HIV Antiretrovirals 101

when to start * what to start * issues to consider

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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.

DHHS guidelines: [DHHS April 2015, http://aidsinfo.nih.gov]
-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 (AIa) and asymptomatic patients with CD4>500 (BIII)
-at any CD4: opportunistic illnesses (AIa), pregnant women (AIa), chronic hep B (AIIa) or hep C coinfxn (CIII), age >60 yo (BIIa), HIV nephropathy (AIIa), 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 (AII)
• **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
[symbols: ★use in initial regimens ☼ qday dosing ◈ renal dosing ☠ avoid]

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 ☠◈
• ddI, didanosine: 250mg qday (<60kg), 400mg qday (≥60kg); sim to d4T ☠☼◈

NNRTIs (non-nucleoside reverse transcriptase inhibitors)
• EFV, efavirenz: 600mg qhs; risk of rash, hepatoxic, ψ; ☠ 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: 800/200mg qday or 400/100mg BID; metab/GI sxs ☼
• FPV/r, bsted fosamprenavir: 1400+100 qday or 700+100 BID; metab/GI sxs ☼
•SQV/r, bsted saquinavir: 1000mg+100mg BID; metab/GI sxs; high pill burden
• TPV/r, bsted tipranavir: 500mg+200mg BID; use in PI resistance; hepatoxic

INSTIs (integrase strand transfer inhibitors) avoid cation antacid use with these
• RAL, raltegravir: 400mg BID; low resistance barrier; mild GI sxs ★
• 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
ABC/3TC=Epzicom
ZDV/3TC=Combivir
LPV-r=Kaletra
ABC/3TC/ZDV=Trizivir
EFV/TDF/FTC=Atripla
RPV/TDF/FTC=Complera
EVG/cobi/TDF/FTC=Stribild (Quad)
DTG/ABC/3TC=Triumeq

DHHS guidelines for ART naïve:
preferred (AI): (avoid TDF in renal failure)
• **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** (BI): EFV+TDF/FTC, ATV-r or c+TDF/FTC (cobi in CrCl≥70)
• DRV-r or c + ABC/3TC (in B5701 neg), or DRV-c + TDF/FTC (in CrCl≥70)
• combo pills: RPV/TDF/FTC (Complera; only in VL<100k and CD4>200)
• 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+IDV, ddI+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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