European Aids Clinical Society (EACS) Guidelines

2008

Version 4 - October 2008

European AIDS Clinical Society (EACS)

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

The European AIDS Clinical Society (EACS) is a not-for-profit group of European physicians, clinicians and researchers in the field of HIV / AIDS

It aims to bring together scientists from all over Europe to help exchange the latest medical and scientific knowledge regarding clinical aspects of HIV/ AIDS and its complications.

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Assessment Of HIV Infected Patients at Initial and Subsequent Visits

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
- PPD if CD4 above 400. Negative PPD does not exclude active or latent tuberculosis

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
  - 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
  - Assess and support patients'readiness to start combined ART (see specific guidelines)
  - 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

New table "Assessing and supporting patients' readiness to start cART" [1]

Goal: Facilitate decision making and starting cART for patients who qualify according to international guidelines.

Before initiating cART, screen for decision making and adherence barriers:

Patient related factors:
A) Depression [2]
B) Harmful alcohol or recreational drug use [3]
C) Cognitive problems [4]
D) Low health literacy.

System related factors:
E) Health insurance and drug supply
F) Continuity of drug supply
G) Social support and disclosure.

Recognise, discuss and reduce problems wherever possible!

Assess patients' readiness and support progress between stages [5]:
"I would like to talk about HIV-medication" <wait> "what do you think about it?" [6]

Remember:

- Set the agenda before every interview
- use open questions whenever possible
- use the WEMS-technique [7]

Precontemplation:
"I don't need it, I feel good"
"I don't want to think about it"

Support: Show respect for patient attitude / Try to understand health and therapy beliefs / Establish trust / Provide individualised short information / Schedule the next appointment.

Restage again

Contemplation:
"I am weighing things up and feel torn about what to do about it"

Support: Allow ambivalence / Support to weigh pros and cons together with patient / Assess information needs and support information seeking / Schedule the next appointment.

NO

Restage again

Preparation
"I want to start, I think the drugs will allow me to live a normal life"

Support: Reinforce decision / Make shared decision on most convenient regimen / Educate: adherence, resistance, side effects / Discuss integration into daily life / Assess self-efficacy
Ask: "*Do you think you can manage to take cART consistently once you have started?*"
Use: VAS 0-10 [8]

0 5 10

NO

YES

Patients presenting in the clinic may be at different stages of readiness: Precontemplation, contemplation or preparation [Transtheoretic model ; Prochaska JO. Am Psychol 47:1102-1114, 1992]. The first step is to assess this stage, and then to support/intervene accordingly. An exception is if a patient presents late or very late, i.e. <200 or <50 CD4/µl. In this case the initiation of cART should not be delayed; the clinician should try to identify the most important adherence barriers which may be present, and support the patient to be prepared for prompt initiation of cART.

Consider skills training:

- Medication-taking training, possibly MEMS (2-4wk) [9]
- Directly Observed Therapy with educational support
- Use aids : Pill boxes, cell phone alarm, involve contact persons where appropriate

START and maintain adherence

Screen: For adherence problems in each meeting [10]
Support: Discuss side effects, educate about surrogate markers, discuss integration of drug taking schedule
Empower: Give positive feedback

Comments to the table Start of cART and patients' readiness (1)

1 This table should facilitate the initiation of cART. Matters for consideration listed in this table, such as decision making or barriers to adherence, have to be judged clinically in their context. For instance the clinician has to judge whether cART has to be initiated immediately despite the detection of possible barriers to adherence or whether delaying initiation is justified. Consider patient's cultural background.

2 Ask: *"During the past month have you often been bothered by feeling down, depressed or hopeless?" "During the past month have you often been bothered by little interest or pleasure in doing things?" "Is this something with which you would like help?"* If answers are positive, then sensitivity is 96%, specificity 89% (Arroll B et al. BMJ 327:1144-1146. 2003).

3 Ask: *"Have you thought about **C**utting down?" "Have you ever become **A**nnoyed when people talk to you about your drinking?" "Have you ever felt **G**uilty about your drinking?" "Do you ever have a drink first thing in the morning (**E**ye opener)?"* An affirmative answer to more than two CAGE-questions means a sensitivity and specificity for problematic alcohol use of more than 90% (Kitchens JM. JAMA 272(22):1782-1787. 1994.). Ask similar questions for recreational drug use.

4 Ask: "*Do you feel that you are having problems concentrating in your daily life?*" "*Do you feel slow in your thinking?*" "*Do you feel that you are having problems with your memory?*" "*Have relatives or friends expressed that they feel you are having problems with your memory or difficulty concentrating?*"

5 Patients presenting in the clinic may be at different stages of readiness: Precontemplation, contemplation or preparation [Transtheoretic model ; Prochaska JO. Am Psychol 47:1102-1114, 1992]. The first step is to assess this stage, and then to support/intervene accordingly. An exception is if a patient presents late or very late, i.e. <200 or <50 CD4/µl. In this case the initiation of cART should not be delayed; the clinician should try to identify the most important adherence barriers which may be present, and support the patient to be prepared for prompt initiation of cART.

6 This is a suggested opening question to assess the patient's stage of readiness. Further discussion will indicate which of the three initial stages the patient has reached: he/she might even be ready for therapy.

7 WEMS: **W**aiting (>3sec), **E**choing, **M**irroring, **S**ummarising (Langewitz W et al. BMJ 325:682-683. 2002).

8 VAS (= Visual Analogue Scale; Range from 0 to 10 i.e. 0 = I will not manage, 10 = I am sure I will manage).

9 Medication training/ MEMS training could be done with vitamins before starting cART.

10 Suggested adherence questions: "In the past 4 wks how often have you missed a dose of your HIV medication: every day, more than once a wk, once a wk, once every 2 wks, once a month, never?" "Have you missed more than one dose in a row?" (Glass TR et al. Antiviral Therapy 13(1):77-85. 2008).

Adapted from: J. Fehr, D. Nicca, F. Raffi, R. Spirig, W. Langewitz, D. Haerry, M.Battegay, NEAT, 2008.

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 ≤ 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 (Urethritis 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.

* If treatment of PHI is considered then patients should be recruited into on-going clinical trials

Recommendations for Initiation of Therapy in Naïve HIV-Infected Patients

Symptomatic	Asymptomatic	Resistance testing	Additional remarks
• CDC stage B and C: treatment recommend ed. • 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…

** See recommendation on "Assessing and supporting patients readiness to start cART

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 • FPV/r • LPV/r** • SQV/r • ATV/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	DRV/r[5]	• ZDV/3TC[6] • 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 Not yet approved by either FDA or EMEA. However, once this is the case DRV/r may be added to the list of recommended boosted PI's for initial treatment
6 Only if unavailable or intolerant to other recommended NRTIs

* Abacavir should be used with caution in patients with a high cardiovascular risk and/or patients with more than 100,000 copies/ml.

** ACTG 5142, randomised study showed lower virological efficacy of LPV/r vs EFV. However no PI mutations were seen in the LPV/r failures.

Virological Failure

Definition	Confirmed Plasma HIV RNA > 50 copies/ml 6 months after starting therapy (initiation or modification) in patients that remain 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 virological 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 (if tropism test shows R5 virus only) • 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 scenarios)	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 virological 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 source patient 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) + either 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

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Guidelines on the Prevention and Management of Metabolic diseases in HIV

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Acknowledgements: The guidelines panel have received helpful comments and suggestions from the following persons: Heiner Bucher, David Burger, Nina Friis-Møller, Jose Gatell, Markku Saraheimo, Signe Worm & Hannele Yki-Järvinen

Abbreviations used throughout this document

- ABC=abacavir
- ART=antiretroviral therapy
- ATV=atazanavir
- CVD=cardiovascular disease
- d4T=stavudine
- ddI=didanosine
- DRV=darunavir
- EFV=efavirenz
- HBV=hepatitis B virus
- HCV=hepatitis C virus
- HDL-c=HDL-cholesterol
- IHD=ischemic heart disease
- LDL-c=LDL-cholesterol
- IDV=indinavir
- LPV=lopinavir
- NFV=nelfinavir
- NNRTI=non-nucleoside reverse transcriptase inhibitors
- NRTI=nucleos(t)ide reverse transcriptase inhibitors
- NVP=nevirapine
- PI=protease inhibitors
- PI/r=protease inhibitors pharmacologically boosted with ritonavir
- RTV=ritonavir (if used as booster= /r)
- SQV=saquinavir
- TC=total cholesterol
- TG=triglycerides
- TDF=tenofovir
- TPV=tipranavir
- ZDV=zidovudine

HIV specific issues to be considered in managing metabolic diseases

In HIV infection, both uncontrolled replication of HIV, co-infections (e.g. HCV) and ART contribute to metabolic diseases. The prevention and management of metabolic diseases in HIV should take all these factors into consideration.

Health care professionals involved with the care of HIV-infected persons who are not familiar with the use of ART should consult HIV specialists before introducing or modifying any type of treatment that HIV patients receive.

Conversely, many HIV physicians are not specialists in metabolic diseases, and should seek proper consultation prior to engaging in the prevention and management of such conditions. Situations where consultation is generally recommended are indicated where appropriate in these guidelines.

Preventing or managing metabolic diseases in HIV often involves polypharmacy, which increases the risk of suboptimal adherence and hence may compromise the continued benefit of ART. Additionally, the possibility of drug-drug interactions with ART should be carefully considered prior to introducing any treatment. Several web-sites exist for this purpose: www.HIV-druginteractions.org, www.HIVpharmacology.com, www.AIDSinfo.nih.gov.

There is limited evidence from randomised controlled trials on how to most effectively manage metabolic diseases in HIV. As a result *management currently is mainly extrapolated from general medical guidelines*. Based on future clinical research findings, these guidelines will be regularly updated at www.europeanaidsclinicalsociety.org. The guidelines posted on the web, as well as updated versions will contain much more detailed information and links to any other relevant websites.

The current guidelines highlight metabolic diseases, which are seen frequently in the routine care of HIV-infected persons and those for which specific issues should be considered.

Other related conditions in the management of HIV disease that are not or not extensively discussed, but may be included in future versions are:

- *Renal impairment.* Both factors related to HIV and certain antiretroviral drugs may impair renal function. Various drugs used in HIV care may need dose adjustment in case of impaired renal function.
- The contribution of HIV as well as ART to *bone disease, which may include loss of bone mineral content and aseptic necrosis of the femoral head*, remains unclear. For the moment these pathologies should be managed as in the general population.
- *Sexual dysfunction* is frequently encountered and its management often requires a multidisciplinary approach that may include both expert psychological counselling and medical interventions.

Screening for metabolic diseases in patients with HIV

	Assessment	Which Patient?	Frequency of assessment
History	• Family history for premature IHD[i], diabetes, hypertension • Concomitant therapy against dyslipidaemia/hypertension/ diabetes • Concomitant therapy with risk for diabetes/dyslipidaemia[ii] • Current lifestyle (alcohol use, smoking, aerobic exercise)	Every patient	At HIV-diagnosis At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated[iv]
Lipids[iv]	• Fasting[iii] TC • Fasting[iii] TG • Fasting[iii] LDL-c+HDL-c	Every patient	At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated[iv]
Glucose[v]	• Fasting[iii] glucose	Every patient	At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated[iv]
Body composition	• Body-mass index • Waist circumference • Waist-to-hip ratio • Clinical lipodystrophy assessment	Every patient	At HIV-diagnosis, before start of ART, annually thereafter
Hypertension	• Blood pressure	Every patient	HIV-diagnosis, before ART, annually thereafter unless specifically indicated[iv]
Cardiovascular disease	• Risk assessment[vi] • ECG	Every patient	Before ART, and annually thereafter Annually
Renal failure	• Estimated glomerular filtration rate[vii] • Dip stick	Patient receiving drugs cleared via the kidneys	Before initiation of drug in question, after 4 weeks, 6 months and if remaining normal then once annually

i Cardiovascular events in a first degree male relative < 55 years or in a first degree female relative < 65 years.

ii E.g. neuroleptic drugs including clozapin, olanzapin; pentamidine, glucocorticoids, IFN-a, thiazide diuretics, furosemide, phenytoin, diazoxide, and others.

iii Fasting defined as a time period without caloric intake of at least 8 hours

iv Assessment and monitoring should increase in frequency in case of severe dyslipidaemia (see p. 30), elevated blood pressure (see p. 40) or elevated fasting blood glucose levels (see p. 36) and/or if medical interventions are instituted to correct these conditions.

v Oral glucose tolerance test may be considered if repeated fasting glucose levels are in the range of 6.1-6.9 mmol/L (110-125 mg/dL) as it may reveal the presence of diabetes in such patients.

vi Use risk calculators for estimating 10-year risk of developing IHD events - http://www.chip.dk/tools.aspx. Of note, if individual patients receive medication to control dyslipidaemia and/or hypertension, interpretation of the estimation should be done with caution.

vii Use calculator to estimate glomerular filtration rate (eGFR) according to Cockcroft- Gault - http://www.cphiv.dk/TOOLS.aspx.

Prevention of cardiovascular disease

Principles: The intensity of efforts to prevent cardiovascular disease depends on the absolute risk of IHD, using Framingham equation (see http://www.cphiv.dk/tools.aspx). The preventive efforts are diverse in nature and require involvement of cardiologists, in particular if the risk of IHD is high.

ESTIMATE RISK OF IHD IN NEXT 10 YEARS

IHD risk < 10%	IHD risk 10-20%	IHD >20%, prior CVD, type II diabetes, type I diabetes with microalbuminuria
Encourage life-style changes (diet, exercise, cessation of smoking), reduce visceral fat, reduce insulin resistance and treat hypertension		
[i]**LDL-c cut off level: 5 mmol/L (~190 mg/dL)** (5-4 mmol/L (~190 - ~155 mg/dl))	[i]**LDL-c cut off level: 4 mmol/L (~155 mg/dL)** (4-3 mmol/L (~155 - ~115 mg/dl))	[i]**LDL-c cut off level: 3 mmol/L (~115 mg/dL)** (3-2 mmol/L (~115 - ~80/mg/dl))
Consider modifying ART, if: [i]LDL-c is above cut off, [ii]ART thought to contribute to ↑LDL-c level, if possible without compromising HIV suppression[ii]	**Consider modifying ART, if:** [i]LDL-c is above cut off, [ii]ART thought to contribute to ↑LDL-c level, if possible without compromising HIV suppression[ii]	**Strongly consider modifying ART, if:** [i]LDL-c is above cut off, [ii]ART thought to contribute to ↑LDL-c level, if possible without compromising HIV suppression[ii]
If life style changes, with or without modification of ART, do not result in sufficient lowering of LDL-c to below target level, use of lipid-lowering medication should be considered (see p. 32).		

i LDL-c cut off levels (unit: mmol/L (mg/dL)) are higher than in guidelines for the general population (more stringent levels where some experts would consider intervention also indicated in parenthesis below). In cases where LDL-c cannot be reliably calculated because of high triglyceride levels, the non-HDL-c target level should be used which is 0.8 mmol/L (30 mg/dl) higher than the corresponding LDL-c target.

ii Options for ART modification include: **(1)** replacing PI/r by NNRTI or by another PI/r known to cause less metabolic disturbances (see p. 34); **(2)** replace d4T or ZDV with TDF. In patients with >20% 10 year risk of CHD or with prior CVD, the risk of CVD events and cardiac death will usually be higher than risk of progression to AIDS or death and in such patients a strategy to reduce risk of CVD by switching ART is hence most appropriate. Recent data suggest ABC should be used with caution in patients at high CV risk; whether patients with high CV risk on ABC should change regimen remains unclear as impact of TDF on CV risk is currently unknown and other NRTI's are also associated with metabolic disorders.

- Blood-pressure: ↑treat hypertension (see p. 40).
- TG levels: Uncertain if TG↑ contributes to CVD risk and whether it should be treated (see p. 32).
- Low dose acetylsalicylic acid: Only indicated in high-risk patients (right column above) as risk of intracerebral bleeding increased by 25% and extracerebral bleeding by 50%; harm likely exceeds benefit if risk of IHD is lower.
- Combined benefit of interventions: Per 10 mmHg reduction of systolic blood pressure, per 1 mmol/L reduction in TC and with use of low dose acetylsalicylic acid, each reduces risk of IHD by 20-25%; the effect is additive. Smoking cessation reduces risk of IHD the most - by 50% - and this is additive to other interventions.

Life style interventions[i]

Intervention	Principles
Stop smoking counselling	• Brief unambiguous statement about need to stop smoking • If patient is not contemplating, try to motivate and emphasize positive short-term aspects (more money for better things, better taste for food, better skin, less dyspnoea), and long-term benefits (prevention of COPD, IHD, stroke, lung cancer) • If patient is contemplating, try to fix stop date, establish reward system • Use nicotine substitution (patch, chewing gum, spray), varenicline, or bupropion (note: bupropion may interact with PI and NNRTI) during weaning phase if necessary • Consider referring patient to specialized stop smoking clinic • Anticipate relapses, explain and consider them as part of the weaning process to final nicotine abstinence
Diet counselling	• Limit intake of saturated fat and cholesterol • Reduce total fat intake to < 30% and dietary cholesterol to <300mg/day • Emphasize intake of vegetables, fruits, grain products with fibre • Emphasize consumption of fish, poultry (without skin), lean meat and low fat dietary intake • Keep caloric intake balanced with energy expenditure • Consider referral to dietician, one week food and drink diary to discover 'hidden' calories • Avoid binge eating ('yo-yo dieting') • In patients with HIV-related wasting and dyslipidaemia address wasting first and consider referral to dietician • Patients with BMI >30 kg/m^2 should be motivated to lose weight. Starvation diets are not recommended in an HIV-infected person (immune defence mechanisms potentially decreased). Malnutrition has to be addressed where observed. Normal BMI range: 18.5-24.9; Overweight: 25.0-29.9, Obesity: > 30.0 kg/m^2
Exercise	• Promote active lifestyle to prevent obesity, hypertension and diabetes • Emphasize regular moderate-intensity exercise rather than vigorous exercise • Encourage self-directed moderate level physical activity (take the stairs, bike or walk to work, cycling, swimming, hiking etc.) • Achieve cardiovascular fitness (e.g. 30 minutes brisk walking 5/7 days a week) • Maintain muscular strength and joint flexibility

i Based on recommendations by the US Preventive Services Task Force. Detailed guidelines with evidence grading (fulltext) available at http://odphp.osophs.dhhs.gov/pubs/guidecps/pcpstoc.htm

Management of dyslipidaemia

Principles: Higher LDL-c levels increase risk of CVD and reduction thereof reduces this risk; the reverse is true for HDL-c.

Conversely, the CVD risk implications from higher than normal levels of TG are less clear, as is the clinical benefit of treating moderate hypertriglyceridaemia. Diet, exercise and maintaining normal body weight tends to reduce dyslipidaemia; if not effective, consider change of ART and then consider lipid-lowering medication in high-risk patients (see p. 26).

Drugs used to treat dyslipidaemia

Drug class	Drug	Dose	Benefit		Side effects	Advice on use of statin together with ART	
						Use with PI/r	Use with NNRTI
Statin	Atorvastatin	10-80 mg QD	LDL-c↓[ii]		Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Relative contraindicated	Consider higher dose[iv]
	Fluvastatin	20-80 mg QD	LDL-c↓[i]			Consider higher dose[iv]	Consider higher dose[iv]
	Pravastatin	20-80 mg QD	LDL-c↓[i]			Consider higher dose[iv-vi]	Consider higher dose[iv]
	Rosuvastatin	5-40 mg QD	LDL-c↓[ii]			Start with low dose[v]	Start with low dose[v]
	Simvastatin	10-80 mg QD	LDL-c↓			Contraindicated	Consider higher dose[iv]
Cholesterol uptake↓	Ezetimibe	10 mg QD	LDL-c↓[iii]		Gastrointestinal symptoms	No known drug-drug interactions with ART	
Nicotinic acid derivative	Acipimox	1.0-1.5 g QD	TG↓		Flushing, rash, headache, gastrointestinal symptoms		
Fibrate	Bezafibrate	400 mg QD	TG↓		Gastrointestinal symptoms, toxic hepatitis, myopathy and rhabdomyolysis		
	Fenofibrate	67-267 mg QD	TG↓				
	Ciprofibrate	100 mg QD	TG↓				
	Gemfibrozil	900 mg QD/600 bid	TG↓				
Omega 3 acid ester	MaxEPA	5 g bid	TG↓				
	Omacor	1-2 g bid	TG↓				

i, ii, iii Expected range of reductions of LDL-c: [i]0.8-1.5 mmol/L (35-60 mg/dL), [ii]1.5-2.5 mmol/L (60-100) mmol/L, [iii]0.2-0.5 mmol/L (10-20 mg/dL)

iv, v The ART drug may [iv]induce (=less effect of statin, ↑dose gradually to achieve expected benefit[i,ii]) or [v]inhibit (statin toxicity, ↓dose) the excretion of the statin.

vi **Exception:** If used with **DRV/r**, start with **lower** dose of pravastatin.

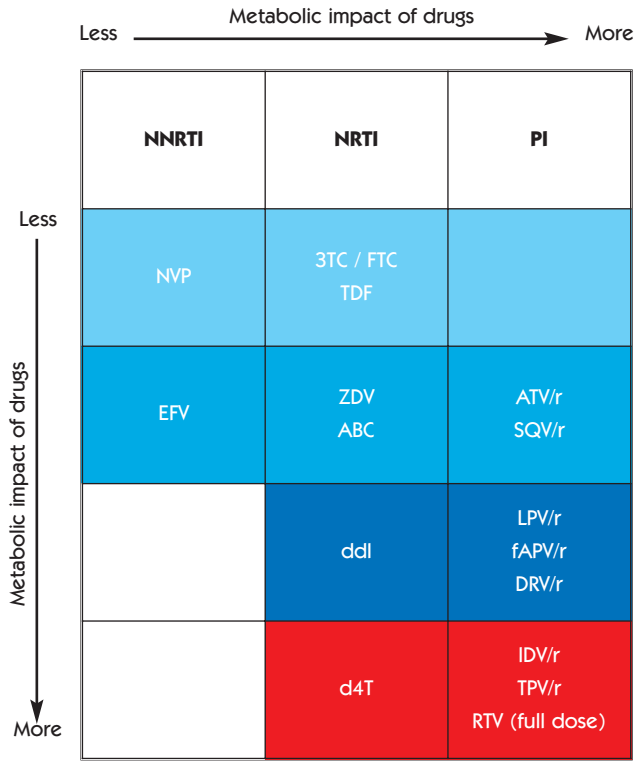
Treatment recommendations

Type of dyslipidaemia	First choice[i]	Combination therapy [i]
Isolated hypercholesterolaemia (LDL-c > cut-off (see p. 26))	Statin[ii]	+ Ezetimibe
Combined hyperlipidaemia (LDL-c > cut-off (see p. 26) and TG 5 - 10 mmol/l[iii])	Statin[ii]	+ Fibrate[iv] (/nicotinic acid derivative)
Isolated hypertriglyceridaemia (TG 2.3-10 mmol/L[iii])	Diet, alcohol abstinence	–
Severe hypertriglyceridaemia (> 10 mmol/l[iii])	Fibrate	+ Omega 3 acid ester (/nicotinic acid derivative)

In cases where dyslipidemia includes low HDL-c and the person has a high underlying risk for CVD, modification of ART to include nevirapine or efavirenz may be considered as long as viral control is not jeopardized; both these drugs may increase HDL-c levels.

i Treatment goal is to reduce LDL-c < cut-off levels (see p. 26). Check lipids (fasting) prior to initiation of therapy, 4-12 weeks after initiation or modification of therapy, and annually once levels are below cut off levels. Consult with lipid expert if treatment goal cannot be reached.
ii Check AST (< x 3 ULN) and CK (< x5 ULN) prior to initiation, 4-12 weeks after treatment initiation, and then annually if within normal range.
iii It is not clear whether these levels of elevated TG carry an excess CVD risk; priority should be given to reducing LDL-c to below cut-off levels (see p. 26).
iv Combination therapy of statin and gemfibrozil (and less so other fibrates) increases risk of rhabdomyolysis and should be avoided whenever possible.

Metabolic impact of individual antiretroviral drugs & drug classes[i]



i Limited data from use of fusion inhibitors (enfuvirtide), integrase inhibitors (raltegravir), and CCR5 inhibitors (maraviroc) suggest these drugs to have little metabolic impact, but length of experience for some of these is limited

Prevention and management of lipodystrophy

Lipoatrophy

Prevention

- Avoid d4T and ZDV or pre-emptively switch away from them

Management

- Modification of ART
  - Switch d4T or AZT to ABC or TDF:
    - ↙ Only ART modification proven to partially restore subcutaneous fat; increase in total limb fat ~400-500g/year
    - ↙ Risk of new toxicity (ABC hypersensitivity reaction?; TDF associated nephrotoxicity?)
  - Switch to regimen not including NRTIs
    - ↙ Increase in total limb fat ~400-500g/year
    - ↙ May increase risk of dyslipidaemia
    - ↙ Less data on virological safety
- Surgical intervention
  - Offered for cosmetic relief of facial lipoatrophy only; fillers may be absorbable (limited effect) or permanent (durability of desired cosmetic effect is unknown)[i]
  - Limited randomized trials and no comparative studies of different approaches
- Pharmacological interventions to treat lipoatrophy have not been proven to be effective and may introduce new complications
  - Pioglitazone - possibly beneficial in patients not taking d4T
  - Rosiglitazone and Pioglitazone - improvement in insulin sensitivity
  - Rosiglitazone: increases in blood lipids and possible IHD.

Lipohypertrophy

Prevention

- No proven strategy
- Weight gain expected with effective ART
- Weight reduction or avoidance of weight gain may decrease visceral adiposity

Management[ii]

- Diet and exercise may reduce visceral adiposity;
  - Limited data, but possibly reduction of visceral adipose tissue and improvement in insulin sensivity and blood lipids, especially in obesity associated with lipohyperthrophy
  - No prospective trials in HIV-infected patients to definitely indicate degree of diet and/or exercise needed to maintain reduction in visceral fat.
  - May worsen subcutaneous lipoatrophy
- Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects and may introduce new complications
  - Growth hormone
    - ↙ Decreases visceral adipose tissue
    - ↙ May worsen subcutaneous lipoatrophy, may worsen insulin resistance
  - Metformin
    - ↙ Decreases visceral adipose tissue in insulin resistant persons
    - ↙ May worsen subcutaneous lipoatrophy.
  - Surgical therapy can be considered for localised lipomas/buffalo humps
    - ↙ Duration of effect variable

i See (http://www.europeanaidsclinicalsociety.org/guidelinespdf/2_Prevention_and_Management_of_Metabolic_diseases_in_HIV.pdf) for list of arguments for and against the use of various types of fillers and some examples of specific types.

ii Tesamorelin was shown to reduce visceral adipose tissue volume; the drug is not currently licensed in Europe.

Treatment of type 2 diabetes

Diagnostic criteria[i]			
	Fasting plasma glucose mmol/l (mg/dl)[ii]		Oral glucose tolerance test (OGTT) 2-h value mM (mg/dl)[iii]
Diabetes	≥ 7.0 (126)	OR ----------→	≥ 11.1 (200)
Impaired glucose tolerance (IGT)	< 7.0 (126)	AND ----------→	7.8 - 11.0 (140 - 199)
Impaired fasting glucose (IFG)	6.1 - 6.9 (110 - 125)	AND ----------→	< 7.8 (140)

i As defined by WHO and International Diabetes Federation (2005)
ii An abnormal finding should be repeated before confirming the diagnosis.
iii Is recommended in patients with fasting blood glucose 6.1 - 6.9 mmol/L (110 - 125 mg/dL) as it may diagnose patients with overt diabetes.

Both IGT and IFG increase CV morbidity and mortality, and increase the risk of developing diabetes by 4-6 fold. These patients should be targeted for life style intervention, and their CV risk factors must be evaluated and treated.

Interventions for treatment of diabetes (only interventions studied in persons receiving ART)				
Intervention	Dose	Expected decrease in HbA1c (%)	Side-effects	Comments
Life-style intervention		1 - 2		Intra-abdominal and subcutaneous fat may↓
Metformin	Start with 500-750mg qd/bid, increase to maximum tolerated dose of 2 (-3) g/d in 4-6 weeks	1.5	Gastrointestinal symptoms, lactic acidosis (rare). Contraindicated in renal insufficiency.	May worsen lipoatrophy
Thiazolidinediones: Rosiglitazone Pioglitazone	4-8mg/d, 15-45 mg/d	0.5 - 1.4	Fluid retention, cardiac failure, weight gain	See also p. 34 Contraindicated if prior or present cardiac failure
Insulin	See below	No limit	Hypoglycaemia, weight gain.	Large doses may be required (1-2 IU/kg).

Individualise treatment: metformin for an overweight patient, pioglitazone (rosiglitazone) for a lipoatrophic patient. Metformin and glitazones can be combined. Diabetes is typically a progressive disease and medication must be modified accordingly. There are currently no data on the use of other antidiabetic drugs (sulfonylureas, glinides, incretin mimetics, alpha-glucosidase inhibitors) in the treatment of HIV-infected patients taking ART. If treatment target cannot be reached with oral agents, insulin should be started. Start with 10 IU of long-acting insulin at bedtime. Teach the patient to self-monitor fasting glucose values and increase the dose by 2 units every 3 days until fasting plasma glucose < 6.1 mmol/l. Oral metformin should be continued with insulin therapy.

Management of patients with diabetes

Treatment goals: glucose control (HbA1c < 6.5-7.0% without hypoglycaemia, fasting plasma glucose 4-6 mmol/l (73-110 mg/dl)); normal blood lipids and blood pressure (see p. 26 and p. 40).

Acetylsalisylic acid (75-150mg/d) should be considered in all patients with diabetes.

Nephropathy and retinopathy screening should be performed as in diabetic patients without HIV.

Consultation with a specialist in diabetology is recommended.

Further reading: www.easd.org
http://www.who.int/diabetes/publications

Prevention and management of hyperlactataemia

Risk factors	Prevention / Diagnosis	Symptoms
✔ Use of d4T > ZDV > ddI ✔ HCV/HBV co-infection ✔ Use of ribavirin ✔ Liver disease ✔ Low CD4 cell count ✔ Pregnancy ✔ Female sex ✔ Obesity	✔ Avoid d4T + ddI combination ✔ Routine monitoring of serum lactate levels not recommended - does not predict risk of lactic acidosis. ✔ Measurement of serum lactate, bicarbonate & arterial blood gases+pH indicated in case of symptoms suggestive of hyperlactataemia ✔ Close monitoring if > 1 risk factors	✔ Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, weight loss ✔ Acidaemia: asthenia,dyspnoea, arrhythmias ✔ Guillain-Barré-like syndrome

Management

Serum Lactate (mmol/L)	Symptoms	Action
> 5[i]	Yes/No	• Repeat test under standardized conditions to confirm & obtain arterial pH and bicarbonate[i] • If confirmed, exclude other obvious causes ✔ Arterial pH↓ and/or bicarbonate↓[i]: Stop NRTIs ✔ Arterial pH and/or bicarbonate normal: Consider switch from high to low risk NRTI & monitor carefully OR Stop NRTI's
2-5	Yes	• Exclude other causes; if none found: watchfully follow up OR consider switch from high to low risk NRTI, OR stop NRTI
2-5	No	• Repeat test ✔ if confirmed: watchfully follow up
<2		• None

i Lactic acidosis is a rare but life-threatening situation usually associated with symptoms; high risk if serum lactate > 5 and especially > 10 mmol/L.

Management of lactic acidosis (irrespective of serum-lactate level): Admit patient. Stop NRTI's. Provide intravenous fluid support. Vitamin supplementation can be used (vitamin B complex forte 4 ml bid, riboflavin 20 mg bid, thiamine 100 mg bid; L-carnitine 1000 mg bid), although benefit not well documented

Management based on blood pressure measurement / diagnosis of hypertension -1/2-

Recommendation for intervention from stratification based on blood pressure level and other risk factors

	Blood pressure (mmHg)[i] - levels				+ diagnosis & grading of hypertension	
Other risk factors and disease history	**Normal:** SBP 120-129 or DBP 80-84	**High normal:** SBP 130-139 or DBP 85-89	**Grade 1:** SBP140-159 or DBP 90-99		**Grade 2:** SBP 160-179 or DBP100-109	**Grade 3:** SBP > 180 or DBP > 110
No other risk factors	Average risk	Average risk	Low added risk		Moderate added risk	High added risk
	No BP intervention	No BP intervention	Lifestyle changes for several months[ii], then possible drug therapy[iii]		Lifestyle changes for several months[ii], then drug therapy[iii]	Immediate drug therapy[iii] and lifestyle changes[ii]
1-2 risk factors[iv]	Low added risk	Low added risk	Moderate added risk		Moderate added risk	Very high added risk
	Lifestyle changes[ii]	Lifestyle changes[ii]	Lifestyle changes for several months[ii], then drug therapy[iii]		Lifestyle changes for several months[ii], then drug therapy[iii]	Immediate drug therapy[iii] and lifestyle changes[ii]
3 or more risk factors[iv] or target organ disease[v] or diabetes	Moderate added risk	High added risk	High added risk		High added risk	Very high added risk
	Lifestyle changes[ii]	Drug therapy[iii] and lifestyle changes[ii]	Drug therapy[iii] and lifestyle changes[ii]		Drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]
Associated clinical conditions[vi]	High added risk	Very high added risk	Very high added risk		Very high added risk	Very high added risk
	Drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]		Immediate drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]

Management based on blood pressure measurement / diagnosis of hypertension -2/2-

i SBP =systolic blood pressure; DBP = diastolic blood pressure. Repeated blood pressure measurements should be used for stratification

ii Recommended life style interventions - see p. 28. Table adapted from J. Hypertension 2003; 21:1779-86.

iii Drug therapy can be initiated either with a low dose of a single agent or with a low dose combination of two agents. To reach target blood pressure, a proportion of patients will require combination therapy. For indications and contraindications for the major classes of antihypertensive drugs see (http://www.europeanaidsclinicalsociety.org/guidelinespdf/2_Prevention_and_Management_of_Metabolic_diseases_in_HIV.pdf).

Medical treatment of uncomplicated hypertension: 1st choice: Thiazide or ACE-inhibitor, 2nd choice: Amlodipine (start with 5mg QD) or combination of two antihypertensives. Await (2-) 6 weeks of therapy to assess lowering of the blood-pressure. Grade 3 hypertension or lack of achievement of goal (see below) 2-6 weeks after commencing 2nd choice: consult hypertension expert.
Co-administration of PIs and calcium channel blockers (CCB) may result in significantly increased CCB-plasma concentrations resulting in increased risk of toxicity and prolonged effect; NNRTI's may decrease plasma concentrations of CCBs and reduce efficacy of CCB. Atenolol is the preferred beta-blocker when combined with ARVs; metoprolol plasma concentrations may be increased by boosted PIs. Consult a clinical pharmacologist or pharmacist when combining another antihypertensive agent with ARVs.

iv Risk factors include age (>45 years for men; > 55 years for women), smoking, family history of premature CVD

v Target organ disease (left ventricular hypertrophy, ultrasound evidence of arterial wall thickening, microalbuminuria)

vi Associated clinical conditions (CVD, IHD, renal disease, peripheral vascular disease, advanced retinopathy);

Goals of treatment: **Reduced SBP to <140/90 mmHg and to lower values if tolerated, with diabetes SBP<130/80 mmHg; SBP values <140 mmHg may be difficult to achieve in the elderly.**

Warning: **Caution regarding drug-drug interactions with antihypertensive drugs and ART.**

EACS
European AIDS Clinical Society

European AIDS Clinical Society (EACS)

Guidelines for the clinical management and treatment of chronic hepatitis B and C co-infection in HIV-infected adults

Management based on blood pressure measurement / diagnosis of hypertension -2/2-

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Guidelines for the clinical management and treatment of chronic hepatitis B and C co-infection in HIV-infected adults

These Euroguidelines result from the short statement of the first European Consensus conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. J Hepatol 2005;42:615-624, the updated recommendations from the HCV-HIV International Panel (Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, Mauss S, Bräu N, Hatzakis A, Pol S, Rockstroh J. Care of patients co-infected with HIV and hepatitis C virus: 2007. AIDS. 2007;21:1073-1089) and from a discussion with the following panel:

PANEL MEMBERS

Jürgen Rockstroh (Chair),
Bonn, Germany

Sanjay Bhagani, London, United Kingdom

Raffaele Bruno, Pavia, Italy

Stefan Mauss, Dusseldorf, Germany

Lars Peters, Copenhagen, Denmark

Massimo Puoti, Brescia, Italy

Vicente Soriano, Madrid, Spain

Cristina Tural, Barcelona, Spain

Yves Benhamou, Paris, France

General recommendations for counselling in patients with HIV and hepatitis co-infection

SCREENING

1. All HIV-infected patients should be screened for hepatitis C at diagnosis and then on an annual basis. Screening for HCV in HIV-infected patients should be done using a third generation anti-HCV antibody test. A positive result should be followed by evaluation for the presence of HCV-RNA and the genotype should be determined. Patients with risk factors (ongoing IVDU, mucosal traumatic sex ;consider recent outbreak of acute HCV in msm) with unexplained increase in hepatic transaminases and a negative HCV antibody test should be offered an HCV-RNA test for early detection of a recent infection.
2. HIV-infected patients should be screened for hepatitis A and B.
3. Hepatitis delta antibodies should be screened for in all HBsAg+ patients.

VACCINATION

4. Patients lacking anti-HAV IgG-antibodies and anti-HBV antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4-count. The response to the vaccine is influenced by the CD4-count and level of HIV-RNA. In patients with low CD4-counts (< 200/µl) and ongoing HIV replication, HAART should be initiated first prior to respective vaccination. In case of insufficient response (anti-HBs < 10 IU/l) re-vaccination should be considered. Double dose re-vaccination (40µg) at 3-4 vaccination time points (month 0, 1, 6 and 12) may help to improve response rates to vaccination.

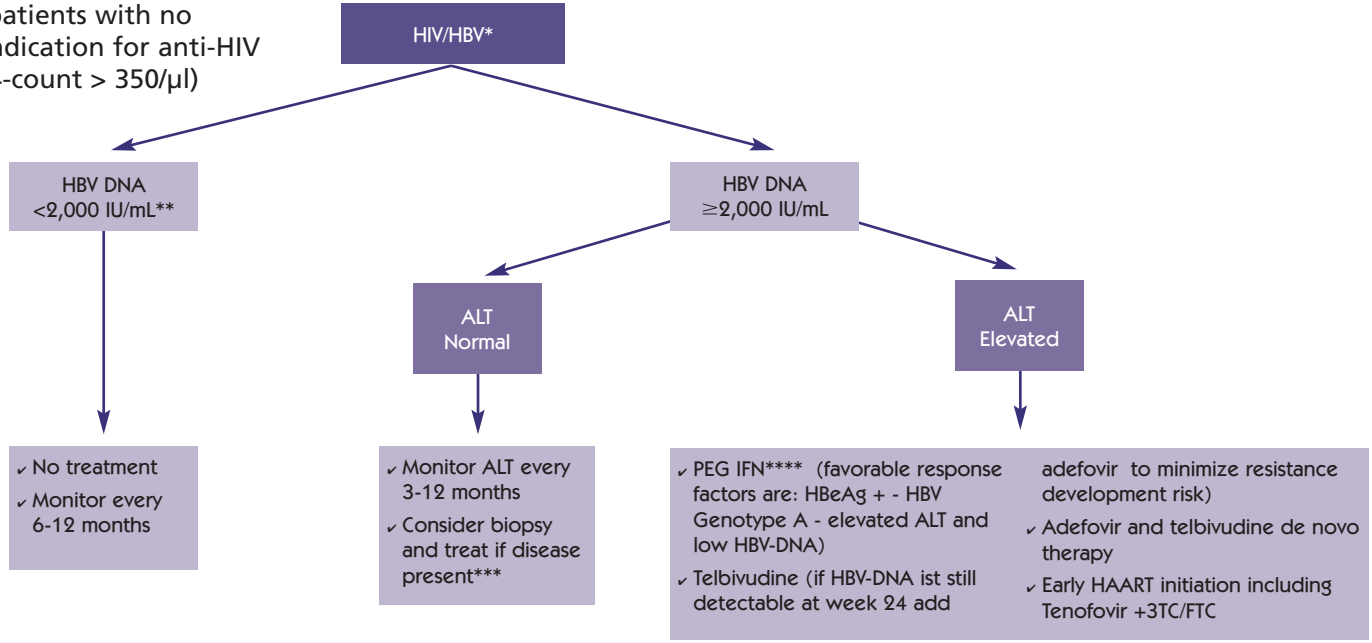
   Patients who failed to seroconvert after hepatitis B vaccination and remain at risk for HBV-infection should be monitored annually for serological markers of HBV-infection.

PREVENTION/SUPPORT

5. Psychological, social and medical support should be made available to stop patients with a high alcohol intake from drinking or to strongly advise them to limit alcohol consumption.
6. Substitution therapy (opioid replacement therapy) in patients with active drug abuse as a step towards cessation of active drug use should be considered; help provided (e.g. through needle- and syringe-exchange programs) reduces the risk of reinfection including parenteral viral transmission (harm reduction strategy).
7. Since HBV and HIV and occasionally HCV are transmitted sexually, adequate counselling including the use of condoms is advisable. Mucosal traumatic sexual practices associated with a high risk of blood contact should be discouraged.

Figure 1:

Management and therapeutic options in compensated HBV/HIV co-infected patients with no immediate indication for anti-HIV therapy (CD4-count > 350/µl)



* chronic HBV-infection defined as HBs-Ag+ > 6 months.

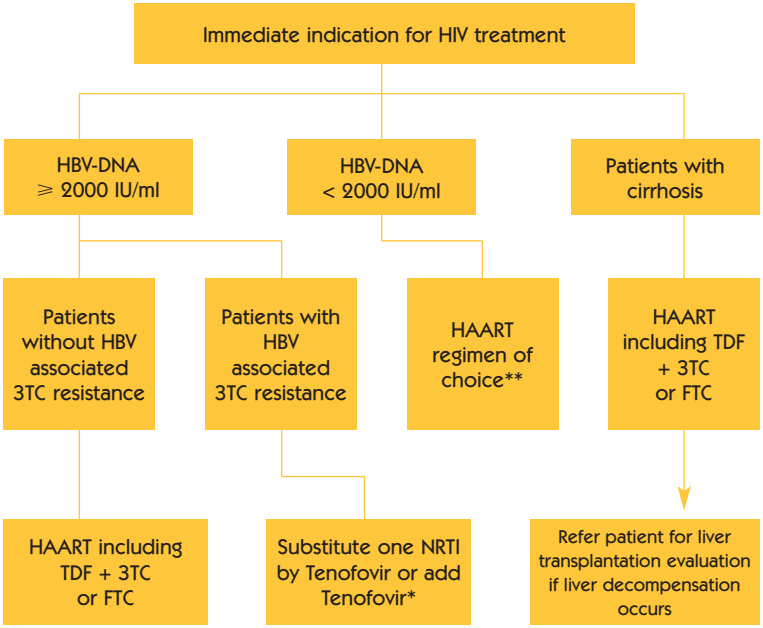
** Serum HBV-DNA levels have been demonstrated to be associated with a linear increased risk for development of liver cirrhosis and HCC; please note that the calculation from copies to IU/ml varies depending on which respective test assay was used; in general 1 IU/ml equals around 5 copies or genome equivalents; one picogram HBV-DNA equals 2,8x10^5 genome/ml.

*** Metavir ≥ A2 and/or F2; Patients with replicating HBV and normal liver enzymes may have significant liver damage, therefore consider assessment of liver damage; this may be done using either liver biopsy or non-invasive tools, including serum fibrosis markers or FibroScan. While liver biopsy may provide additional information on inflammation and other lesions (e.g., steatosis), non-invasive markers can be used at more frequent intervals.

**** Treatment length: 48 weeks for PEG INF. In those not requiring HAART and on treatment with telbivudine +/- adefovir, or those on HAART where nucleoside back-bone needs changing, anti-HBV therapy may be stopped cautiously in HBeAg+ patients who have achieved HBe-seroconversion or HBs-seroconversion for at least six months or, after HBs-seroconversion for at least six months in those who are HBeAg-.

Figure 2:

Management and therapeutic options in compensated or cirrhotic HBV/HIV co-infected patients with an indication for HIV treatment (CD4-count ⩽ 350/µl or already on HAART)



* if feasible and appropriate from the perspective of maintaining HIV suppression
In some cases of tenofovir intolerance (i.e. renal disease), entecavir 1 mg/day ± adefovor or tenofovir at adjusted doses in combination with effective HAART may be advisable.

** some experts strongly think that any HBV-infected patient requiring HAART should receive TDF +3TC or FTC unless history of TDF intolerance, particularly in HIV/HBV coinfected patients with advanced liver fibrosis (F3/F4).

Table 1:

Treatment recommendations for therapy of hepatitis C in HIV co-infection

1. HCV treatment offers the possibility of eradicating HCV within a defined treatment period. This is potentially advantageous for the subsequent management of the patient with HIV, and every patient should therefore be considered for treatment when the benefits of therapy outweigh the risks. This also needs to be seen in the context of faster liver fibrosis progression in HIV/HCV co-infection and with better HCV treatment outcome with improved management in these patients.
2. Information on liver fibrosis staging is important for making therapeutic decisions in co-infected patients. However, a liver biopsy is not mandatory for considering treatment of chronic HCV. Current therapy is particularly recommended in patients with a high likelihood of achieving sustained virological response (SVR): genotype 2 or 3 and patients infected with genotype 1 if the viral load is low (<400.000-500.000 IU/ml). More recently, insulin resistance (which can be determined using the homeostasis model assessment of insulin resistance (HOMA IR) has been repeatedly reported as a negative predictor of achievement of SVR and therefore may also be considered during pretreatment evaluation.
3. In case of the availability of a liver biopsy or Fibroscan demonstrating lower grades of liver fibrosis (F0-1), regardless of HCV genotype, treatment can be deferred. A liver disease stage assessment is especially important to perform in patients with a low chance of SVR.

4. The combination of Peg-IFN-alpha and ribavirin (RBV) is the treatment of choice for HCV infection. The standard dose for Peg-IFN 2a is 180µg once weekly, and for Peg-IFN 2b it is 1.5 µg/kg bodyweight once weekly. An initial weight-adapted dose of RBV of 1000 (wt < 75kg) -1200 (wt > 75kg) mg daily (administered bid) is recommended for all genotypes.

5. The primary aim of anti-HCV treatment is sustained virological response defined as undetectable serum HCV-RNA 24 weeks after the end of therapy, evaluated using sensitive molecular tests.

6. If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of HAART is necessary), treatment for chronic HCV is advised. However, if a co-infected patient has severe immunodeficiency (CD4 count < 200 cells/µl), the CD4 count should be improved using HAART prior to commencing anti-HCV treatment. Patients with a CD4 relative percentage >25% are more likely to achieve SVR than lower CD4 percentage.

7. If an early virological response of at least 2 log10 reduction in HCV-RNA compared to baseline is not achieved at week 12, treatment should be stopped (figure 3).

8. During Peg-FN plus ribavirin therapy, ddI is contraindicated in patients with cirrhosis and should be avoided in patients with less severe liver disease. D4T and AZT also if possible should be avoided. The role of abacavir is uncertain at this point but cohort data at least suggests lower SVR results in patients receiving abacavir containing HAART.

9. In patients with acute HCV-infection HCV therapy is recommended if the HCV-RNA is confirmed positive (1 week apart) by week 12 post HCV transmission as SVR rates following treatment of acute HCV-infection are higher than for treatment of chronic HCV.

Table 2:

Diagnostic procedures for hepatitis C in HIV-co-infection

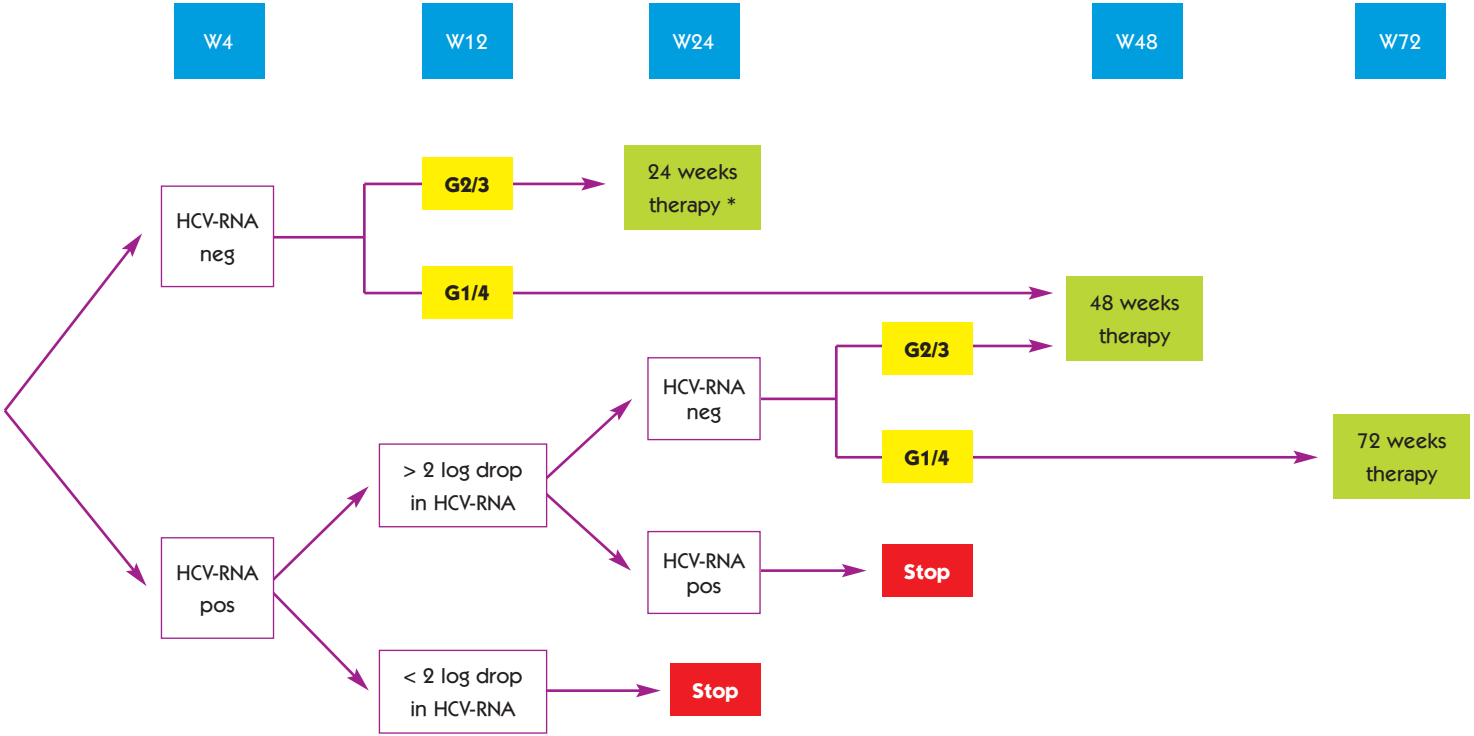
Diagnosis of hepatitis C
HCV-Ab (positive 1-5 months after infection, may rarely be lost with immunosuppression)
HCV-RNA levels* (while not prognostic for progression, it is for response to treatment)
Status of liver damage
Grading of fibrosis (e. g. Fibroscan, liver biopsy, serum fibromarkers**)
Hepatic synthetic function (e. g. coagulation, protein, albumin, CHE)
Ultrasound and AFP every 6 months in cirrhotics (gastroscopy upon diagnosis of cirrhosis and every 1-2 years thereafter)
Before HCV treatment
HCV genotype and serum HCV-RNA
TSH, thyroid autoantibodies if applicable;
Monitoring of HCV treatment
Differential blood count and liver enzymes every 2-4 weeks
HCV-RNA at week 4 (to evaluate rapid virological response), week 12, 24, 48, (72 if applicable) and 24 weeks after stopping HCV therapy
CD4-count every 12 weeks
TSH every 12 weeks

* Low viral load defined as less than 400,000 IU/l when using pegIFN+RBV. There is no standard conversion formula for converting the amount of HCV-RNA reported in copies/ml to the amount reported in IU. The conversion factor ranges from about one to five HCV-RNA copies per IU.

** Serum fibromarkers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore, Hyaluronic acid, and other indexes; Recently, more complex tests such as Fibrometer, Fibrotest and Hepascore have shown to more accurately predict liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.

Figure 3:

Proposed optimal duration of HCV therapy in HCV/HIV-co-infected patients.



* In patients with baseline low viral load (<400 000 IU/l) and minimal liver fibrosis.

Table 3:

Classification of and interventions for HCV/HIV-co-infected non-responders/relapsers to prior interferon-based therapies.

Category	Subgroup	Suggested Intervention
Suboptimal Treatment	Suboptimal schedule ✓ *Interferon (monotherapy or with ribavirin)* ✓ *Low ribavirin doses* ✓ *Short length of therapy*	Re-treatment using combination therapy with peginterferon plus weight-based ribavirin doses
	Limiting toxicities & poor adherence	Optimal support (SSRI, paracetamol/NSAID, adherence support, use of hematopoietic growth factors*)
Optimal treatment with Virologic Failure	Relapse (HCV-RNA negative at the end of treatment)	Re-treatment using combination therapy with peginterferon plus weight-based ribavirin doses (consider longer treatment duration)
	Non Response (no HCV-RNA negativization during treatment)	Wait until new antivirals come to the market.

* Data on the use of hematopoietic growth factors in HIV(HCV coinfection so far is limited to an improvement in quality of life but not antiviral efficacy; treatment with growth factors is currently mostly off-label in Europe.

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The European AIDS Clinical Society (EACS) Guidelines are freely downloadable from www.www.europeanaidsclinicalsociety.org. A declaration of potential conflict of interest of the panel members can be found at the same address.