European AIDS Clinical Society (EACS)

Guidelines for the Clinical Management and Treatment of HIV Infected Adults in Europe

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Assessment Of HIV Infected Patients at Initial and Subsequent Visits -1/2-

Initial visit

- Complete medical history
- Physical examination, including height, weight, BMI, blood pressure
- Laboratory evaluation
  - Confirmation of HIV antibody positive
  - Plasma HIV RNA
  - Resistance testing (genotype) with determination of HIV subtype
  - CD4 absolute count + percentage (optional: CD8 and %)
  - Complete blood count, AST, ALT, Alk phosphatase, calcium phosphate, glucose, creatinine, calculated creatinine clearance
  - Antibody tests for toxoplasma, CMV, Hepatitis A, B and C, and syphilis
  - Fasting blood glucose and lipids including fasting total LDL & HDL cholesterol, and triglycerides (see metabolic guidelines)
  - Urine dipstick for protein and sugar
  - HLA B*5701 determination (if available)
- Sexually Transmitted Infection screen if appropriate
- Women: cervical pap smear
- Assessment of social and psychological condition: provide support and counselling if needed
- Consider HAV and HBV vaccination (depending on serology results) and pneumococcal vaccination

Subsequent visits

(Asymptomatic patients not receiving antiretroviral therapy)

- At least every 6 months
  - Complete blood count, CD4 count and %, plasma HIV RNA
- Every year
  - Physical examination
  - Evaluation of social and psychological support, smoking cessation

Assessment Of HIV Infected Patients at Initial and Subsequent Visits -1/2-

- Repeat serologic testing (syphilis, CMV, toxoplasmosis, hepatitis B, hepatitis C) if previously negative
- AST, ALT
- Women: cervical pap smear
- If cirrhosis (regardless of cause): alphafoetoprotein + ultrasound examination
- Fasting lipids

■ Treatment initiation

- Physical examination, including height, weight, BMI, blood pressure
- Plasma HIV RNA
- Resistance testing (genotype), if not yet obtained
- CD4 count and % (optional: CD8 count and %)
- Complete blood count, AST, ALT, bilirubin, creatinine, calculated creatinine clearance, calcium, phosphate
- Fasting glucose and lipids
- Urine dipstick for protein and sugar
- Other laboratory parameters may be useful according to selected first-line regimen eg protein creatinine ratio, amylase, lipase

■ Visits on therapy

- Plasma HIV RNA
- CD4 count and % (optional: CD8 count and %)
- Complete blood count, creatinine, calculated creatinine clearance, AST, ALT bilirubin
- Other laboratory parameters according to selected regimen
- Fasting glucose and lipids

Primary HIV infection (PHI)

Definition of Acute primary HIV infection

- High risk exposure within previous 2-8 weeks,
- and Clinical symptoms,
- and detectable HIV in the plasma (p24 Ag and/or HIV RNA > 10 000 c/ml)
- and negative or indeterminate serologic testing (negative or weakly positive ELISA, and WB $\leq$ 1 band)
- Recommendation: confirm HIV infection by HIV antibody test (WB) performed 3-6 weeks later.

Treatment:

- Favour clinical trial
- Treatment indicated if:
  - AIDS defining events
  - confirmed CD4 <350/mm3 at month 3 or beyond
- Treatment should be considered if
  - Severe illness/prolonged symptoms (especially CNS symptoms)
- Treatment optional, as indication relies only on theoretical considerations. In most situations, wait till month 6 (with CD4 and plasma HIV-RNA monitoring) and follow criteria for initiation of treatment in chronic HIV infection. Some experts recommend treatment as a tool for prevention of HIV transmission.

Duration of treatment: unknown but maybe should be lifelong. Maintain closer follow-up in case of treatment interruption

Resistance testing:

- Recommended in all situations as soon as acute HIV infection is diagnosed, even if treatment not initiated
- In case it cannot be performed, store blood for further testing.

Transmission:

- Recognize sexually transmitted infections (STIs), including syphilis, gonorrhoea, Chlamydia (uretritis and LGV), HPV, hepatitis B and hepatitis C.
- Counsel newly diagnosed patient on high risk of transmission and preventive measures (condoms) including notifying and testing partners.

Recommendations for Initiation of Therapy in Naive HIV-Infected Patients

Symptomatic	Asymptomatic	Resistance testing	Additional remarks
• CDC stage B and C: treatment recommended . • If OI, initiate as soon as possible*	• CD4 < 200: Treatment recommended, without delay. • CD4 201-350: treatment recommended. • CD4 350-500: treatment may be offered if VL>10^5 c/ml and/or CD4 decline >50-100/mm3/year or age >55 or hepatitis C co-infection • CD4 > 500: treatment should be deferred, independently of Plasma HIV RNA; closer follow-up of CD4 if VL > 10^5 c/ml. Whatever CD4 and Plasma HIV RNA, treatment can be offered on an individual basis, especially if patient seeking and ready for ARV therapy	Genotypic testing and subtype determination recommended, ideally at the time of HIV diagnosis, otherwise before initiation of first-line regimen If genotypic testing is not available, a ritonavir-boosted PI could be preferred in the first-line regimen	• Before starting treatment, CD4 should be repeated and confirmed • Time should be taken to prepare the patient, in order to optimize compliance and adherence

* Pay particular attention to drug-drug interactions, drug toxicities, immune reconstitution syndrome and adherence, etc…

Initial Combination Regimen for Antiretroviral-Naïve patient

Select 1 drug in column A and 1 NRTI combination in column B	A	B	Remarks
Recommended	NNRTI • EFV[1] • NVP[4] or ritonavir-boosted PI • fAPV/r • LPV/r • SQV/r	ABC/3TC[2-3] TDF/FTC	• ABC/3TC co-formulated • TDF/FTC co-formulated • fAPV/r:700/100 mg bid or 1400/200 mg qd • LPV/r:400/100 mg bid or 800/200 mg qd • SQV/r:1000/100 mg bid or 1500/100 mg qd or 2000/100 mg qd
Alternative	ATV/r[5]	• ZDV/3TC • ddI/3TC or FTC[6]	ZDV/3TC co-formulated

1 EFV: not recommended in pregnant women or women with no reliable and consistent contraception; not active on HIV-2 and HIV-1 group O
2 Contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory
3 ABC + NVP contra-indicated, unless HLA B*5701 negative
4 NVP: Use with extreme caution in women with CD4 >250 and men with CD4 >400/µL; not active on HIV-2 and HIV-1 group O
5 Approved by FDA but not yet approved by EMEA. Some physicians use ATV/r in first line regimen
6 Only if unavailable or intolerant to other recommended NRTIs

Virologic Failure

Definition	Confirmed Plasma HIV RNA > 50 copies/ml 6 months after starting therapy (initiation or modification) in patients that remains on ART
General measures	• Evaluate adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues • Perform resistance testing on failing therapy (usually reliable with plasma HIV RNA levels >500-1000 copies/ml) and obtain historical resistance testing for archived mutations • Consider TDM • Review antiretroviral history • Identify treatment options, active, potentially active drugs/combinations
Management of virologic failure (VF)	If Plasma HIV RNA > 50 and <500-1000 copies/ml • Check for adherence • Check Plasma HIV RNA 1 to 2 months later • Improve boosted PI's PK (if applicable) If Plasma HIV RNA confirmed > 500/1000 copies/ml, change regimen as soon as possible: what to change will depend on the resistance testing results: • No Resistance mutations found: re-check for adherence, perform TDM • Resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary experts discussion advised Goal of new regimen: Plasma HIV RNA < 400 c/ml after 3 months, Plasma HIV RNA < 50 c/ml after 6 months
In case of resistance mutations demonstrated	General recommendations: • Use 2 or preferably 3 active drugs in the new regimen (including active drugs from previously used classes) • Any regimen should use at least 1 drug from a class not used previously e.g. fusion, integrase or CCR inhibitor • Defer change if < 2 active drugs available, based on resistance data, except in patients with low CD4 count (<100/mm3) or with high risk of clinical deterioration for whom the goal is the preservation of immune function through partial reduction of Plasma HIV RNA (> 1 log reduction) by recycling. • If limited options, consider experimental and new mechanistic drugs, favouring clinical trials (but avoid functional monotherapy) • Treatment interruption is not recommended Optimisation of new regimen: • Avoid NNRTI in NNRTI-experienced patients; Etravirine potentially active in selected NNRTI-resistance profiles • Consider continuation of 3TC or FTC even if documented resistance mutation (M184V/I) • Select other potentially active NRTI(s), on treatment history and full resistance (past and present) evaluation • Select 1 active ritonavir-boosted PI. If at all possible avoid double boosted PIs • Always check for drug-drug-interactions, and when necessary perform TDM of drugs of new regimen if available If many options are available, criteria of preferred choice include: simplicity of the regimen, toxicity risks evaluation, drug-drug-interactions, future salvage therapy

Treatment of HIV Pregnant Women

Pregnant women should be monitored every month and as close as possible to the predicted delivery date.

Criteria for starting ART in pregnant women (see different scenario's)	Same as for non pregnant
Objective of treatment in pregnant women	Full Plasma HIV RNA suppression by third trimester and specifically at time of delivery
Resistance testing	Same as for non pregnant, i.e. before starting ART and in case of virologic failure
SCENARIO 1. Women becoming pregnant while already on ART 2. Women becoming pregnant while treatment naïve and who fulfil the criteria (CD4) for initiation of ART 3. Women becoming pregnant while treatment naïve and who do not fulfil the criteria (CD4) for initiation of ART 4. Women whose follow up starts after W28 of pregnancy	 1. Maintain ART but switch drugs that are potentially teratogenic 2. Start ART at start of 2nd trimester is optimal 3. Start ART at start of W28 of pregnancy (at the latest 12 weeks before delivery) ; start earlier if high plasma viral load or risk of prematurity 4. Start ART immediately
Antiretroviral regimen in pregnancy	Same as non pregnant, • Except avoid EFV • ABC, NVP and TDF not to be initiated but continuation is possible if started before pregnancy • Among PI/r, prefer LPV/r or SQV/r • ZDV should be part of the regimen if possible
Drugs contra-indicated during pregnancy	Efavirenz, ddI + d4T, Triple NRTI combinations
IV zidovudine during labour	Benefit uncertain if Plasma HIV RNA < 50 c/ml
Single dose nevirapine during labour	Not recommended
Caesarean section	Indicated except if Plasma HIV RNA < 50 c/ml at W34-36

Post-Exposure Prophylaxis

	POST-EXPOSURE PROPHYLAXIS (PEP) RECOMMENDED IF	
	Nature of exposure	Status of source patient
Blood	Subcutaneous or intramuscular penetration with IV or IM needle, or intravascular device	HIV + Or serostatus unknown but presence of HIV risk factors
	• Percutaneous injury with sharp instrument (lancet), IM or SC needle, suture needle • Contact > 15 min of mucous membrane or non intact skin	HIV +
Genital secretions	Anal or vaginal sex	HIV + Or serostatus unknown but presence of HIV risk factors
	Receptive oral sex with ejaculation	HIV +
Intravenous drug user	Exchange of syringe, needle, preparation material or any other material	HIV +

- Rapid testing of the source patient for HCV and HIV (if HIV status unknown) recommended,
- If patient source HIV+ on ARV therapy, order genotyping testing if HIV-RNA > 1000 copies/µL
- PEP to be started ideally < 4 hours after the exposure, and no later than 48 hours
- Duration of PEP: 4 weeks
- PEP regimen: TDF/FTC (alternative: ZDV/3TC) + [LPV/r tablets 400/100 mg bid or SQV/r 1000/100 mg bid]
- Full sexual health screen in case of sexual exposure
- Follow-up:
  - HIV serology + HBV and HCV, pregnancy test (women) within 48 hours of exposure
  - Reevaluation of PEP indication by HIV expert within 48-72 hours
  - Assess tolerability of ARV PEP regimen
  - Transaminases, HCV-PCR and HCV serology at month 1 if source of exposure were HCV+ (observed or suspected]
  - Repeat HIV serology after 2 and 4 months, syphilis serology after 1 month if sexual exposure