HIV and viral hepatitis co-infection: State of the Art

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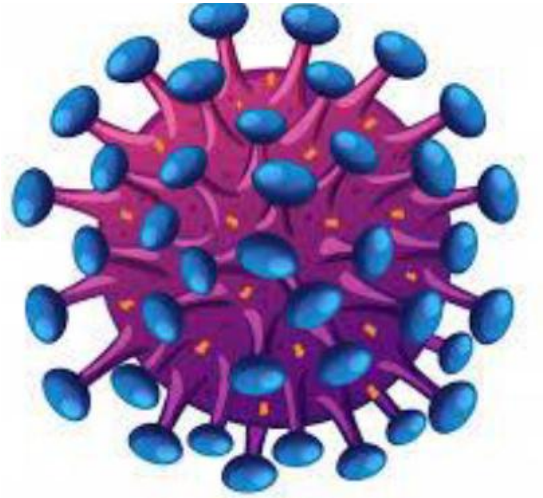
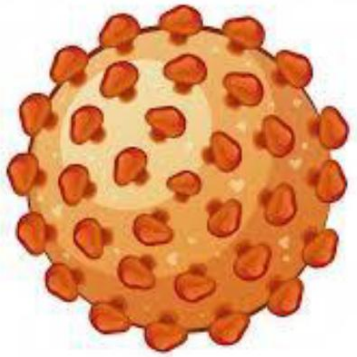
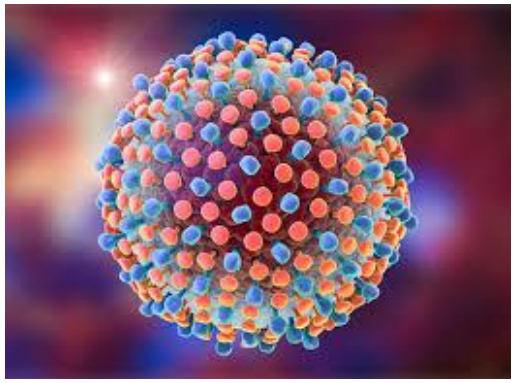
- WAVE WORKSHOP Odessa Ukraine
- 18. September 2020





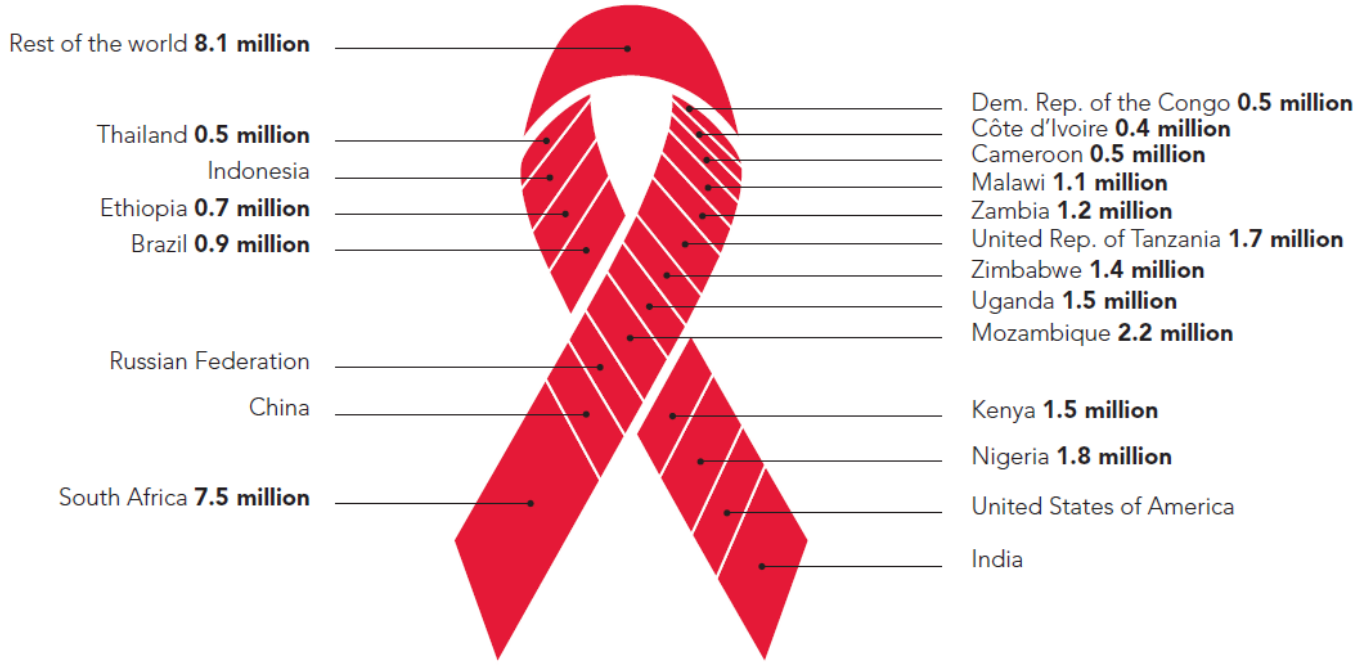


HIV and viral hepatitis co-infection

- Epidemiology
- Prophylaxis
- Clinical Screening, Monitoring and Follow-Up
- Treatment
- Summary

Epidemiology

38 million people are living with HIV around the world



UNAIDS

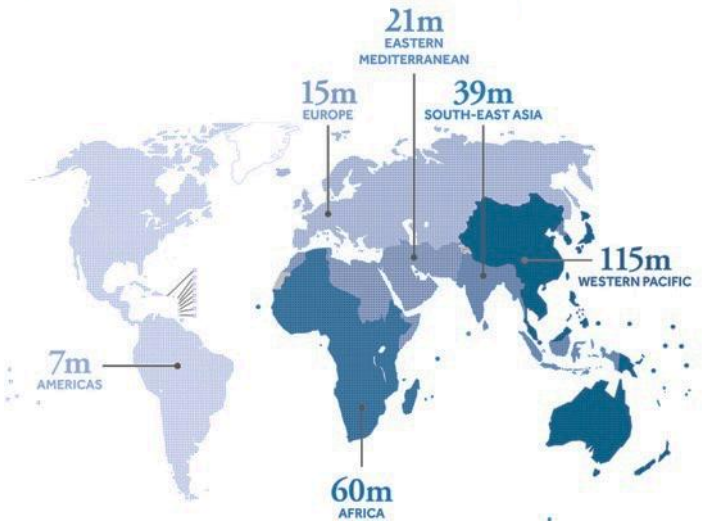
Source: UNAIDS, 2020 estimates.

1 in 4 people with HIV don't know they have it.
Know your risks – know your status.

Chronic Viral Hepatitis

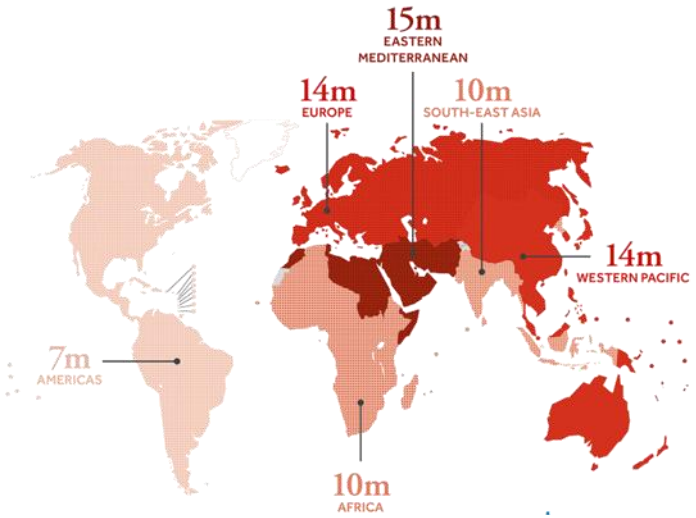
HBV

257 million individuals globally



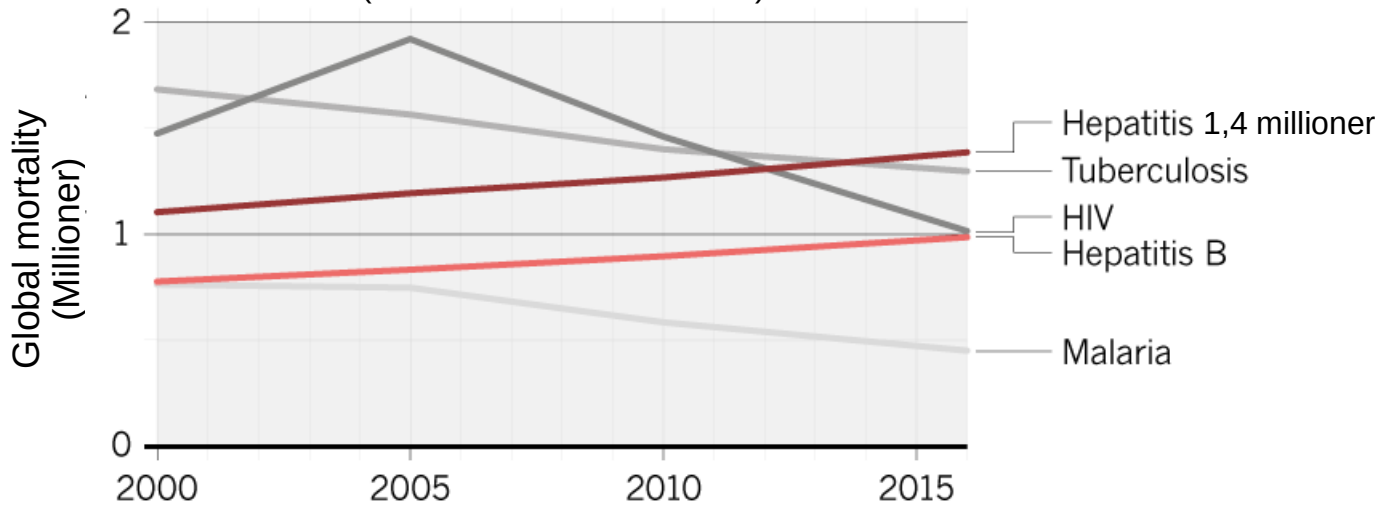
HCV

71 million individuals globally

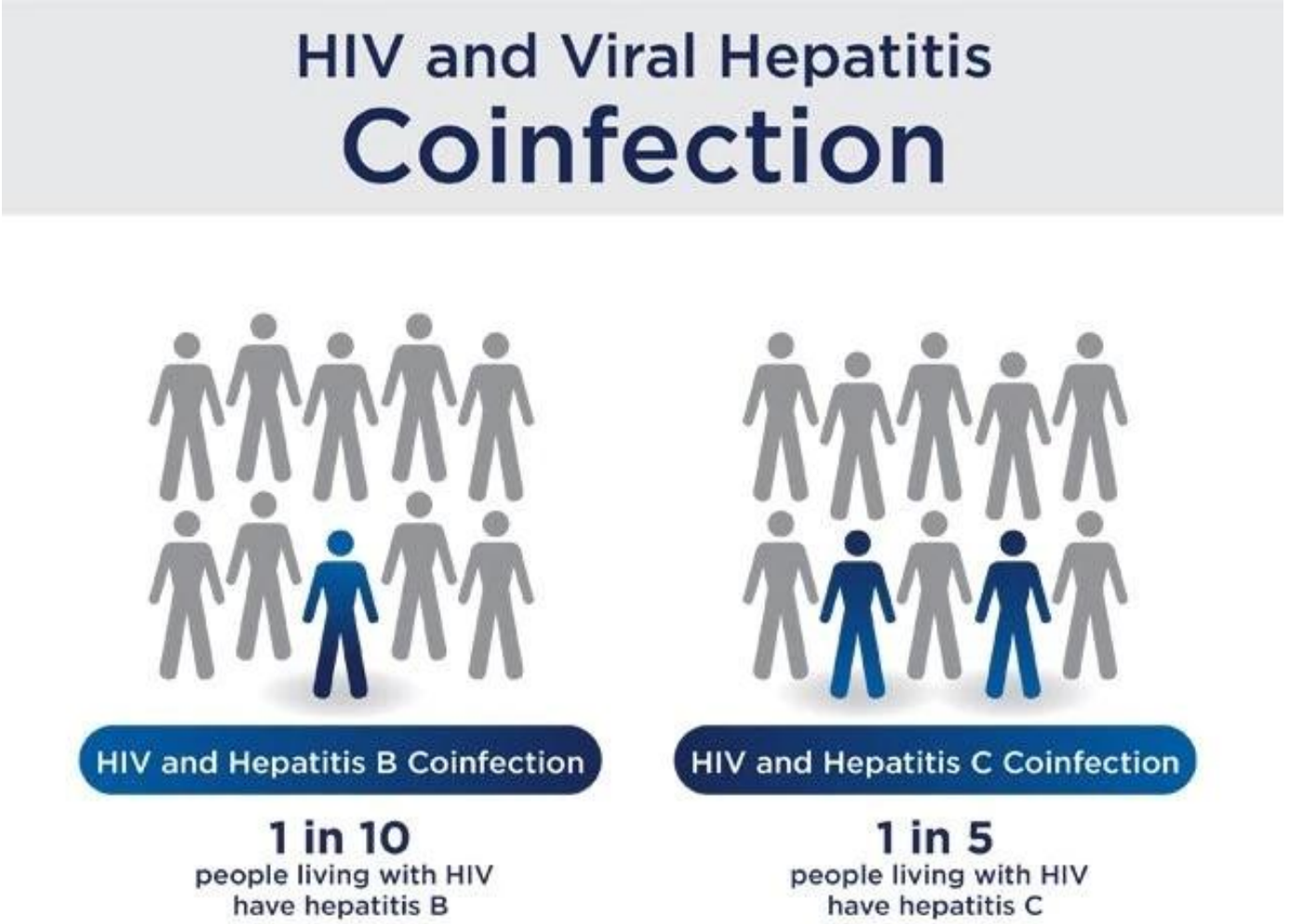


Increasing mortality due to viral hepatitis

(Nature News Feature 2018)



Prevalence of HIV viral hepatitis co-infection



Open Forum Infectious Diseases

MAJOR ARTICLE

The Prevalence of Human Immunodeficiency Virus Coinfection Among Patients Newly Diagnosed With Chronic Hepatitis B or C in Denmark: A Nationwide Cohort Study

Sofie Hallager,[1] Andreas Lundh,[1,2,3] Steen Ladelund,[4] Jan Gerstoft,[5] Alex Lund Laursen,[6] Mette Rye Clausen,[7] Ulla Balslev,[8] and Nina Weis[1,9]

2018

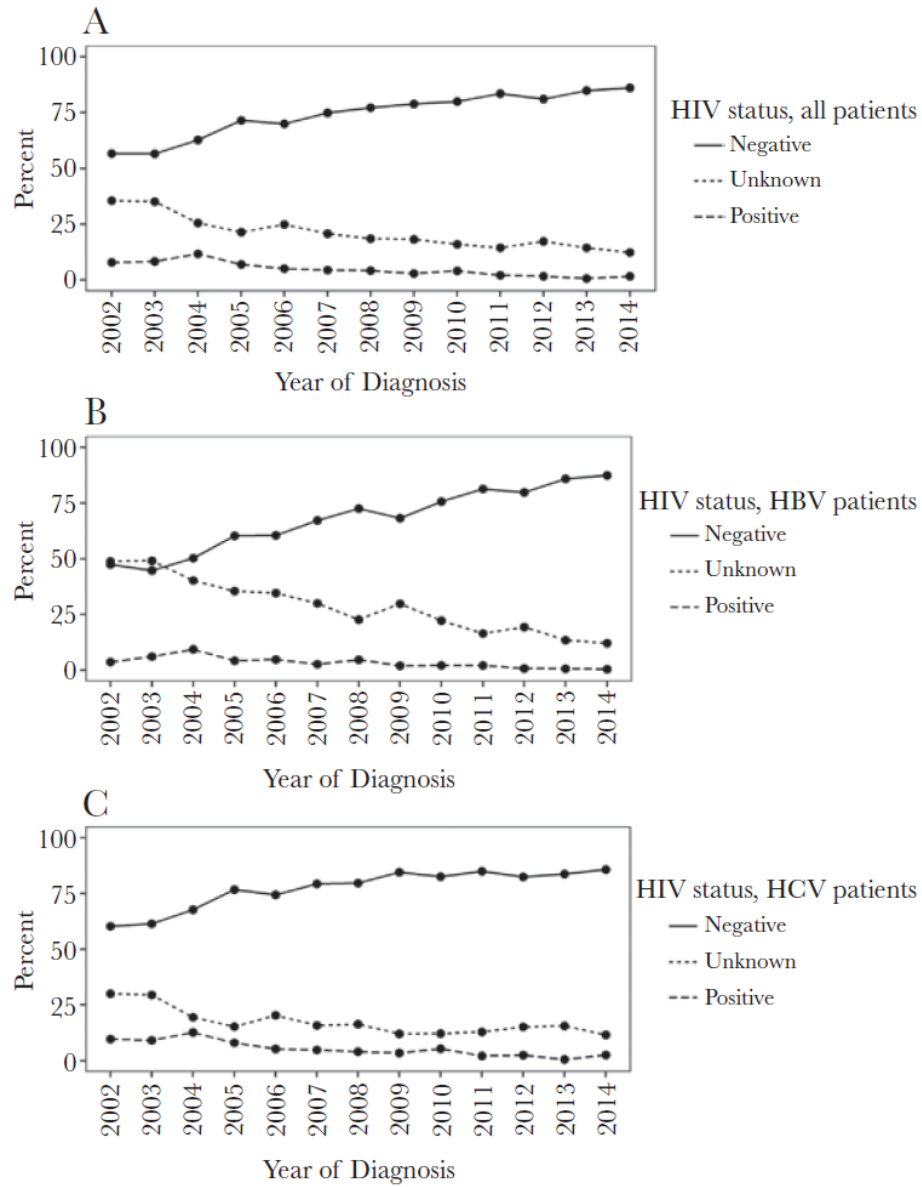


Figure 1. Human immunodeficiency virus (HIV)-status in percentage among all newly diagnosed patients with chronic viral hepatitis between 2002 and 2014. (A) All patients. (B) Patients with chronic hepatitis B virus (HBV) infection. (C) Patients with chronic hepatitis C virus (HCV) infection.

Table 3. Risk Factors Associated With HIV Coinfection Among Patients With Newly Diagnosed Chronic Viral Hepatitis B and/or C

Risk Factor	Odds Ratio (95% CI)	N
Patients with CHC vs CHB[a]	1.89 (1.48–2.41)	8490
Patients with CHB-CHC vs CHB[a]	2.3 (0.98–5.40)	8490
Age[b], years		
≤35	2.64 (0.83–8.39)	8490
>35–≤50	4.42 (1.40–13.94)	
>50–≤65	2.41 (0.75–7.73)	
>65	Reference	
Sex, men vs women[c]	2.21 [1.74; 2.81]	8490
Year of enrollment[d]	0.84 [0.82; 0.87]	8135
Country of birth, Africa vs WE[e]	0.91 [0.62; 1.34]	8135
Country of birth, Asia vs WE[e]	0.31 [0.22; 0.44]	8135
Country of birth, Eastern Europe vs WE[e]	0.60 [0.37; 0.96]	8135
Country of birth, North America vs WE[e]	0.76 [0.10; 5.67]	8135
Country of birth, South America vs WE[e]	3.62 [1.67; 7.86]	8135
Route of transmission, blood exposure vs IDU[f]	0.67 [0.34; 1.29]	5023
Route of transmission, sexual transmission vs IDU[f]	8.81 [6.30; 12.33]	5023
Route of transmission, tattoo/piercing vs IDU[f]	0.30 [0.07; 1.26]	5023
Route of transmission, vertical transmission vs IDU[f]	0.09 [0.03; 0.29]	5023

Abbreviations: CHB, chronic hepatitis B virus; CHC, chronic hepatitis C virus; CI, confidence interval; IDU, intravenous drug use; OR, odds ratio; WE, Western Europe.

[a]Univariate, type 3 test ($P < .0001$).

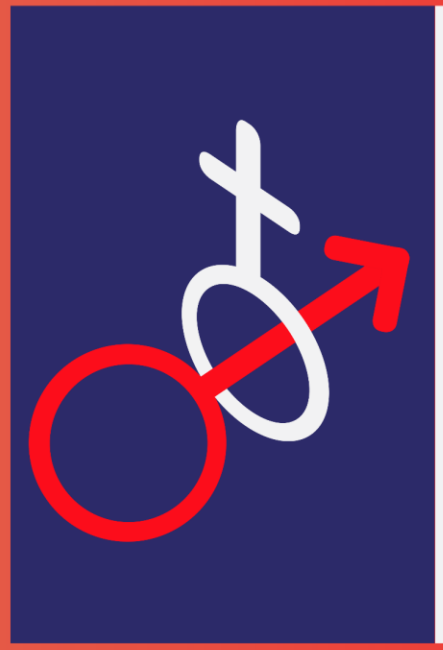
[b]Univariate, type 3 test ($P < .0001$).

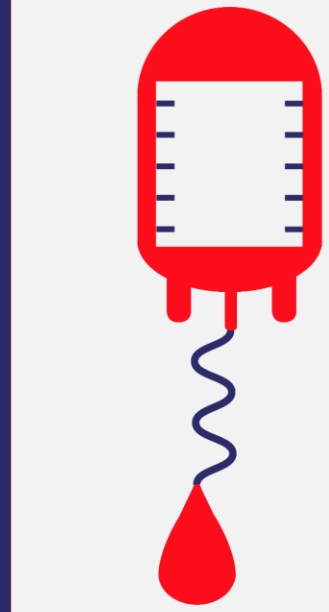
[c]Univariate.

[d]Adjusted for sex, age, and country of birth.

[e]Univariate, type 3 test ($P < .0001$).

[f]Adjusted for age, sex, year of enrollment, country of birth, type 3 ($P < .0001$).

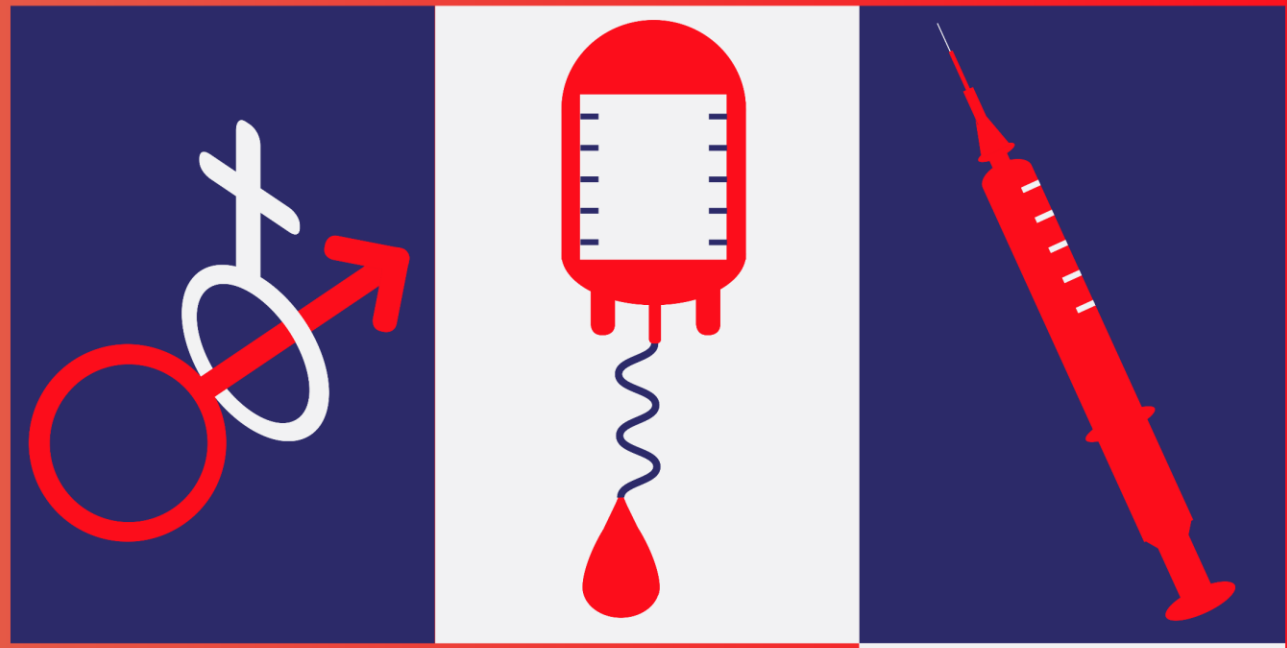




You can be at risk of HIV if you:

- Have sex without a condom
- Receive unsafe blood transfusion
- Are exposed to contaminated injecting equipment

HIV can also be transmitted from mother to child.



You can be at risk of HIV if you:

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HIV can also be transmitted from mother to child.

HCV

HBV

Prophylaxis

Prohylaxis HIV

•practice safe sexual behaviours such as using condoms;

•get tested and treated for sexually transmitted infections, including HIV to prevent onward transmission;

•avoid injecting drugs, or if you do, always use sterile needles and syringes;

•ensure that any blood or blood products that you might need are tested for HIV;

•access voluntary medical male circumcision if you live in one of the 15 African countries where this intervention is promoted;

•if you have HIV start antiretroviral therapy as soon as possible for your own health and to prevent HIV transmission to your sexual or drug using partner or to your infant (if you are pregnant or breastfeeding);

•use pre-exposure prophylaxis prior to engaging in high risk behaviour; demand post-exposure prophylaxis if there is the risk that you have been exposed to HIV infection in both occupational and non-occupational settings

Prophylaxis viral hepatitis

Vaccination, see page 79

12. PLWH lacking anti-HAV IgG antibodies or anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4 count. The response to the HBV vaccine is influenced by the CD4 count and level of HIV-VL. In PLWH with low CD4 count (< 200 cells/µL) and ongoing HIV replication, ART should be initiated first, prior to respective vaccination. Because of the lack of data on the impact of immunisation in isolated anti-HBc IgG positive persons (HBsAg negative, anti-HBc positive and anti-HBs negative profile), vaccination is not recommended in this population. However, if anti-HBc results are not available, HBV vaccination is recommended in all HBs-Ag negative persons
13. In PLWH vaccinated for HBV with insufficient response (anti-HBs < 10 IU/L), re-vaccination should be considered. Double-dose (40 µg) at 3-4 time points (months 0, 1, 6 and 12) may help to improve response rates to the HBV vaccine. Persons who fail to seroconvert after HBV vaccination and remain at risk for HBV should have annual serological tests for evidence of HBV infection. TDF based cART has been associated with prevention of HBV infection in these persons and ART including TDF or TAF is recommended

Hepatitis B Virus (HBV)	Shared risk with HIV of contracting infection. HIV accelerates liver disease progression	Vaccinate if seronegative. Repeat doses until anti-HBs antibodies ≥ 10 IU/L / ≥ 100 IU/L according to national guidelines. In order to reach ≥ 100 IU/L in non-responders repeat 3 doses if anti-HBs < 10 IU/L, 1 dose if anti-HBs < 100 IU[1]; consider double dose (40 µg) in particular with low CD4 count and high HIV-VL. See page 95
Hepatitis A Virus (HAV)	According to risk profile (travel, close contact with children, MSM, IVDU, active hepatitis B or C infection, chronic liver disease)	Vaccinate if seronegative. Consider checking antibody titres in PLWH with high risk. Weaker immune response expected with HAV/HBV co-vaccine. See page 95

Clinical Screening, Monitoring and Follow-Up

Screening at baseline

1. PLWH should be screened for HCV at time of HIV diagnosis and annually thereafter[I]. Screening should use an anti-HCV antibody test[II]
   A positive result should be followed by HCV-RNA[III] and genotype determination. Alternatively, HCV core-antigen testing can be performed to establish chronic HCV infection. PLWH engaging in activities associated with increased risk of HCV transmission[IV] should be tested for HCV infection every 3 to 6 months. PLWH suspected of recently acquired primary HCV infection with a negative anti-HCV antibody test should be tested for HCV-RNA. HCV-RNA or HCV core-antigen testing is also recommended in PLWH with ongoing risk behavior for HCV re-infection after successful treatment or spontaneous clearance at 3 to 6-monthly intervals
2. PLWH should be screened for HAV and HBV. PLWH who are anti-HBc positive and HBsAg negative, in particular those with elevated liver transaminases, should be screened for HBV-DNA in addition to HBsAg to rule out occult HBV infection
3. HDV antibodies should be screened for in all HBsAg positive persons.
4. PLWH with viral hepatitis co-infection should be assessed for concurrent causes of liver disease such as alcohol consumption, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases (e.g. genetic haemochromatosis, diabetes mellitus or obesity) and drug-induced hepatotoxicity
5. Status of liver damage should be assessed in all PLWH with viral hepatitis co-infection with a complete blood count, ALT, AST, GGT, ALP, hepatic synthetic function (e.g. coagulation, albumin, cholinesterase) and staging of fibrosis (e.g. FibroScan, liver biopsy, serum fibrosis markers[V], see Table on cut-off values of non-invasive tests for the detection of significant fibrosis and cirrhosis

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Screening for complications

6. HCC screening is indicated in all cirrhotic HBV or HCV co-infected PLWH (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in persons with F3 fibrosis is uncertain, surveillance may be considered based on an individual risk assessment, see page 52. In HBV-positive non-cirrhotics, HCC screening should follow current HCC EASL guidelines (https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/). Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH, see pages 8, 52 and 71
7. Screening for oesophageal varices upon diagnosis of cirrhosis in co-infected persons is also indicated (every 2-3 years thereafter according to presence of ongoing liver disease if negative for oesophageal varices at initial screening), see page 70

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End Stage Liver Disease (ESLD)

8. PLWH with liver cirrhosis require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative persons, see page 70-71 and Diagnosis and Management of Hepatorenal Syndrome (HRS)
9. Persons with viral hepatitis/HIV co-infection suffering from ESLD warrant particular attention in the management of liver insufficiency, see Dose Adjustment of ARVs for Impaired Hepatic Function. ART in cirrhotic PLWH improves overall survival
10. PLWH with HCC or a MELD-score > 15[M], CD4 count > 100 cells/µL and options for efficacious and durable ART should be evaluated for liver transplantation (OLTX), see Solid Organ Transplantation (SOT) in PLWH
11. Renal complications are frequent, see page 64 and Diagnosis and Management of Hepatorenal Syndrome (HRS)

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Prevention/Support

14. Psychiatric, psychological, social and medical support should be made available to persons with alcohol intake to stop drinking
15. Substitution therapy (opioid replacement therapy) in persons with active drug use as a step towards cessation of active drug use should be encouraged. Help provided (e.g. through needle and syringe exchange programs) reduces the risk of re-infection including parenteral viral transmission (harm reduction strategy), see Drug Dependency and Drug Addiction
16. Since HBV and HIV, and occasionally HCV, are transmitted sexually, adequate counselling including the use of condoms is advisable. Information on the risk of HCV transmission due to mucosal traumatic sexual practices associated with a high likelihood of blood contact or ongoing IDU, "chemsex" (sex under the influence of recreational drugs taken predominantly intravenously immediately before and/or during sexual contacts), should be provided and risk reduction should be discussed
17. In women of childbearing age, HCV treatment should be initiated prior to conception because of limited safety data in pregnancy, and to reduce the risk of MTCT of HCV

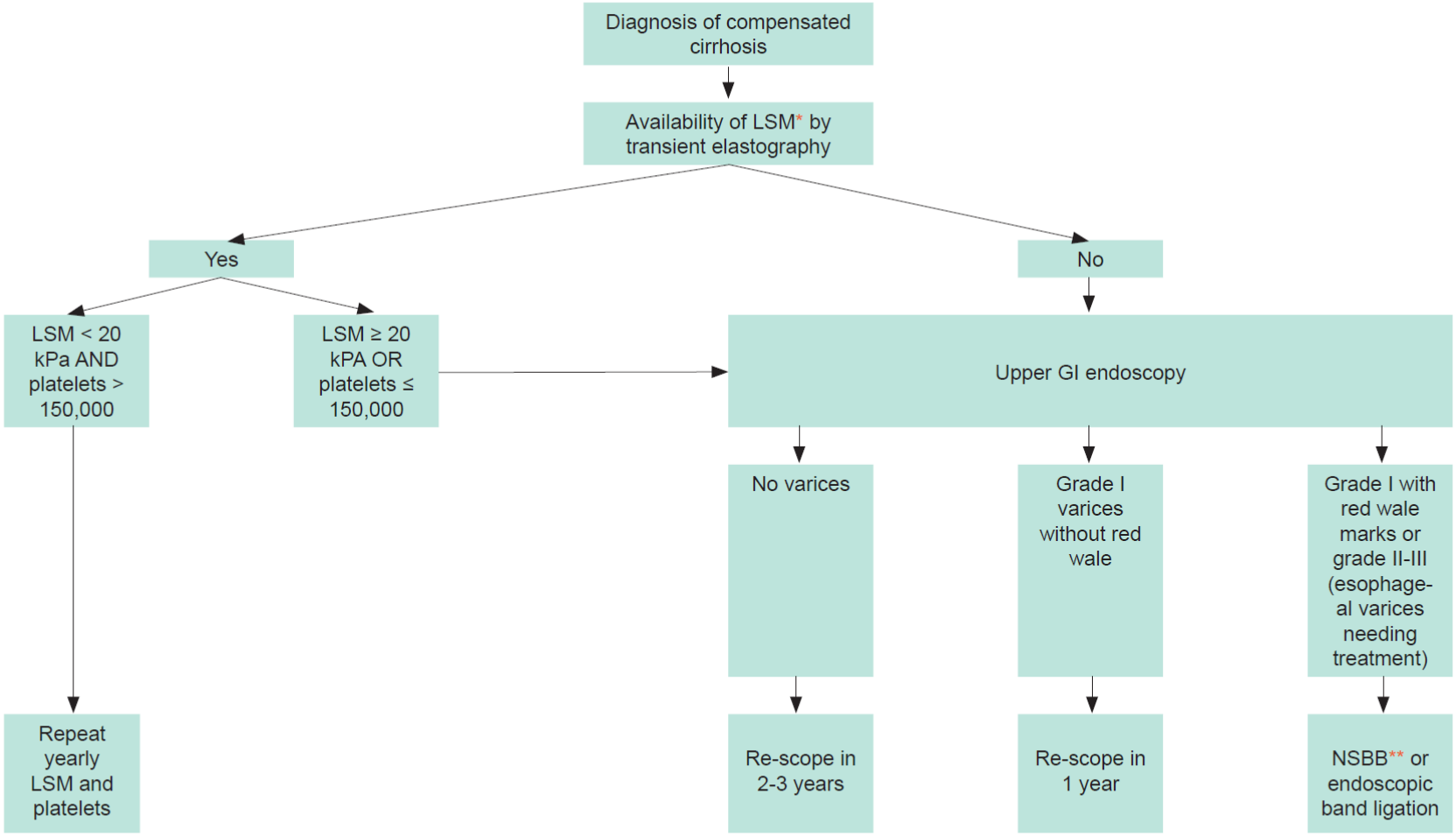
Liver Cirrhosis: Classification and Surveillance

Child-Pugh classification of the severity of cirrhosis

	Points[i]		
	1	2	3
Total bilirubin, mg/dL (µmol/L)	< 2 (< 34)	2-3 (34-50)	> 3 (> 50)
Serum albumin, g/L (µmol/L)	> 35 (> 507)	28-35 (406-507)	< 28 (< 406)
INR	< 1.7	1.7-2.20	> 2.20
Ascites	None	Mild/Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I-II (or suppressed with medicine)	Grade III-IV (or refractory)

i 5-6 points: Class A
7-9 points: Class B
10-15 points: Class C

Algorithm for surveillance for varices and primary prophylaxis



Based on Baveno VI consensus (EASL) and guideline on portal hypertension (AASLD) [15], [16]
* LSM, liver stiffness measurement;
** NSBB, non-selective beta-blocker e.g. propranolol 80-160 mg/day or carvedilol 6.25-50 mg/day
Persons with compensated cirrhosis without varices on screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence)
Hepatic Venous Pressure Gradient (HVPG) when available, allows a direct measure of portal hypertension and prognostic stratification of persons with compensated cirrhosis
HVPG<6 mmHg: no portal hypertension
HVPG 6-9 mmHg: portal hypertension non clinically significant
HVPG≥10 mmHg: clinically significant portal hypertension
In primary and secondary prophylaxis for variceal bleeding HVPG measurement allows to monitor efficacy of beta-blockers

Screening for HepatoCellular Carcinoma (HCC)

- HCC screening is indicated in all cirrhotic HBV or HCV co-infected PLWH (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in PLWH with F3 fibro-sis is uncertain, surveillance may be considered based on an individ-ual risk assessment https://easl.eu/publication/easl-clinical-practice-guide-lines-management-of-hepatocellular-carcinoma/
- In HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines. Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to as-sess the HCC risk, however this score has not been validated in PLWH; see pages 8, 52 and 95. Table on fibrosis cut-offs, page 102
- Ultrasound (US), with or without AFP, every 6 months. Alpha-foetoprotein (AFP) should not be used alone.AFP is a suboptimal surveillance tool because of low sensitivity and specificity

When to refer for liver transplantation
Best to refer early as disease progresses rapidly

= MELD[i] score 10-12 (listing at 15)

Decompensated cirrhosis (at least one of the following complications)

- Ascites
- Hepatic encephalopathy
- Variceal bleeding
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- NASH cirrhosis[ii]
- HCC

See Solid Organ Transplantation (SOT) in PLWH

i Unit for both s-creatinine and s-bilirubin is mg/dL.
MELD score = 10 {0,957 Ln (serum creatinine (mg/dL)) + 0.378 Ln (total bilirubin (mg/dL)) + 1.12 Ln (INR) + 0.643}, see http://www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/

ii Particularly with metabolic decompensations

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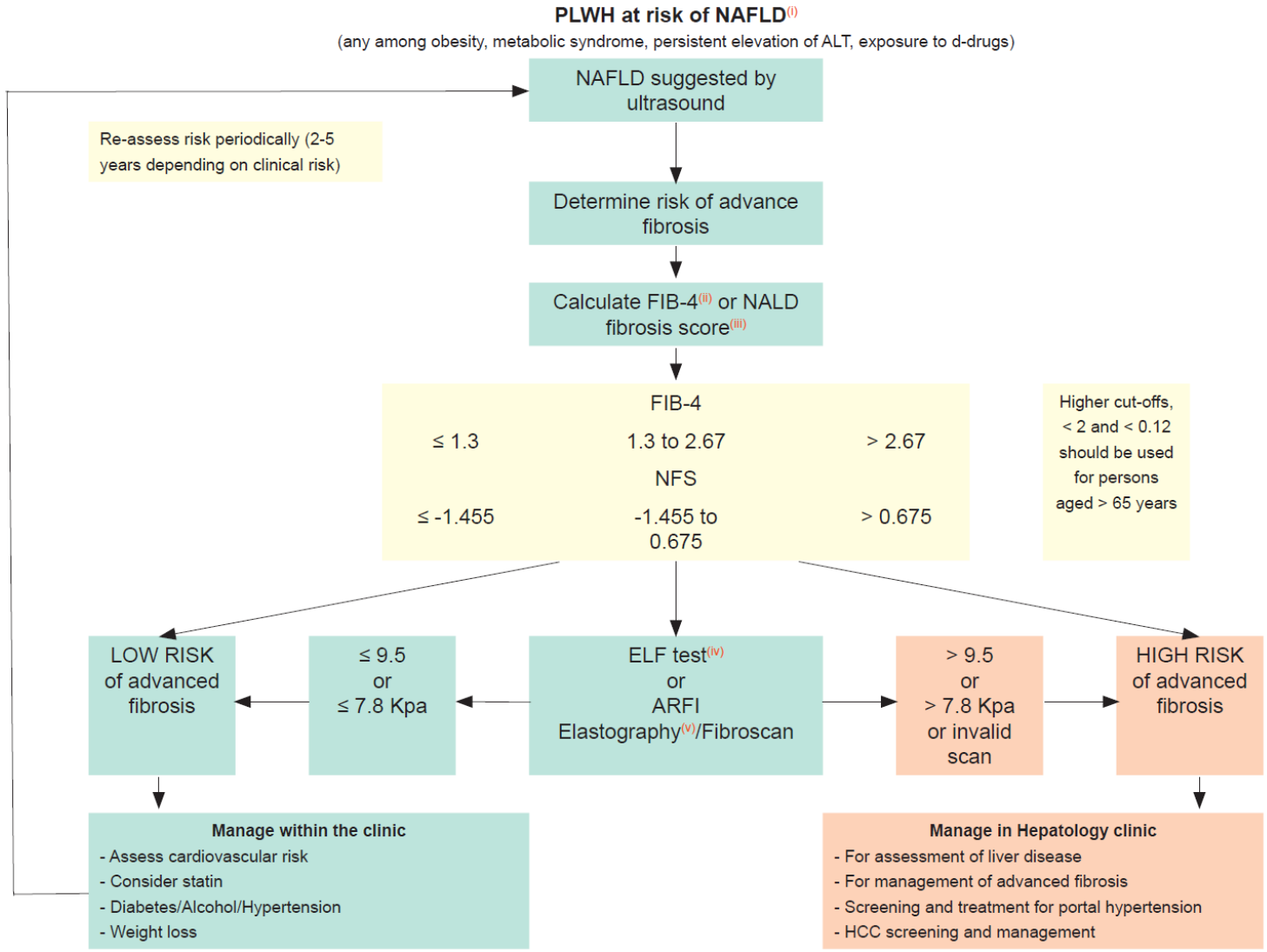
Diagnostic Flow-chart to Assess and Monitor Disease Severity in Case of Suspected NAFLD and Metabolic Risk Factors



These recommendations are largely inspired by the EASL–EASD–EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease: European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity [18]

i NAFLD, Non-alcoholic fatty liver disease

ii FIB-4 = Age ([years] x AST [U/L]) / ([platelet [10^9/L]) x ALT [U/L])

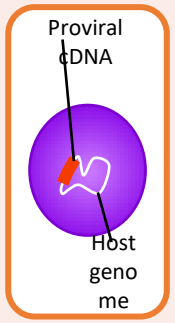
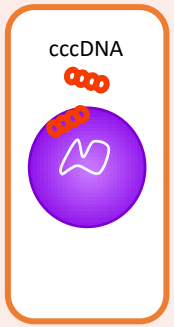
iii NFS, Non-alcoholic fatty liver disease Fibrosis Score = -1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x impaired fasting glucose/diabetes mellitus(iv) (yes=1/no=0) + 0.99 x AST/ALT ratio-0.013 x platelet (x10^9)-0.66 x albumin(g/dL)

iv ELF™ test, Enhanced Liver Fibrosis Test is a blood test that provides an estimate of liver fibrosis severity by measuring Hyaluronic Acid (HA), Amino-terminal propeptide of type III procollagen (PIIINP), Tissue inhibitor of metalloproteinase 1 (TIMP-1)

v ARFI elastography, Acoustic Radiation Force Impulse

Treatment

Possible to completely cure Hepatitis C but only to functionally cure HIV and Hepatitis B

	HIV	HBV	HCV
Daily virus production	10^{10}	10^{12}–10^{13}	10^{12}
Half-life of free virus (h)	1	3–24	2–3
Half-life of intracellular virus (h)	Days	Months	Hours
Intracellular viral reservoir	YES  Proviral cDNA integrated into host genome	YES  Stable cccDNA persists in hepatocytes	NO  Viral RNA not converted to DNA and present only in cytoplasm
Goal of treatment	Lifelong viral suppression	Long-term viral suppression	Cure (SVR)

cDNA: complementary DNA; cccDNA: Covalently closed circular DNA; HCV: Hepatitis C virus; SVR: Sustained virologic respons.

Soriano V et al. *J Antimicrob Chemother* 2008;62:1–4. Kieffer T, et al. *J Antimicrob Chemother* 2010;65:202–212

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Treatment and Monitoring of Persons with HBV/HIV Co-infection

Treatment indication

1. All PLWH with HBV/HIV co-infection should receive ART that includes TDF or TAF unless history of tenofovir intolerance
2. Stopping anti-HBV active ART should be avoided in persons with HIV/HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis

Treatment selection

3. If TDF or TAF is strictly contraindicated, entecavir may be prescribed in PLWH with no prior 3TC exposure and together with fully active ART
4. PLWH with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes (for management of cirrhotic PLWH, see pages 70-74). Please note that diagnosis of cirrhosis may be difficult in persons already on HBV treatment
5. Caution is warranted to switch from a TDF/TAF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pre-treated cirrhotic PLWH as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir
6. Prior to ART simplification with a regimen without TDF/TAF, HBV status should be re-checked
7. For HBV/HIV co-infected persons with BMD changes or CKD, see recommendations for Dose Adjustment of ARVs for Impaired Renal Function and pages 61-66

Treatment goal

8. The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy. In those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously in non-cirrhotic HBeAg-positive PLWH who have achieved HBe-seroconversion for at least one year or after confirmed HBs-seroconversion in those who are HBeAg-negative. In PLWH with liver cirrhosis, stopping of effective anti-HBV treatment is not recommended, in order to avoid liver decompensation due to flares of liver enzymes

Treatment monitoring

9. Liver blood tests should be performed every 3 months during the first year and every 6-12 months thereafter
10. HBV-DNA should be determined every 3-6 months during the first year and every 12 months thereafter
11. HBsAg should be checked at 12 months intervals at least until loss of HBsAg

HBV reactivation

12. In HBs-Ag negative, anti-HBc positive PLWH undergoing immunosuppression:
    - Those treated with severe immunosuppressive therapy (chemotherapy for lymphoma/leukaemia or stem-cell or solid-organ transplantation) should receive TDF/TAF therapy to prevent HBV reactivation. For persons with other markers of possible HBV exposure including isolated anti-HBs positivity (without a history of vaccination) careful monitoring for HBV reactivation is required
    - In PLWH treated with B-cell-depleting agents (rituximab, ofatumumab, natalizumab, alemtuzumab, ibritumomab) TDF/TAF should be part of the ART. If TDF/TAF is contraindicated, second line options include 3TC and FTC. However, cases of reactivation due to 3TC resistance have been described
    - Those treated with other immunosuppressive therapy (e.g. TNF alpha inhibitor) careful monitoring with HBV-DNA and HBsAg is required for HBV reactivation. If this is not possible, addition of TDF/TAF is recommended

Editorial: Carving a new path to a hepatitis B cure

- To better understand the biology of hepatitis B, the effect of epidemiological factors such as age and geographical origin, and the interplay of co-infections with HIV and other viral hepatitis viruses
- To refine tools by incoporating molecular mechanisms, improving biomarker assays, and creating data repositories
- To improve adherence and to limit transmission

www.thelancet.com Vol 394 December 21/28, 2019

Treatment and Monitoring of Persons with HCV/HIV Co-infection

Treatment indication

1. Every person with HCV/HIV co-infection must be considered for DAA-based (IFN- and preferably also RBV-free) anti-HCV treatment regardless of liver fibrosis stage
2. Due to similar HCV cure rates and tolerability in HCV/HIV co-infected persons as in HCV mono-infected persons under DAA therapy, treatment indication and regimens are to be the same as in HCV mono-infection

Treatment selection

3 IFN- and preferably also RBV-free DAA combinations are now standard of care for chronic HCV see Tables HCV Treatment Options in HCV/HIV Co-infected Persons. IFN-containing HCV regimens are no longer recommended. For diagnostics and management of IFN-containing HCV regimens please refer to previous versions of these Guidelines, available online at http://www.eacsociety.org/files/guidelines_8.2-english.pdf

4. Selection of DAA combinations is based upon HCV GT(i), stage of liver fibrosis, pre-treatment history and resistance-associated substitutions (RAS) if tested
5. Use of older, first generation HCV PIs (boceprevir and telaprevir) are no longer recommended because of increased toxicities
6. Due to drug-drug interactions in particular with HIV and HCV PIs, careful checking for interactions is urgently recommended prior to starting HCV therapy, see Drug-drug Interactions between DAAs and ARVs or http://www.hep-druginteractions.org
7. Resistance testing, if available, should be performed before re-treatment of persons who failed after a PI-and/or NS5A inhibitor-containing agent. The triple combination of SOF/VEL/VOX for 12 weeks is the treatment of choice for re-treatment, especially if resistance testing is not available. In persons with complex mutations patterns SOF+GLE/PIB + RBV for 12-16 weeks can also be considered. In case of unavailability of SOF/VEL/VOX or SOF + GLE/PIB other regimens with at least two active DAAs could be combined with the preferential use of one drug with high genetic barrier to resistance and with extended treatment durations and potentially addition of RBV. In patients with decompensated cirrhosis SOF/VEL + RBV for 24 weeks is the only available option for re-treatment in case of contraindication to liver transplantation

Treatment goal

8. The primary aim of HCV treatment is SVR_{12} defined as undetectable HCV-RNA 12 weeks after the end of therapy (evaluated using sensitive molecular tests) or HCV core antigen levels where HCV- RNA assays are not available or not affordable. SVR_{12} corresponds to a definitive cure of HCV infection in the vast majority of cases

i If the PLWH is a candidate for pangenotypic drugs, HCV GT determination is not mandatory before starting anti-HCV treatment. Re-testing for GT and sub-type should be performed in persons with tests carried out before second-generation tests were available (second-generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection' for whom the GT/sub-type should be performed on most recent available specimen

See online video lectures HCV/HIV Co-infection-Part 1, HCV/HIV Co-infection-Part 2 and HCV/HIV Co-infection-Part 3 from the EACS online course Clinical Management of HIV

Treatment monitoring

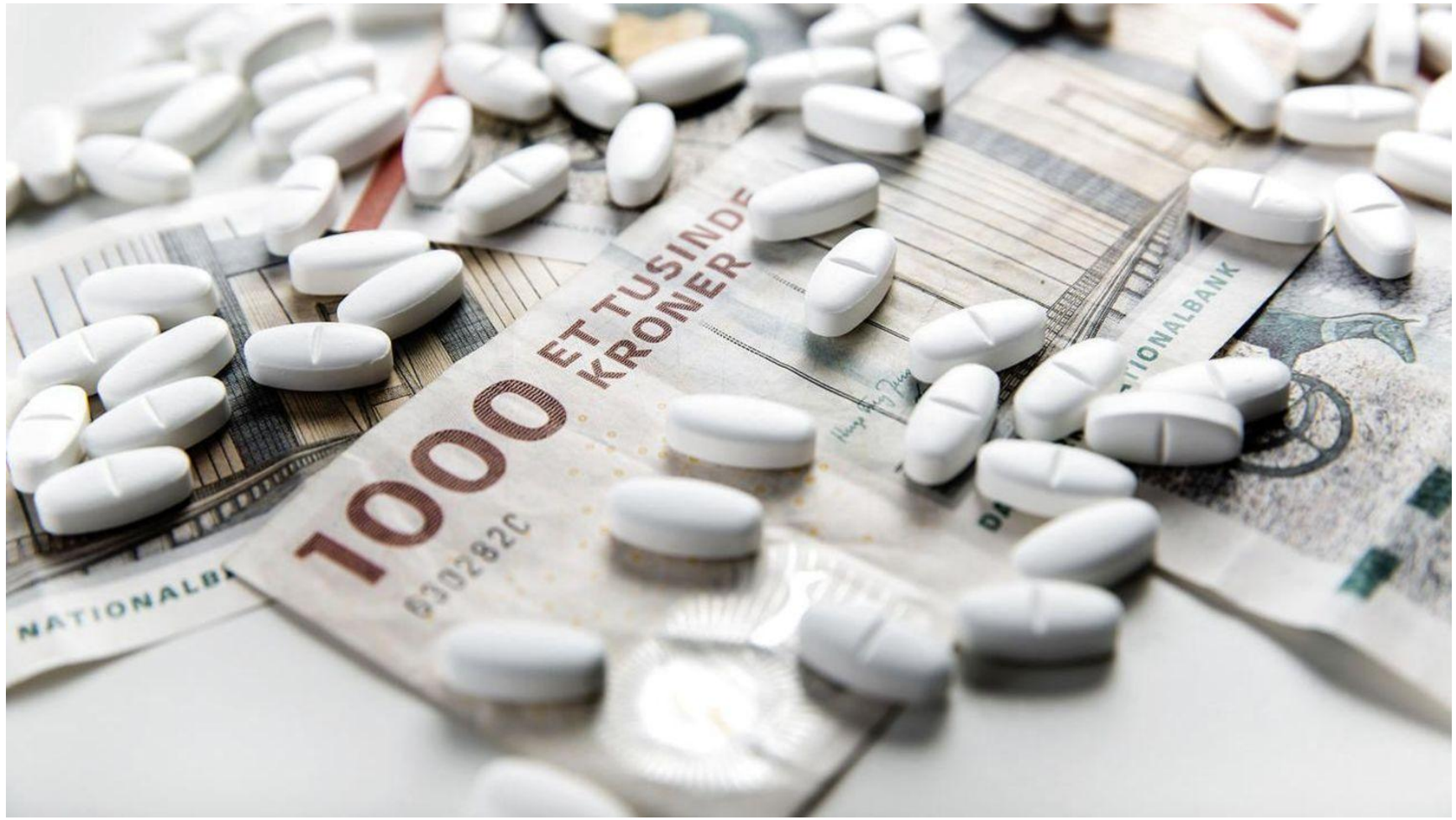
9. In PLW with advanced fibrosis (≥ F3) differential blood count, creatinine, liver enzymes, bilirubin, albumin and INR measurement after 2-4 weeks of therapy is recommended. In HBsAg negative PLWH with positive anti-HBc, monitoring of ALT and HBV-DNA in case of ALT elevation is recommended
10. In PLWH with impaired renal function undergoing SOF based treatment creatinine should also be monitored
11. HCV-RNA measurement during therapy should only be performed in order to assess compliance and/or break-through in PLWH experienced to oral DAAs; HCV-RNA should be measured at end-of-treatment and at week 12 or 24 after treatment cessation (to assess SVR). In PLWH receiving all oral DAA therapy, no association between viral load at any given time-point during therapy and SVR has yet been found. If HCV-RNA determination is not available SVR can be identified by a negative HCV core antigen 24 weeks after treatment end
12. HIV-VL every 12 weeks

Post-Treatment monitoring

13. Surveillance for HCC and for oesophageal varices should be continued if the respective indications were present pre-treatment, despite achieving SVR, see pages 8, 52, 70 and 71
14. All PLWH with concurrent causes of liver disease should undergo periodical clinical assessments
15. Increase in body weight and changes in lipid and glucose metabolism have been described after SVR. Thus, surveillance, counseling and treatment for obesity and metabolic alterations should be enforced after SVR, see page 75

Treatment of recently acquired HCV infection

16. IFN-containing HCV regimens are no longer recommended. For diagnostics and management of IFN-containing HCV regimens please see online EACS Guidelines v8.2 at http://www.eacsociety.org/files/ guidelines_8.2-english.pdf
17. After diagnosis of recently acquired HCV infection, HCV-RNA should be re-measured 4 weeks later. Treatment recommended in PLWH without a decrease of 2*log of HCV-RNA at 4 weeks compared with initial HCV-RNA, due to the very low probability of spontaneous clearance, and in persons with persistent serum HCV-RNA 12 weeks after diagnosis of recently acquired HCV, see Algorithm for Management of Recently aquired HCV in Persons with HIV Co-infection. HCV treatment immediately after diagnosis is recommended in PLWH with ongoing risk behavior to reduce onward transmission. IFN-free treatment with DAAs is recommended as in naïve non-cirrhotic (except for those with pre-existing cirrhosis), see pages 98-99
18. For more detailed information on the management of recently acquired HCV infection we refer to the European AIDS Treatment Network (NEAT) consensus conference guideline, www.neat-id.org



Direct Acting Antiviral (DAA) Therapy

Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Management of Hepatitis C/HIV Coinfection in the Era of Highly Effective Hepatitis C Virus Direct-Acting Antiviral Therapy

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Table 1. Sustained Virologic Response Rates From Clinical Trials Investigating the Efficacy of Direct-Acting Antiviral Therapies in Human Immunodeficiency Virus/Hepatitis C Virus Coinfection

Study Name	Type and No. of Patients	ARV Allowed	SVR Rates	Adverse Events	Reference
PHOTON-1	223 patients enrolled Treatment naive GT 1: 114 • 4.4% cirrhosis GT 2 and 3: 68 • 10.4% cirrhosis Treatment experienced GT 2 and 3: 41 • 24.4% cirrhosis	212 of 223 patients were on ARV therapy. The following agents were allowed: TDF + FTC, EFV, ATV/r, DRV/r, RAL, RPV, other	Treatment naive 76% GT 1 88% GT 2 67% GT 3 Treatment experienced 92% GT 2 94% GT 3	Most common were fatigue, insomnia, headache, and nausea No adverse events on HIV disease or treatment	[19]
PHOTON-2	275 patients enrolled Treatment naive GT 1: 112 • 15% cirrhosis GT 2: 19 • 5% cirrhosis GT 3: 58 • 5% cirrhosis GT 4: 31 • 26% cirrhosis Treatment experienced GT 2: 6 • 33% cirrhosis GT 3: 49 • 47% cirrhosis	265 of 275 patients were on ARV therapy. The following agents were allowed: TDF + FTC, EFV, ATV/r, DRV/r, RAL, RPV, other	Treatment naive 85% GT 1 89% GT 2 91% GT 3 84% GT 4 Treatment experienced 83% GT 2 86% GT 3	Most common were fatigue, insomnia, asthenia, and headache One patient experienced HIV viral breakthrough	[20]
ION-4	335 patients enrolled GT 1: 327 GT 4: 8 20% cirrhosis overall	335 (100%) patients were on ARVs consisting of TDF and FTC with EFV, RPV, or RAL	Both treatment naive and experienced 96% GT 1 100% GT 4	Most common were headache, fatigue, and diarrhea	[33]

Table 1. Sustained Virologic Response Rates From Clinical Trials Investigating the Efficacy of Direct-Acting Antiviral Therapies in Human Immunodeficiency Virus/Hepatitis C Virus Coinfection

Study Name	Type and No. of Patients	ARV Allowed	SVR Rates	Adverse Events	Reference
ALLY-2	203 patients enrolled 151 treatment naive • 101: DCV + SOF for 12 wk ○ 9% cirrhosis • 50: DCV + SOF for 8 wk ○ 10% cirrhosis 52 treatment experienced • 52: DCV + SOF for 12 wk ○ 29% cirrhosis	199 (98%) patients were on ARVs consisting of DRV/r, ATV/r, LPV/r, EFV, NVP, RPV, RAL, or DTG	GT 1:96.4% naive for 12 wk 75.6% naive for 8 wk 97.7% experienced for 12 wk GT 1–497% naive for 12 wk 76% naive for 8 wk 98.1% experienced for 12 wk	Most common were fatigue, nausea, and headache	[11]
C-EDGE COINFECTION	218 patients enrolled GT 1a: 144 GT 1b: 44 GT 4: 28 GT 6: 2 16% cirrhosis overall	211 (97%) patients were on ARVs consisting of ABC, TDF, RAL, DTG, or RPV	96.5% GT 1a 95.5% GT 1b 96.4% GT 4 100% GT 6	Most common were fatigue, headache, and nausea. No patient discontinued treatment because of an AE. Two patients receiving ART had transient HIV viremia.	[34]
C-WORTHY	218 patients enrolled; 59 (arms 7 and 8) were HCV/HIV coinfected Arm 1: GT 1a + 1b;12 wk Arm 2: GT 1a + 1b;12 wk Arm 3: GT 1b; 12 wk Arm 4: GT 1a; 8 wk Arm 5: GT 1a + 1b; 12 wk Arm 6: GT 1a; 12 wk Arm 7: GT 1a + 1b; 12 wk Arm 8: GT 1a + 1b; 12 wk	59 (100%) of coinfected patients were on ARVs consisting of RAL plus 2 nucleoside or nucleotide reverse transcriptase inhibitors	Arm 1: 93% Arm 2: 93% Arm 3: 98% Arm 4: 80% Arm 5: 93% Arm 6: 98% Arm 7: 97% Arm 8: 87%	Most common were mild to moderate fatigue, headache, nausea, and diarrhea.	[35]
ERADICATE	50 patients enrolled	37 (74%) patients were receiving ARVs consisting of TDF/FTC plus EFV, RAL, RPV, RAL plus RPV, or RAL plus EFV	98%	Most common AEs were nasal congestion, myalgia, headache, and fatigue. No participants discontinued study medications due to adverse effects.	[36]
TURQUOISE-I	63 patients enrolled with HCV GT 1 31 with 12 wk of treatment 19% with cirrhosis 32 with 24 wk of treatment 19% with cirrhosis	63 (100%) patients were receiving ARVs consisting of an atazanavir- or RAL-inclusive ARV regimen	94% with 12 wk of treatment 91% with 24 wk of treatment	Most common AEs were fatigue, insomnia, nausea, and headache. No patient had a confirmed HIV-1 breakthrough of ≥200 copies/mL during treatment.	[37]

Abbreviations: ABC, abacavir; AE, adverse event; ART, antiretroviral therapy; ARV, antiretroviral; ATV/r, ritonavir-boosted atazanavir; DCV, daclatasvir; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; SOF, sofosbuvir; SVR, sustained virologic response; TDF, tenofovir disoproxil fumarate.

HCV Treatment Options in HCV/HIV Co-infected Persons

Preferred DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors)				
HCV GT	**Treatment regimen**	**Treatment duration & RBV usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 4	EBR/GZR	12 weeks[i]		Not recommended
	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/LDV +/- RBV	8-12 weeks without RBV[ii]	12 weeks with RBV[iii]	
2	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV
3	GLE/PIB	8 weeks[iv]	12 weeks[iv]	Not recommended
	SOF/VEL +/- RBV	12 weeks[v]	12 weeks with RBV[vi] or 24 weeks without RBV	
	SOF/VEL/VOX	-	12 weeks	Not recommended
5 & 6	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/LDV +/- RBV	12 weeks +/- RBV[vii]	12 weeks with RBV[iii]	
	SOF/VEL	12 weeks		12 weeks with RBV

EBR = elbasvir
GLE = glecaprevir
GZR = grazoprevir
LDV = ledipasvir
PIB = pibrentasvir
RBV = ribavirin
SOF = sofosbuvir
VEL = velpatasvir
VOX = voxilaprevir
RAS = resistance associated substitutions

i Extension of treatment to 16 weeks and addition of RBV in PLWH with GT1a with baseline HCV-RNA > 800.000 IU/mL and/or NS5A RASs causing at least 5-fold reduction in activity of EBR to minimise the risk of treatment failure and in HCV GT4 experienced PLWH with HCV-RNA > 800.000 IU/mL. 8 weeks can be considered in GT 1b treatment-naïve with F0-F2

ii 8 weeks treatment without RBV only in treatment-naïve PLWH with F < 3 and baseline HCV-RNA < 6 million IU/mL

iii In persons intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS

iv Treatment duration in HCV GT3 who failed previous treatment with IFN and RBV +/- SOF or SOF and RBV should be 16 weeks

v Addition of RBV in treatment experienced PLWH with baseline NS5A RASs, if RAS testing available; if these persons are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV

vi If RAS testing is available and demonstrates absence of NS5A RAS Y93H, RBV can be omitted in treatment naive PLWH with compensated cirrhosis

vii In treatment experienced (exposure to IFN/RBV/SOF) PLWH RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV

DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors) to be used if preferred option is not avaible				
HCV GT	**Treatment regimen**	**Treatment duration & RBV usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 4	OBV/PTV/r + DSV	8[i]-12 weeks in GT 1b	12 weeks in GT 1b	Not recommended
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4		Not recommended
	SOF + DCV +/- RBV	12 weeks +/- RBV[ii]	12 weeks with RBV[iii]	
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended
3	SOF + DCV +/- RBV	12 weeks +/- RBV[v] or 24 weeks without RBV	24 weeks with RBV	
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended
5 & 6	SOF + DCV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[vi]	12 weeks with RBV[iii]	
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended

DCV = daclatasvir
DSV = dasabuvir
OBV = ombitasvir
PTV/r = paritaprevir/RTV
RBV = ribavirin
SOF = sofosbuvir
VEL = velpatasvir
VOX = voxilaprevir
RAS = resistance associated substitutions

i 8 weeks treatment without RBV only in PLWH without cirrhosis
ii Addition of RBV in GT1a treatment experienced PLWH, but not in PLWH without NS5A RASs, if RASs testing is available
iii In PLWH intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS
iv Extension of treatment to 12 weeks in DAA treatment experienced PLWH
v Addition of RBV only in treatment experienced persons with baseline NS5A RASs, if RAS testing available; if these PLWH are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV
vi In treatment experienced (exposure to IFN/RBV/SOF) PLWH RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV

Drug-drug Interactions between DAAs and ARVs

HCV drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
DAAs	daclatasvir	↑31% a	↑110% a	↑	↑41%	↑15%	↔	↓32% b	↓	↓	↔	↔	↔	↓2% E33%	↑ a	↔	↔	↔	↔	↔	↑10% E10%
	elbasvir/ grazoprevir	↑	↑376% ↑958%	↑	↑66% ↑650%	↑271% ↑1186%	↓4% ↑7%	↓54% ↓83%	↓	↓	↑7% ↓2%	↔	↔	↓2% ↓19%	↑118% ↑436%	↓19% ↓11%	↔	↔	↔	↔	↓7% ↓14%
	glecaprevir/ pibrentasvir	↑	↑553% ↑64%	↑	↑397% -	↑338% ↑146%	↔	↓	↓	↓	E 84%	E	E	↔	↑205% ↑57% E47%	E47%	↔	↔	↔	↔	E29%
	paritaprevir/r/ ombitasvir/ dasabuvir	↑	↑94% ↓17% ↓18% c	↑	D d	↑117% ↑17% ↓7%	E	f	↓	↓E	E 225% g	E	E	↓16% ↓5% ↓2%	↑	E134%	↓18% ↓9% ↓9%	↓16% ↓1% ↓15%	↓18% ↓9% ↓9%	E	↓16% ↓1% ↓15%
	paritaprevir/r/ ombitasvir	↑	↑187% c	↑	↑ e	↑510% -	E	f	↓	↓E	E g	E	E	↔	↑	E20%	↔	↔	↔	E	↔
	simeprevir	↑	↑	↑	↑159%	↑	↔	↓71%	↓	↓	↑6% E12%	↔	↔	↔	↑	↓11% E8%	↔	↔	↔	↔	↓14% E18%
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↓6%	↔	↔	↑9%	↔	↔	↔	↔	↓5% D27%	↔	↓6%	↔	↔	↓6%
	sofosbuvir/ ledipasvir	↑ h	↑8% ↑113% h	↑ h	↑34% ↑39% h	↔ h	↑4% ↓8%	↓6% ↓34%	↔	↔	↑10% ↑8% h	E	↑7% ↓13%	↔	↑36% ↑78% h	↓5% ↓9% D~20%	↑21% ↑18% D 10%	↔	↑21% ↑18% D 6%	E32%	E h
	sofosbuvir/ velpatasvir	↔ h	↑22% ↑142% h	↔ h	↓28% ↓16% h	↓29% ↑2% h	↔	↓3% ↓53%	↓	↓	↑16% ↓1%	E	↔	↓8% ↓9%	↑ h	↑24% ↓2%	↔	↔	↔	↔	E h
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40% ↑93% ↑331%	↑ h	↓28% ↓5% ↑143% i	↑	↔	↓	↓	↓	↔	E	↑9% ↓4% ↓9%	↔	↑22% ↑16% ↑171% h	↔	↔	↔	↔	E	E h

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑	Potential elevated exposure of DAA
↓	Potential decreased exposure of DAA
↔	No significant effect
D	Potential decreased exposure of ARV drug
E	Potential elevated exposure of ARV drug

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to decreased/increased AUC as observed in drug interactions studies. First/second numbers refer to AUC changes for EBR/GZR or GLE/PIB or SOF/LDV or SOF/VEL.
First/second/third numbers refer to AUC changes for SOF/VEL/VOX

Interactions with ZDV
No clinically relevant interactions expected with ZDV and DAAs

Comments

a DCV should be reduced to 30 mg qd with ATV/c, ATV/r or EVG/c. No dose reduction with unboosted ATV
b DCV should be increased to 90 mg qd
c Study details are with unboosted ATV. Use only with unboosted ATV (ATV increased PTV exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without DSV)
d Co-administration decreased DRV trough concentration by ~50%. Although co-administration of DRV with OBV/PTV/r + DSV is not recommended in the US Prescribing Information, the European SmPC advises that DRV (dosed at 800 mg qd and administered at the same time as OBV/PTV/r + DSV) can be used in the absence of extensive HIV PI resistance and should be taken without additional RTV
e Not recommended due to increase in PTV exposure when co-administered with DRV 800 mg given with OBV, PTV, RTV (Viekirax). Of note: exposures of PTV greater than this have been evaluated in phase 2 studies and were not expected to have a clinically meaningful impact on safety
f Severe tolerability issues
g Not recommended unless benefit outweighs the risk due to potential for QT interval prolongation with higher concentrations of RPV. Co-administration should be only considered in persons without known QT prolongation and without other QT prolongation co-medicines
h Monitoring of kidney function recommended due to increase of tenofovir concentration if the regimen contains TDF
i Study details are with once daily DRV/r. Twice daily DRV has not been studied and should be used with caution as VOX concentrations may increase more than with once daily DRV (this would be of further significance in cirrhotic patients). Monitoring of kidney function recommended due to increase of tenofovir concentrations if the regimen contains TDF

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

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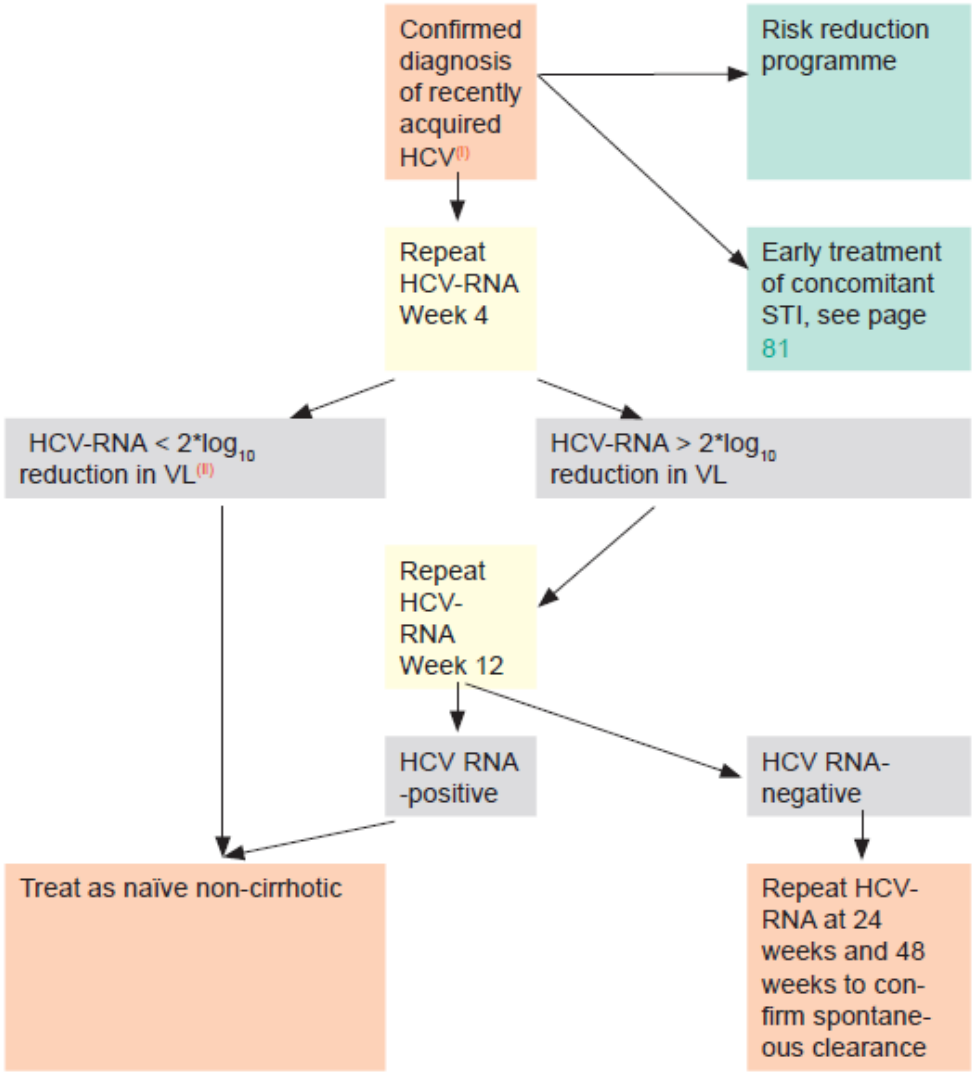
Version 10.0
November 2019
English

Algorithm for Management of Recently Acquired HCV Infection in PLWH



i Where available initiate DAA-based treatment immediately in persons with risk of onward transmission

ii HCV-RNA < 2*$\log_{10}$ reduction at week 4 is considered as chronic HCV infection

Summary

HIV Viral hepatitis Co-Infection is of global concern

Respectively 38, 257 and 71 million individuals infected

Prophylaxis is important and possible

Screening for and Treatment of HBV and HCV should be considered in all individuals living with HIV