

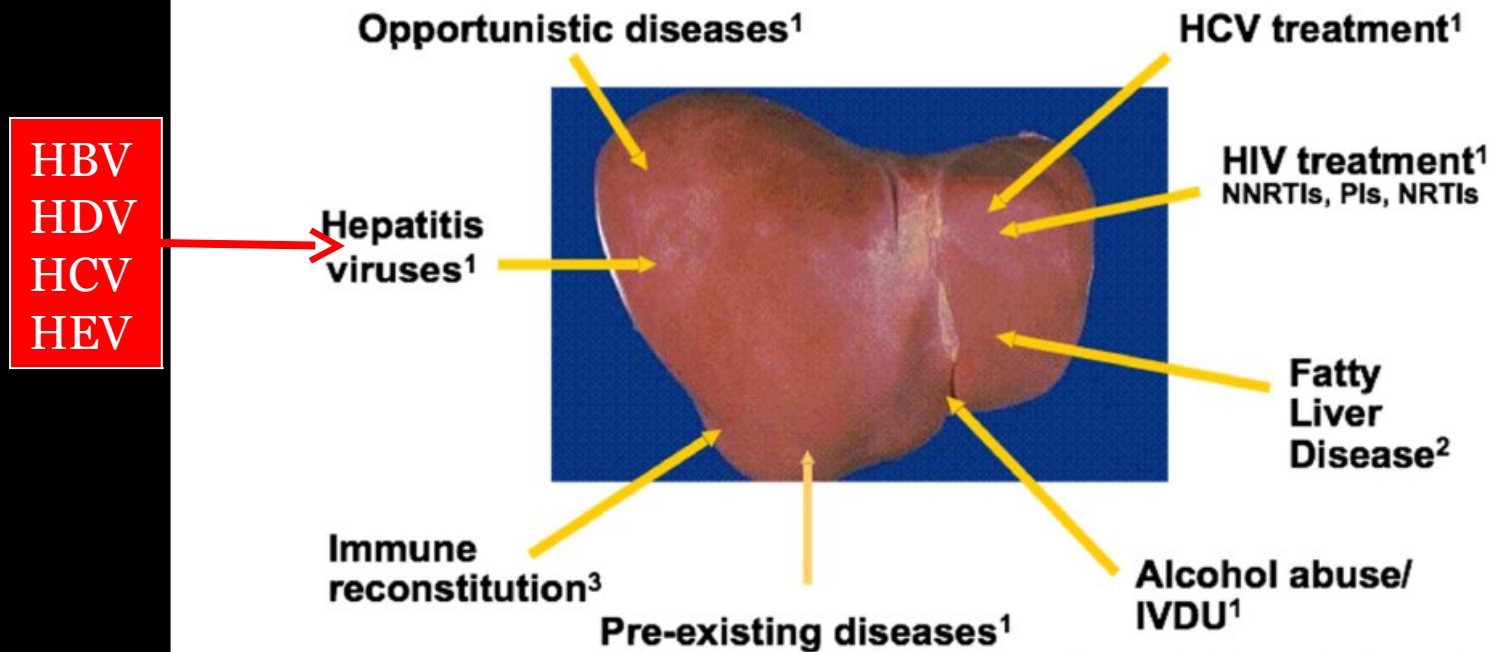
Severe liver disease in HIV patients
- two stories of HIV/HBV co-infection -

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Liver disease in HIV patients

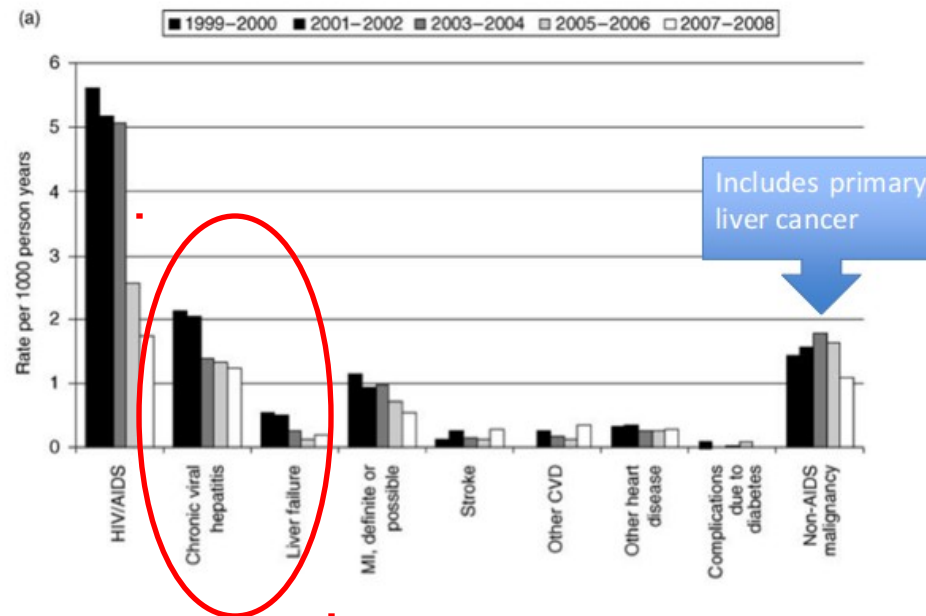
Liver Disease in HIV-infected Patients



1. Sulkowski M. *et al.* Ann Intern Med. 2003;138:197-207 2. Guaraldi G *et al* Clin Infect Dis 2008 47(2): 250-257
3. Greub G *et al.* Lancet 2000;356:1800-1805

Liver disease in HIV patients

Causes of death in HIV



1. Weber R, Sabin CA, Friis-Møller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch. Intern. Med. 2006;166:1632-1641.

Case 2 – optimistic story

March 2009

- 40 yrs old male, army officer returned from Ghana***
- apparently healthy***
- routinely tested for possible infections***

Case 2 – optimistic story

March 2009

- HIV positive***
- CD4 140 cells/mm³***
- HIV RNA 325014 copies/ml***
- AgHBs negative***
- antiHCV negative***
- normal ALT***
- antiHBc positive***

Case 2 – optimistic story

March 2009

- ***What additional tests should be done?***
 - ***HBV ADN ?***
 - ***liver biopsy ?***
 - ***noninvasive fibrosis tests ?***

Case 2 – optimistic story

March 2009

- ***What additional tests should be done?***
 - ***HBV ADN < 400 copies/ml***

Case 2 – optimistic story

March 2009

- ART was started with

- Stavudine + Tenofovir + Indinavir boosted with Ritonavir

Case 2 – optimistic story

September 2009

- significant increase in ALT and AST (5 X upper limits and 8 X upper limits)***
- hepatomegaly***
- increasing in BMI***

Case 2 – optimistic story

September 2009

- **What additional test should be done?**
 - **AgHBs - negative**
 - **HAV IgM - negative**
 - **antiHCV - negative**
 - **VHB DNA < 400 copies/ml**
 - **abdominal ultrasound – liver steatosis**
 - **liver biopsy – declined by patient**
 - **noninvasive fibrosis tests - unavailable**
 - **autoimmune hepatitis tests - negative**
 - **CMV, EBV tests – negative**
 - **cholesterol and triglycerides – moderately high**

Case 2 – optimistic story

September 2009

- ***What is the most probable cause of aminotransferases elevation?***
 - ***ART hepatotoxicity***
 - ***steatohepatitis***
 - ***immune reconstruction***

Case 2 – optimistic story

September 2009

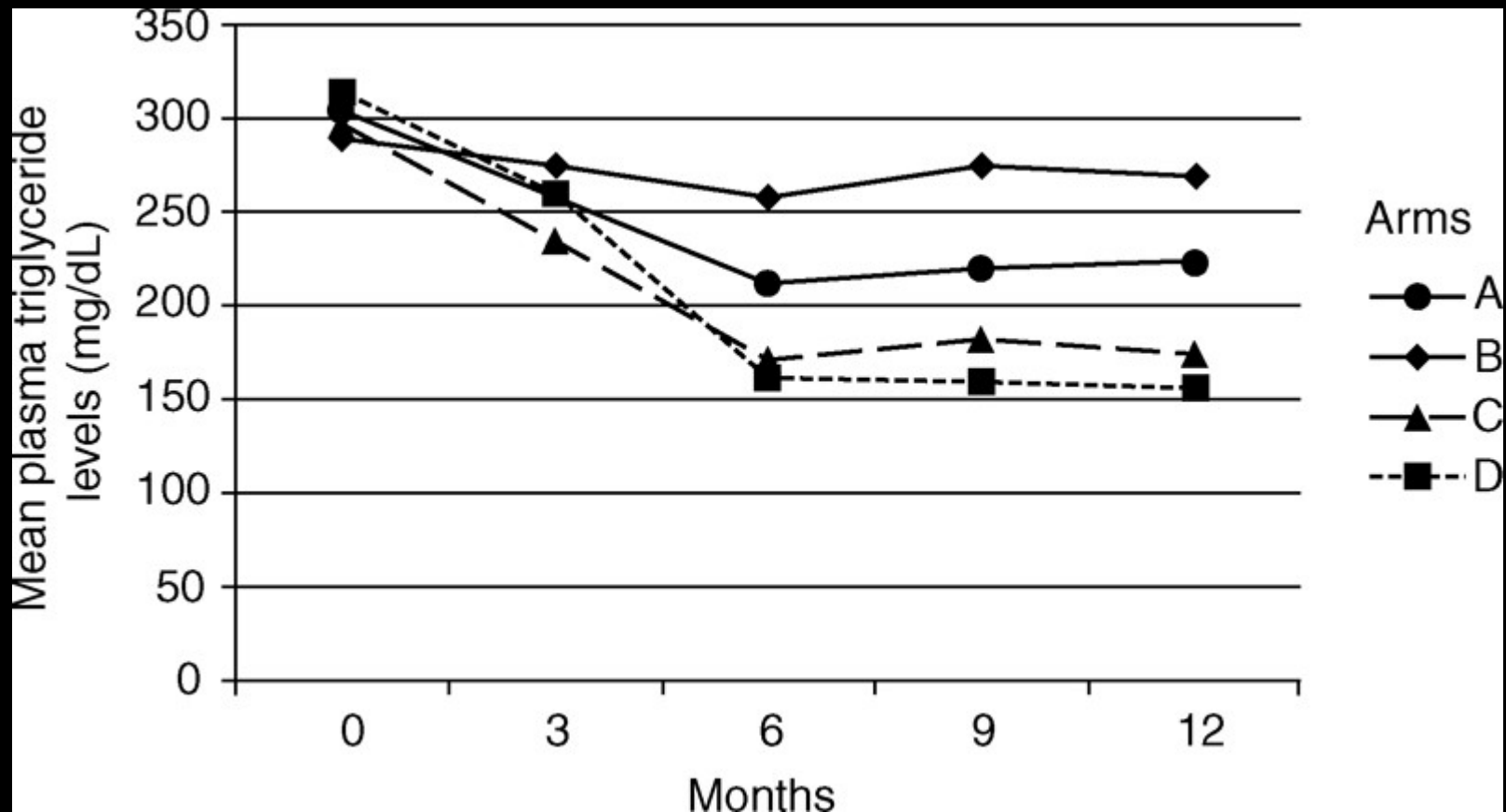
- ***What would you change in patient management?***
 - ***advise on lifestyle - diet and physical exercise***
 - ***stop ART***
 - ***switch ART***
 - ***monitoring***
 - ***treatment with fibrates and/or statines***

Case 2 – optimistic story

September 2009

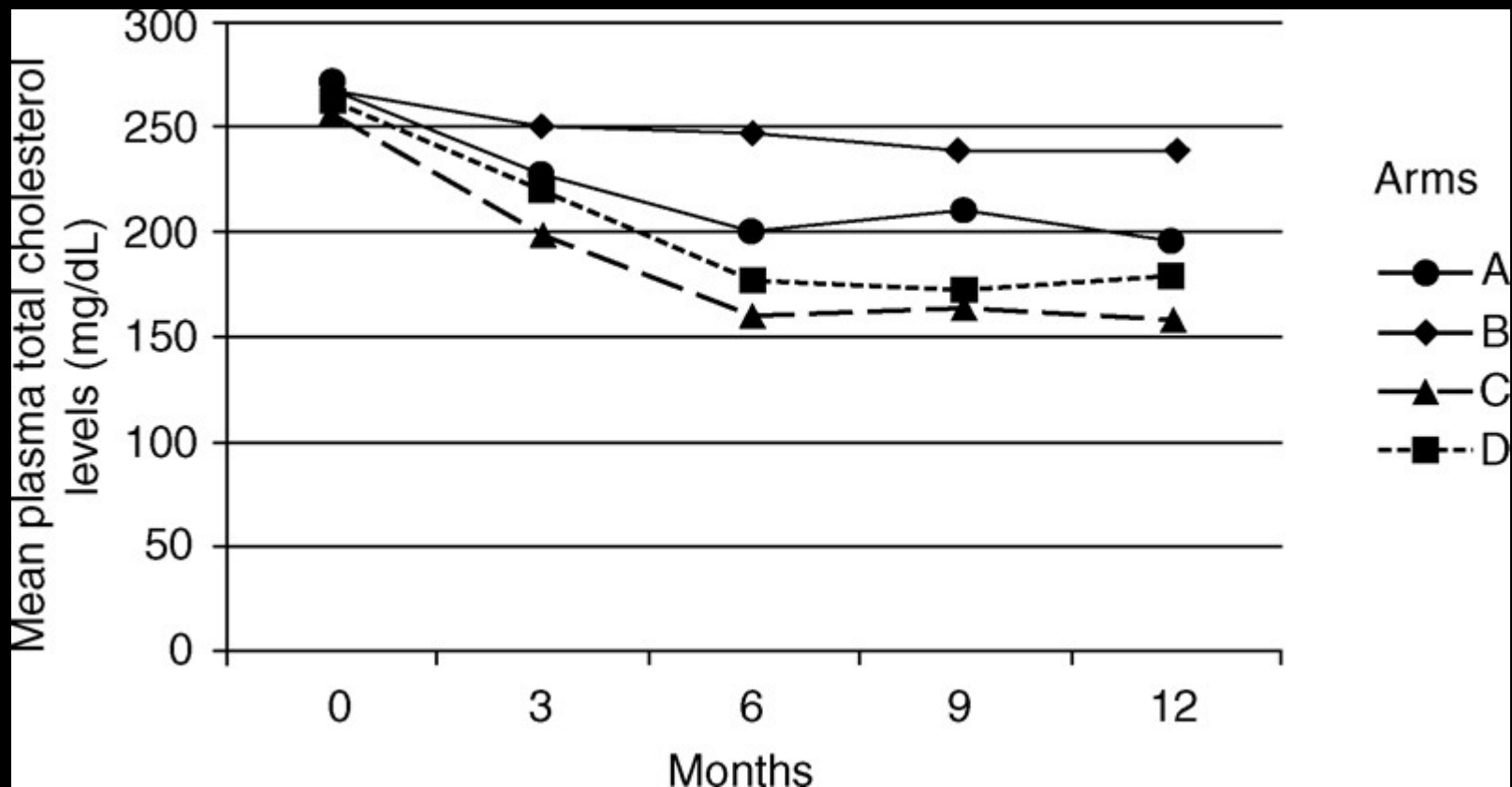
- ***What would you change in patient management?***
 - ***advise on lifestyle - diet and physical exercise***
 - ***stop ART***
 - ***switch ART : stop indinavir/ritonavir and replace by lamivudine***
 - ***monitoring***
 - ***treatment with fibrates and/or statines : gemfibrozil***

Switch ART regimen or initiate lipid-lowering pharmacotherapy?



*Trend of mean plasma **triglyceride** levels of 130 evaluable patients switched from protease inhibitor to nevirapine (arm A) or efavirenz (B), or treated with pravastatin (C) or bezafibrate (D), at baseline and after 3, 6, 9 and 12 months of follow-up.*

Switch ART regimen or initiate lipid-lowering pharmacotherapy?



*Trend of mean plasma total **cholesterol** levels of 130 evaluable patients switched from protease inhibitor to nevirapine (arm A) or efavirenz (B), or treated with pravastatin (C) or bezafibrate (D), at baseline and after 3, 6, 9, and 12 months of follow-up.*

Lipid-Lowering Agents and ARV Therapy: Potentially Dangerous Drug Interactions

<i><u>Agent</u></i>	<i><u>Recommendation</u></i>
<i>Pravastatin</i>	<i>No dose adjustment</i>
<i>Atorvastatin</i>	<i>Dose titration</i>
<i>Lovastatin</i>	<i>Avoid</i>
<i>Simvastatin</i>	<i>Avoid</i>
<i>Gemfibrozil</i>	<i>No dose adjustment</i>
<i>Fenofibrate</i>	<i>No dose adjustment</i>
<i>Niacin</i>	<i>Associated with insulin resistance</i>
<i>Bile sequestrants</i>	<i>Avoid</i>

Case 2 – optimistic story

September 2009

- ART with

- Stavudine + Tenofovir + Lamivudine

Case 2 – optimistic story

December 2009

- ALT 3 X upper limits; AST 3 X upper limits***
- CD4 380 cells/mm³***
- HIV RNA: undetectable***
- HBV DNA < 400 copies/ml***

Case 2 – optimistic story

December 2009

- Decision make to stop ART !

Case 2 – optimistic story

January 2010

- Normal ALT and AST***
- CD4 358 cells/mm³***

Case 2 – optimistic story

April 2010

- ***Increasing of ALT to 3 X upper limit and AST 2 X upper limit***
- ***CD4 350 cells/mm³***
- ***HIV RNA < 50 copies/ml***
- ***AgHBs positive***
- ***HBV DNA 120000 copies/ml***
- ***FIBROSCAN 5.6 KPa***

Interferon Therapy

- ***Pros***
 - ***Finite duration of therapy***
 - ***Durable response***
 - ***No resistance or cross resistance***
- ***Cons***
 - ***Route of administration—injection***
 - ***Frequent side effects***
 - ***Cost***

Ideal Clinical Situation for IFN Therapy

- ***High ALT ($> 5 \times \text{ULN}$) and low HBV DNA level ($< 200,000 \text{ IU/mL}$)***
- ***Younger patient***
- ***Black***
- ***Well-compensated cirrhosis***
- ***No contraindications to use of interferon***
- ***? Genotype A or B***
- ***?HIV/HBV with high CD4, low HIV-RNA***

Lamivudine

- ***Pros***
 - ***Oral***
 - ***Negligible side effects***
 - ***Excellent safety profile***
 - ***Low cost***
- ***Cons***
 - ***High rate of resistance and cross-resistance with other nucleoside analogues***
 - ***Long/indefinite duration of therapy***
 - ***Cannot be used as monotherapy in HIV/HBV***

Ideal Clinical Situation for Lamivudine Use

- ***Short duration of therapy***
 - ***Prevention of disease flares/reactivation during chemotherapy***
 - ***Protracted or severe acute hepatitis***
- ***Safety a concern***
 - ***During pregnancy***
- ***Cost a concern***
 - ***HBeAg-negative CHB in developing countries***

Lamivudine in HAART Regimen

- ***Lamivudine used in HAART regimen for coinfecting individual may result in the development of HBV resistance mutations***
- ***If HAART interrupted or changed, anticipate flare in HBV/hepatitis if lamivudine also stopped***

Adefovir

- **Pros**
 - ***Route of administration: oral***
 - ***Low rate of resistance***
 - ***Effective against lamivudine resistant virus***
 - ***Can be used as monotherapy in HIV/HBV without inducing HIV resistance mutations***
- **Cons**
 - ***Slow response and high rate of primary nonresponse***
 - ***? Renal toxicity with long-term use***
 - ***Long/indefinite duration of therapy***

Ideal Clinical Situation for Adefovir Use

- ***HBeAg-positive and HBeAg-negative chronic hepatitis B with low HBV DNA***
- ***Management of lamivudine-resistant chronic hepatitis B***
- ***HIV/HBV coinfectd individual not requiring HAART***

Entecavir

- **Pros**
 - ***Route of administration: oral***
 - ***Potent with low rate of resistance***
 - ***Effective against LAM-R***
- **Cons**
 - ***Long-term safety unknown***
 - ***Long/indefinite duration of therapy***
 - ***Cannot be used in HIV/HBV coinfecting patient not on HAART – will select for M184V mutation***

Ideal Clinical Situation for Entecavir Use

- ***HBeAg-positive or HBeAg-negative chronic hepatitis B with high viral load***
- ***Management of lamivudine resistance***
- ***Can be used in HIV/HBV coinfection in patients who are on HAART if preferable to other HBV agents***

FTC and TDF for HIV/HBV Coinfected Individuals

- ***Evidence supports benefit of this combination for coinfectd individuals requiring both HIV and HBV treatment***
- ***Should be used in combination with a fully HIV suppressive regimen***
- ***If HAART regimen interrupted or altered, anticipate potential HBV flare if FTC and/or TDF withdrawn without continued HBV suppression***

Case 2 – optimistic story

April 2010

- What guidelines recommend in 2013?

8.2.1.1 Summary of when to start recommendations

CD4 cell count (cells/ μ L)	HBV requiring treatment*	HBV not requiring treatment	HCV with immediate plan to start HCV treatment*	HCV with no immediate plan to start HCV treatment
>500	Start ART (1C) (Include TDF and FTC)	Consider ART (2C) (Include TDF and FTC)	Consider ART before HCV treatment commenced (2C)	Consider ART (2D)
\leq 500	Start ART (1B) (Include TDF and FTC)	Start ART (1B) (Include TDF and FTC)	Start ART before HCV treatment commenced (1C) Discuss with HIV and viral hepatitis specialist	Start ART (1C)

*See BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV 2013 [1] for indications to treat hepatitis B and C

Case 2 – optimistic story

April 2010

- ART was restart with tenofovir/emtricitabine + efavirenz

Case 2 – optimistic story

January 2013

- HIV RNA undetectable***
- HBV DNA undetectable***
- CD4 840 cells/mm³***
- ALT normal***
- abdominal ultrasound: mild hepatomegaly, improved steatosis, mild splenomegaly, right lobe nodule 0.9 cm***
- AFP 38 ng/ml***

Case 2 – optimistic story

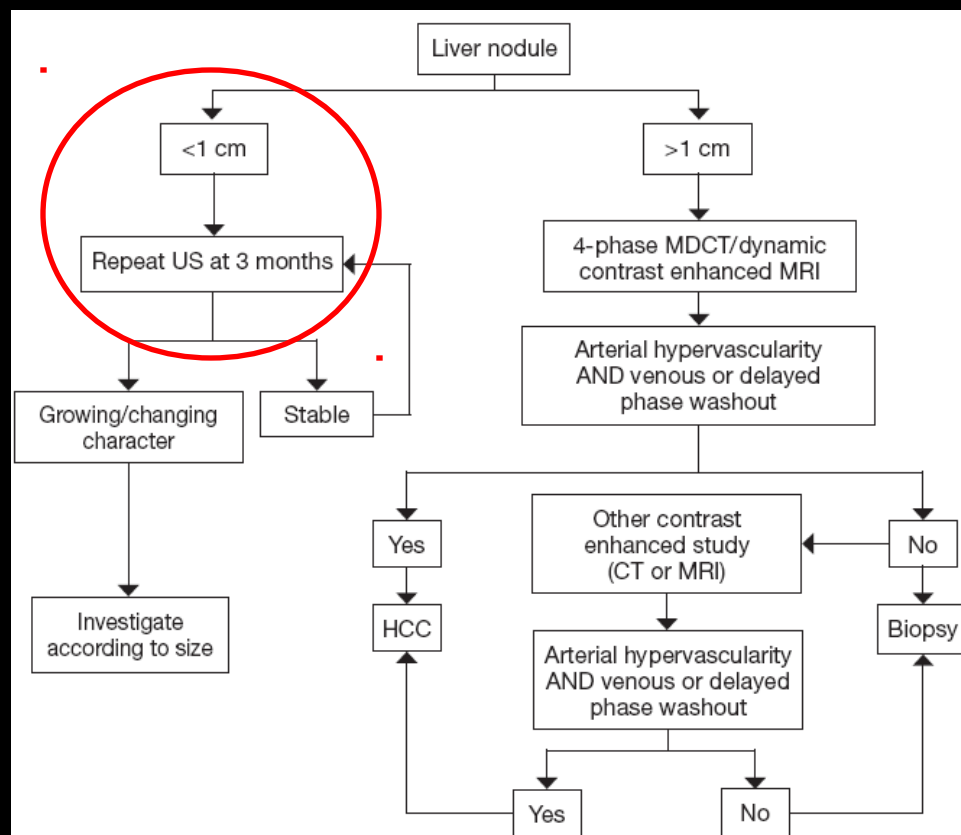
January 2013

- ***What additional test should be done?***
 - ***abdominal MRI/triphasicCT***
 - ***nodule biopsy***
 - ***active monitoring***

Case 2 – optimistic story

January 2013

- What guidelines recommend ?



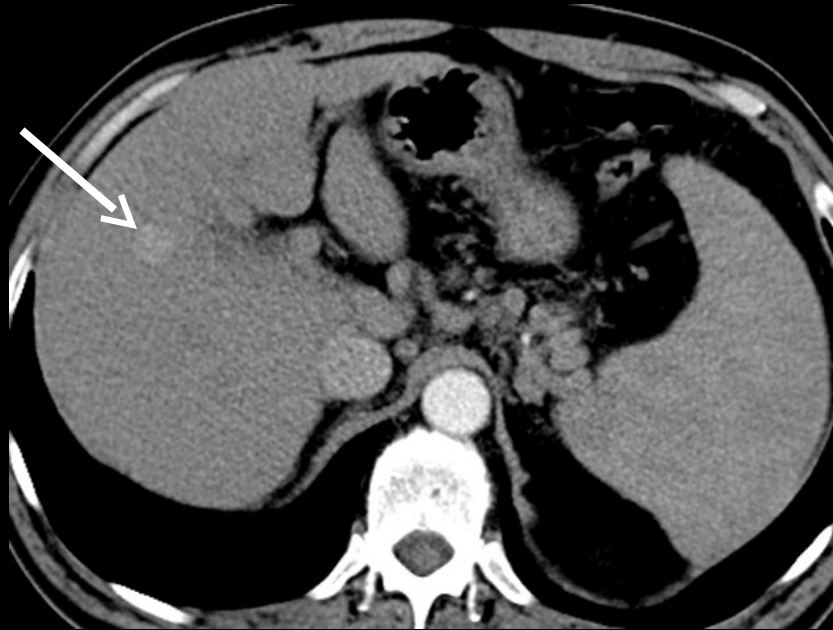
Case 2 – optimistic story

April 2013

- **HIV RNA undetectable**
- **HBV DNA undetectable**
- **CD4 680 cells/mm³**
- **ALT normal**
- **abdominal ultrasound: mild hepatomegaly, improved steatosis, mild splenomegaly, mild ascites **right lobe nodule 2.5 cm****
- **AFP 145 ng/ml**
- **serum albumin 3.2 g/dl; total bilirubin 1.2 mg/dl, INR 1.3, no HE**

Case 2 – optimistic story

- ***May 2013 - triphaseCT: segment V liver focal lesion suggestive for HCC***



Case 2 – optimistic story

***May 2013: HIV/HBV patient with single nodule of HCC < 3 cm,
CHILD B cirrhosis***

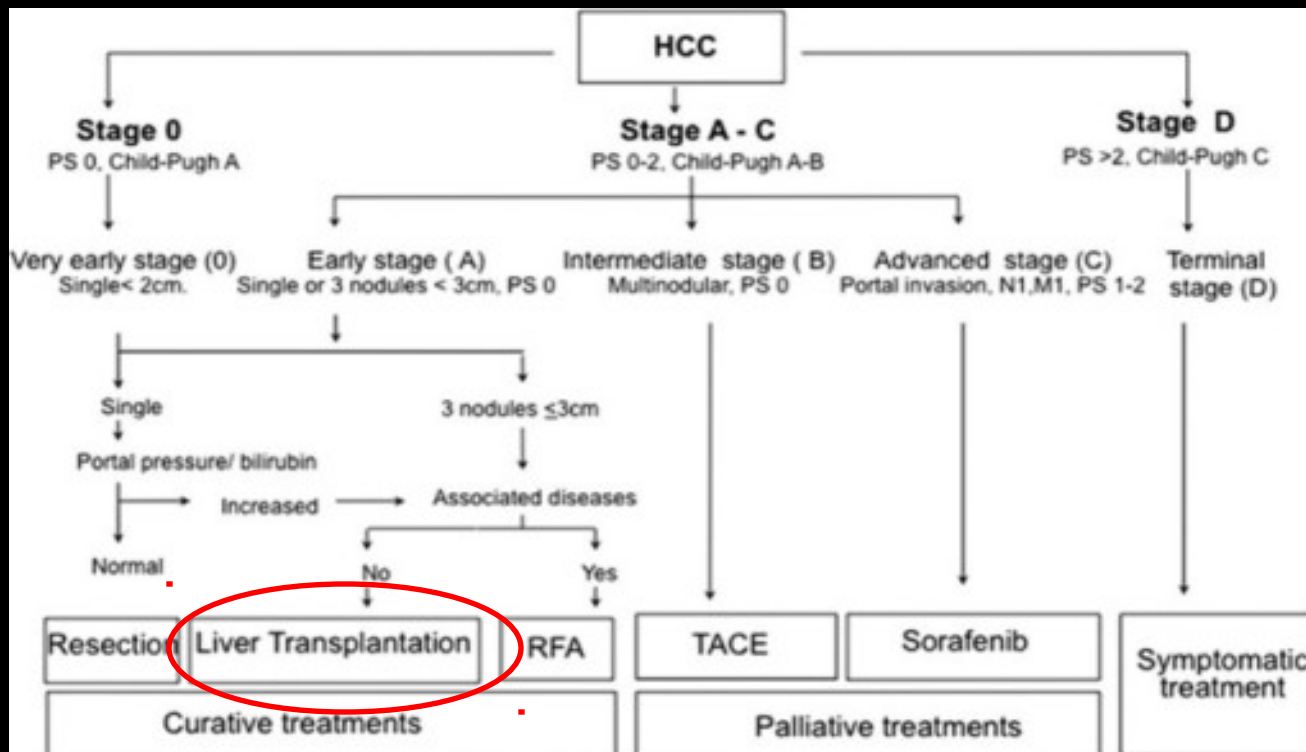
***- What would be the most appropriate management in this
settings?***

- surgical resection***
- ablation***
- TACE***
- liver transplant***

Case 2 – optimistic story

May 2013: HIV/HBV patient with single nodule of HCC < 3 cm, CHILD B cirrhosis

- What guidelines say?



Case 2 – optimistic story

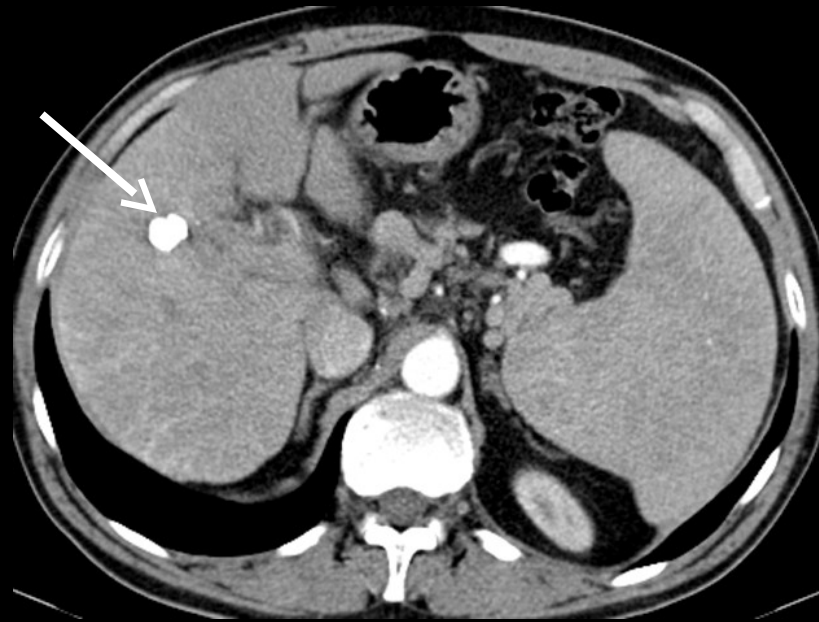
May 2013

- What would be the most appropriate management in this settings?

- surgical resection***
- ablation***
- TACE – scheduled as bridging to liver transplant***
- liver transplant – patient was listed for liver transplant***

Case 2 – optimistic story

- ***June 2013 cATCE was performed with complete response at 1 and 3 month (mRECIST); patient still on waiting list for liver transplant***



Liver transplantation and HIV-Infection

- ***In the pre-HAART era¹:***
 - No difference in immediate postoperative survival between HIV+ and HIV- patients***
 - Long-term high mortality rate due to infections and AIDS-related complications***
 - Rapid progression of HIV to AIDS***
- ***In the HAART era²:***
 - No difference in postoperative survival between HIV+ and HIV- patients***
 - Survival worse for low CD4-counts (<100/ μ l), post OLTX antiretroviral intolerance, VL > 400 copies/ml and HCV infection***

1) Tzakis AG et al., *Transplantation* 1990;49:354-358

2) Ragni MV et al, *J Infect Dis* 2003;188:1412-1420

Liver transplantation and HIV-Infection

Current practice is targeting liver transplantation at patients with:

- ***CD4 counts >200 cells/ul or >100 cells/ul in the presence of portal hypertension***
- ***Undetectable HIV RNA***
- ***Absence of AIDS defining illness after immune reconstitution,***
- ***Therapeutic options available if HIV disease reactivates.***

1) Tzakis AG et al., *Transplantation* 1990;49:354-358

2) Ragni MV et al, *J Infect Dis* 2003;188:1412-1420

Case 2 – optimistic story

December 2013

- ***Liver transplant was performed with good immediate outcome***
- ***Immunosuppression started with tacrolimus and mycophenolate mofetil – monitored every week for 2 month, every 2 weeks for additional 4 month and monthly after 6 month (increased doses required for tacrolimus)***
- ***ART continued with tenofovir/emtricitabine + efavirenz***
- ***HBIG***

Case 2 – optimistic story

- ***Jun. 2015: Liver transplant follow-up***



Case 2 – optimistic story

- ***Jun. 2015: Liver transplant follow-up***
 - ***CD4: 480 cells/mm³***
 - ***HIV RNA < 50 copies/ml***
 - ***HBV DNA undetectable***
 - ***antiHBs 620 UI (on immunoprophylaxis with hepatitis B immune globulin)***

Case 2 – optimistic story

Conclusion

- Markers of HBV exposure are present in the majority of HIV infected individuals and 10-15% have chronic HBV**
- the annual risk of developing cirrhosis in HBV appears to be much higher in those coinfecting with HIV. This may especially true in those with low CD4 counts**
- coinfection with HBV has been associated with increased hepatotoxicity to highly active antiretroviral therapy (HAART)**
- stopping the antiHBV therapy could induce severe flares with bad outcome**
- HCC is more frequent in HIV/HBV coinfecting patients**
- Liver transplant is effective in selected patient with HCC and HIV/HBV coinfection**

Case 1 – sad story

- 16 yrs old boy***
- Constanta County***
- HIV+HBV infection diagnosed at age of 4***
- no data on compliance***

Case 1 – sad story

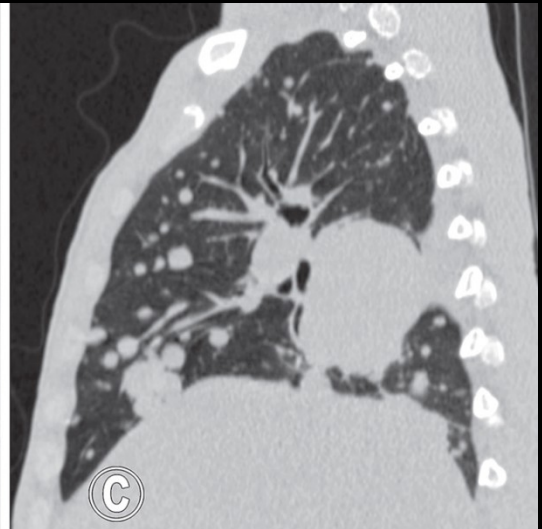
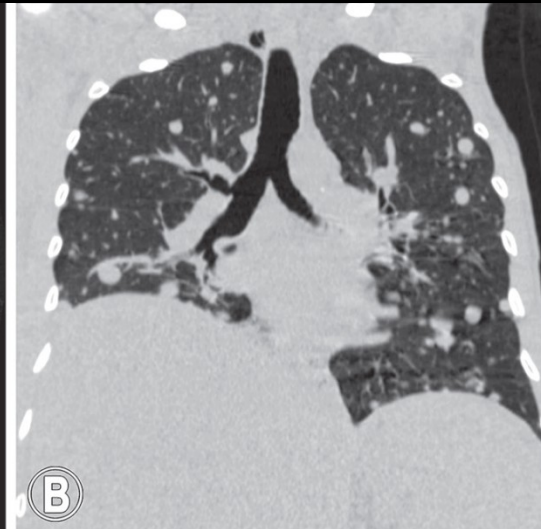
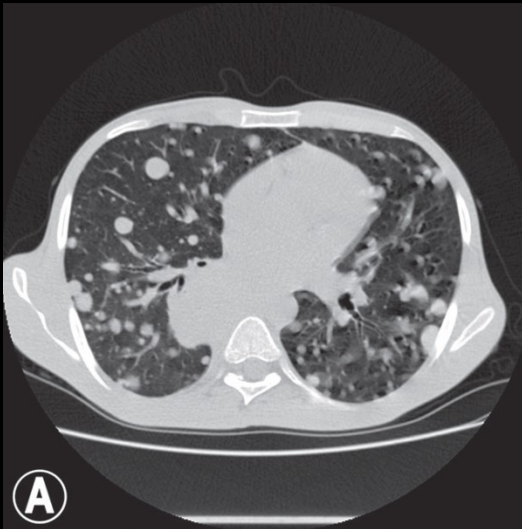
- *admitted in Jan. 2015 for shortness of breath*
- *CD4 600 cells/mm³*
- *HIV RNA undetectable*
- *HBV – DNA 8400 copies/ml*

Case 1 – sad story

- *radiological examination of thorax: multiple macro- and micronodular lesions (0.3 – 9 cm)*
 - *abdominal ultrasound: hepatosplenomegaly and mild ascites*
- AFP > 1000 ng/ml*

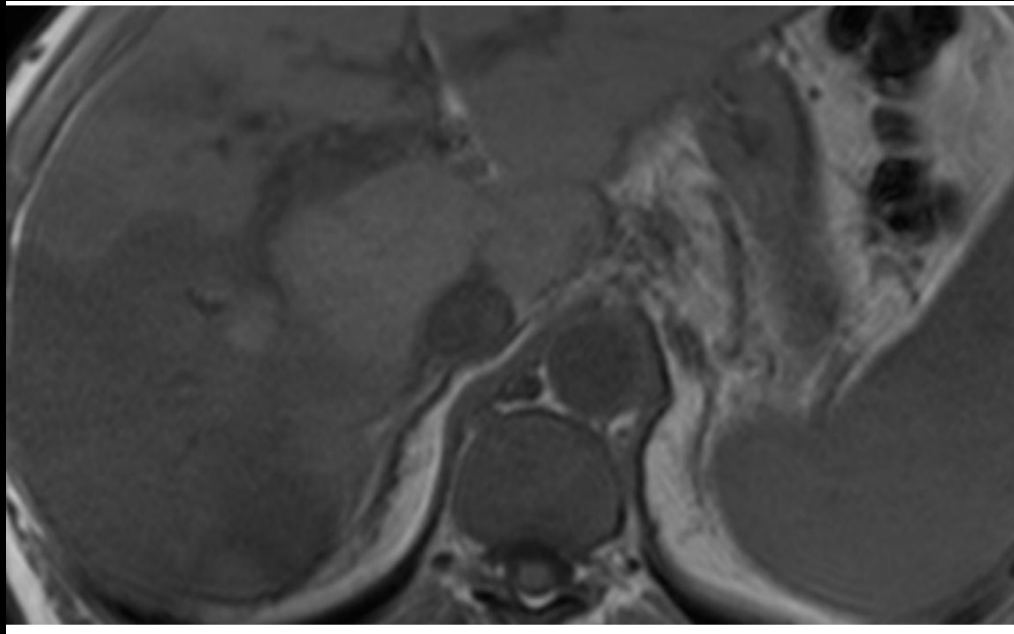
Case 1 – sad story

- *CT scan of thorax:*



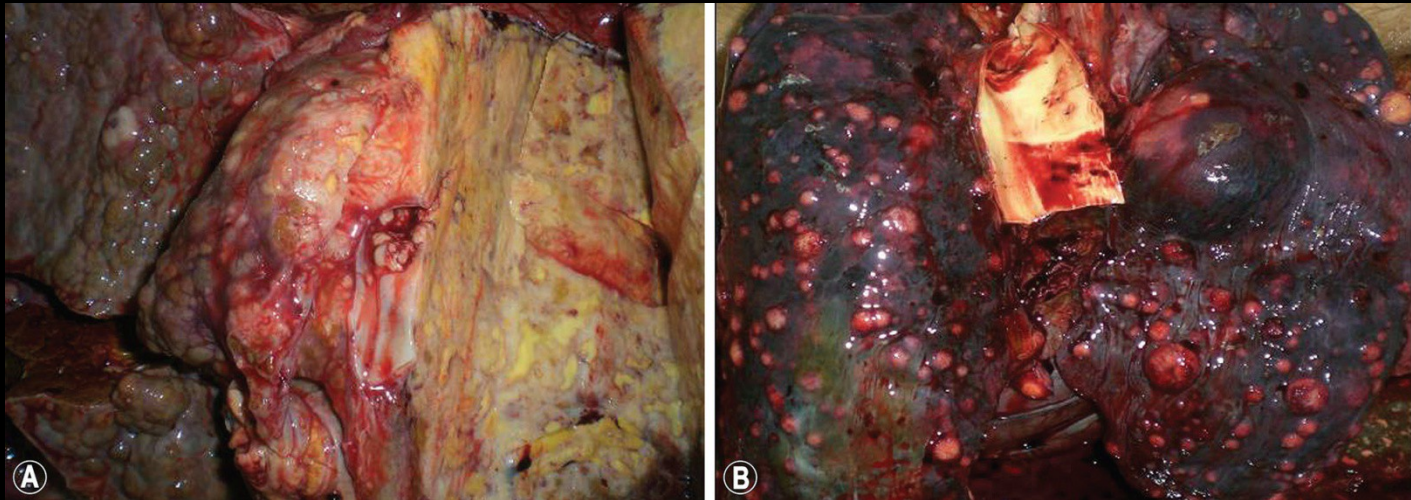
Case 1 – sad story

- Abdominal MRI: tumoral mass segments VI, VII, V !!!



Case 1 – sad story

- Outcome: **death in 20 days from admission** –
respiratory failure due to metastatic lesion from advanced HCC



Liver (A) and lungs (B) on autopsy

Case 1 – sad story

Conclusion

- *HCC may have aggressive phenotype in HIV/HBV coinfecting patients*
- *younger age on presentation*
- *active monitoring is demanding*