORD and ART-CC, ACTG 5127, Okulicz JAMA 2014]

**Arguments for deferred treatment:**
- side effects and toxicities; resistance and adherence issues over a longer-term; fewer drug options once resistance occurs [When to Start Consortium, Hecht JID 2006]

(When to start, continued)

**In the setting of an OI:**
- morbidity and mortality lower in patients with OIs who started ART within 14 days after OI tx started (not including TB) [ACTG 5164]
- careful timing in cryptococcal meningitis; reduce ICP first [BIII, COAT 2012]

**In active TB,** optimal timing of initiating ART is being studied, but in general 2-8 weeks after starting TB treatment; WHO recommends to start ART in all patients with TB [SAPIT trial]. Watch for IRIS and continue therapy (AIII). IAS/DHHS recommend to start ART on this schedule, with DOT:
- CD4 <50: start ARVs within 2 weeks of TB treatment (AI)
- CD4 =50+: start ARVs by 2-4 wks if severe (BI-III) or by 8-12 wks (AI)
- TB meningitis: start ARVs within 2-8 weeks with help from experts (BIII)
- Pregnant women with TB: start ART asap (AIII)

**Other issues to consider:**
- **ART toxicity:** peripheral neuropathy, anemia, renal insufficiency
- **age > 50 yo:** start asap due to poorer survival without treatment
- **discordant couples:** less transmission when viral load undetectable (HPTN 052 Partners trial, June 2010: 96% reduction in hetero couples)
- **Hep B:** check DNA, use TDF+FTC/3TC (BII), add entecavir if on 3TC monotherapy (BI); avoid treatment interruptions to risk of hep B flares (All)
- **Hep C:** studies suggest slower liver fibrosis progression in pts on ARVs
- **Women on OCPs:** ART may OCP levels, so choose regimen with no interactions, or use additional or alternative contraception (AIII)
- **CV disease:** consider avoiding ABC, LPV, FPV (IAS rec)
- **Multi-drug resistant HIV:** consider regimen with boosted DRV BID (AI)

**How to start** → see the HIV health care maintenance handout
- history, physical, risk reduction, partner counseling
- baseline labs, including genotype, CD4, viral load, and HLA-B*5701
- assess patient readiness and preferences: keys to adherence
- interpreting genotypes: Stanford database (http://hivdb.stanford.edu/)
- drug interactions: HIV InSite (http://hivinsite.com/)

Rating of Recommendations: A = Strong; B = Moderate; C = Optional; Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion
What HIV antiretrovirals (ART) to start & ART list (as of January 2015)

Putting together a regimen: use 3 active drugs based on genotype
- for ART naïve, generally use 2 NRTIs and 1 NNRTI or boosted PI or INSTI

NRTIs (nucleoside reverse transcriptase inhibitors)
- 3TC, lamivudine: 300mg qday; low resistance barrier; anti-HBV ★ ○ ○
- FTC, emtricitabine: 200mg qday; same mech as 3TC; anti-HBV ★ ○ ○
- TDF, tenofovir: 300mg qday; in renal failure except HD; anti-HBV ★ ○ ○
- ABC, abacavir: 600mg qday; CV& hypersens. risk, in B5701; VL >100k ○
- ZDV (AZT), zidovudine: 300mg BID; risk of cytopenia, in sig anemia ○
- d4T, stavudine: 30mg BID; risk of pancreatitis, lactic acidosis, PN ○)
- ddl, didanosine: 250mg qday (<60kg), 400mg qday (≥60kg); sim to d4T ○ ○ ○

NNRTIs (non-nucleoside reverse transcriptase inhibitors)
- EFV, efavirenz: 600mg qhs; risk of rash, hepatoxic, in 1st tri pregnancy ★ ○ •
- NVP, nevirapine: 200mg BID; risk of rash, hepatoxic esp in CD4>250, lead-in
- ETR, etravirine: 200mg BID; use in NNRTI resistance; risk of rash & hsn
- RPV, rilpivirine: 25mg qday w/food; PPIs inhibit absorption; VL >100K ○

PIs (protease inhibitors)
- ATV/r, bsted atazanavir: 300mg+100mg qday; PPIs inhibit absorption ○ ○ •
- DRV/r, bsted darunavir: 800mg+100mg qday in tx-naïve; BID in tx-exp ★ ○
- LPV/r, bsted lopinavir: 200/100mg qday or 400/100mg BID; metab/GI sxns ○
- FPV/r, bsted fosamprenavir: 1400+100 qday or 700+100 BID; metab/GI sxns ○
- SQV/r, bsted saquinavir: 1000mg+100mg BID; metab/GI sxns; high pill burden
- TPV/r, bsted tipranavir: 500mg+200mg BID; use in PI resistance; hepatotoxic

INSTIs (integrase strand transfer inhibitors) avoid cation antacid use with these
- RAL, raltegravir: 400mg BID; low resistance barrier; mild GI sxns ★
- EVG, elvitegravir: 150 mg must be used with cobicistat 150 mg qday; CKD ○
- DTG, dolutegravir: 50 mg qday or BID w/ INSTI mutations or P450 inducers ★ ○

CCR5-antagonist: MVC, maraviroc: dosed for interactions; check CCR5 tropism
Fusion Inhibitor: T20, enfuvirtide: 90mg SQ BID; salvage tx; injxn site rxns

Fixed-dose combinations (all except Kaletra are ):
- TDF/FTC=Truvada  EFV/TDF/FTC=Atripla
- ABC/3TC=Epzicom  RPV/TDF/FTC=Complera
- ZDV/3TC=Combivir  EVG/cobi/TDF/FTC=Stribild (Quad)
- LPV-r=Kaletra  DTG/ABC/3TC=Triumeq
- ABC/3TC/ZDV=Trizivir

DHHS guidelines for ART naïve:
- preferred (AI): avoid TDF in renal failure
- EFV/TDF/FTC = Atripla (avoid if wanting to get pregnant)
- ATV-r + TDF/FTC (not if on PPI)
- qday DRV-r + TDF/FTC
- RAL BID + TDF/FTC
- EVG/cobi/TDF/FTC=Stribild ( in CrCL>70, not if on cation antacid)
- DTG/ABC/3TC=Triumeq (if HLA B*5701 neg, not if on cation antacid)
- DTG/TDF/FTC (not if on cation antacid)
- alternative (AI): EFV+ABC/3TC, ATV-r+ABC/3TC (if HLA B*5701 neg)
- combo pills: RPV/TDF/FTC (Complera; avoid in vl>100k)
- IAS alternatives: regimens containing NVP, LPV-rit, DRV-cobi, ATV-cobi
- do NOT use: monotherapy with NRTI or boosted PI (AI), dual-NRTI or triple-NRTI, ATV-cobi, d4T, dual-NNRTI, EFV in 1st tri pregnancy,
- FTC+3TC, ETR+ unboosted PI or ATV-r or FPV-r or TPV-r, NVP in tx-naïve
- women CD4>250 or men >400, unboosted DRV or SQV or TPV, d4t+AZT

WHO guidelines for ART-naïve:
- Adults: TDF+3TC/FTC+EFV (alt ABC or AZT instead of TDF); children 3-10: ABC+3TC+EFV; children<3: ABC/AZT + 3TC + LPV-rit; phasing out d4T

Also consider: Don’t stop once you start! (AI), resistance barrier of regimen (PI>INSTI>NNRTI), hep B (use TDF/3TC), PUD on PPI (avoid ATV, RPV), cation antacid use (avoid INSTIs), hep C tx (avoid Stribild?)
- Treatment goals: long-term HIV VL suppression, restore immunologic function, prolong survival, reduce morbidity, prevent HIV transmission
- When to switch: patient intolerance, unacceptable side effects, unavoidable drug interactions, resistance: virologic failure of sustained VL>200, get a genotype on ART & switch based on 2+ active drugs (AI)

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