Liver disease in the HIV infected patient – not always what it seems

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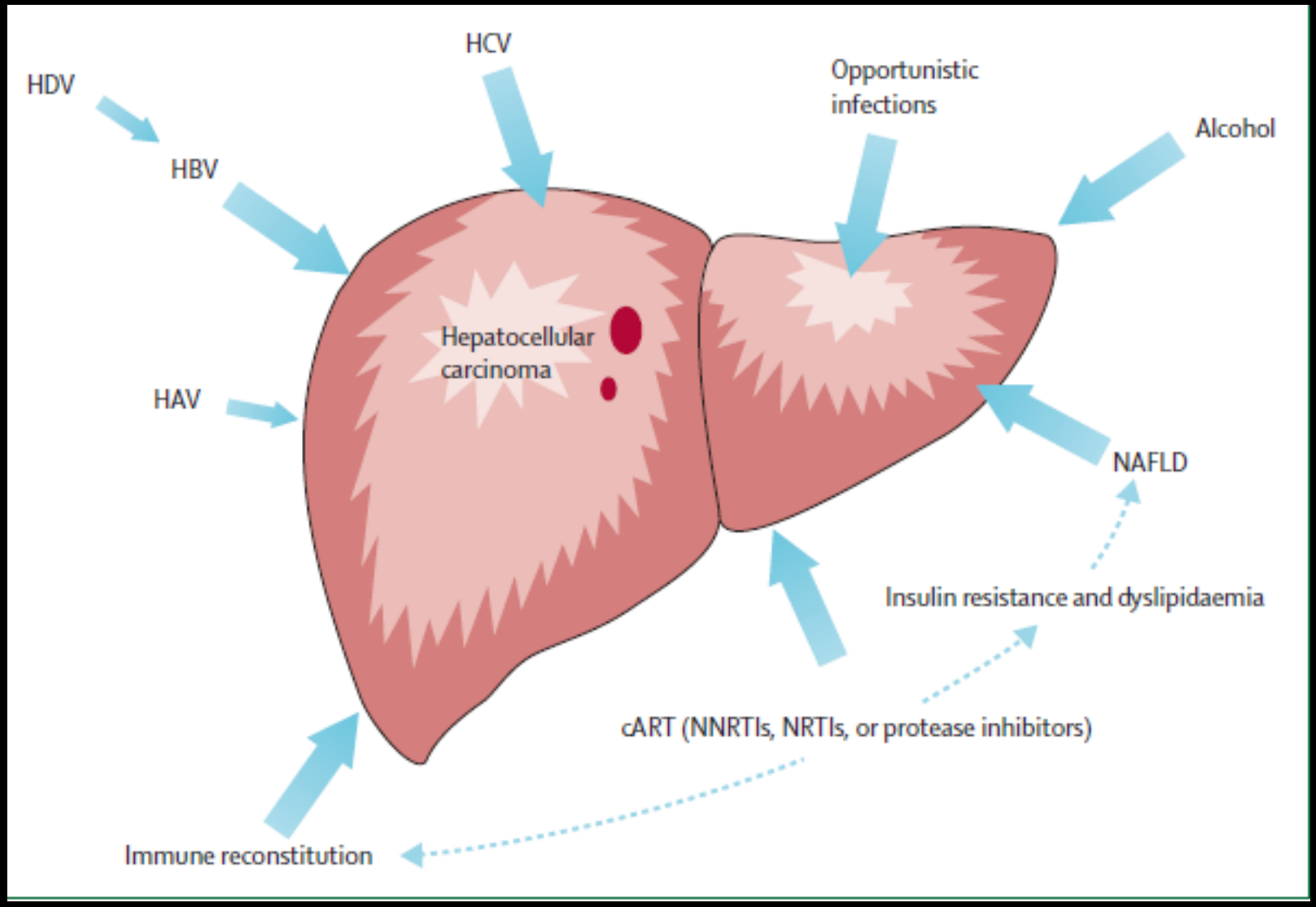
September 2014


HDV
HBV
HAV
HCV
Opportunistic infections
Alcohol
Hepatocellular carcinoma
NAFLD
Insulin resistance and dyslipidaemia
cART (NNRTIs, NRTIs, or protease inhibitors)
Immune reconstitution

Case 1

A 26 yr old female presenting with jaundice. Fatigue, abdominal pain, dark urine and pruritus.

PMH: HIV infected diagnosed in Feb 2011.

Current: CD4 420 Nadir: CD4 274

TDF/3TC/EFV May 2013 uneventful course until August 2013.

SH: No current ETOH or use of traditional meds

Past ETOH misuse.

Case 1

OE: Deep jaundice. No ascites, tender along the liver edge.

No palpable spleen.

No liver flap, no evidence of encephalopathy

Laboratory Results:

T Bili 72, C Bili 66, ALP 1198, GGT 3369, ALT 249, INR 1.2., platelets 240

Hepatitis C antibody negative, HEV PCR and antibody negative, HBsAg positive, antiHBe positive, HBV VL ND

ASMA neg, ANA Pos 1:160, IgG 25.5 (3.0-16.0), AMA neg, ALKM neg.

Ultrasound:

Coarse liver echopattern, size lower limits of normal, no focal lesions. Portal vein normal. Spleen normal.

Q 1

Possible diagnoses?

A. DILI
B. AIH
C. IRIS
D. Gallstones
E. Fibrosing cholestatic hepatitis

ANSWER

- A B C all possible

Fibrosing cholestatic hepatitis

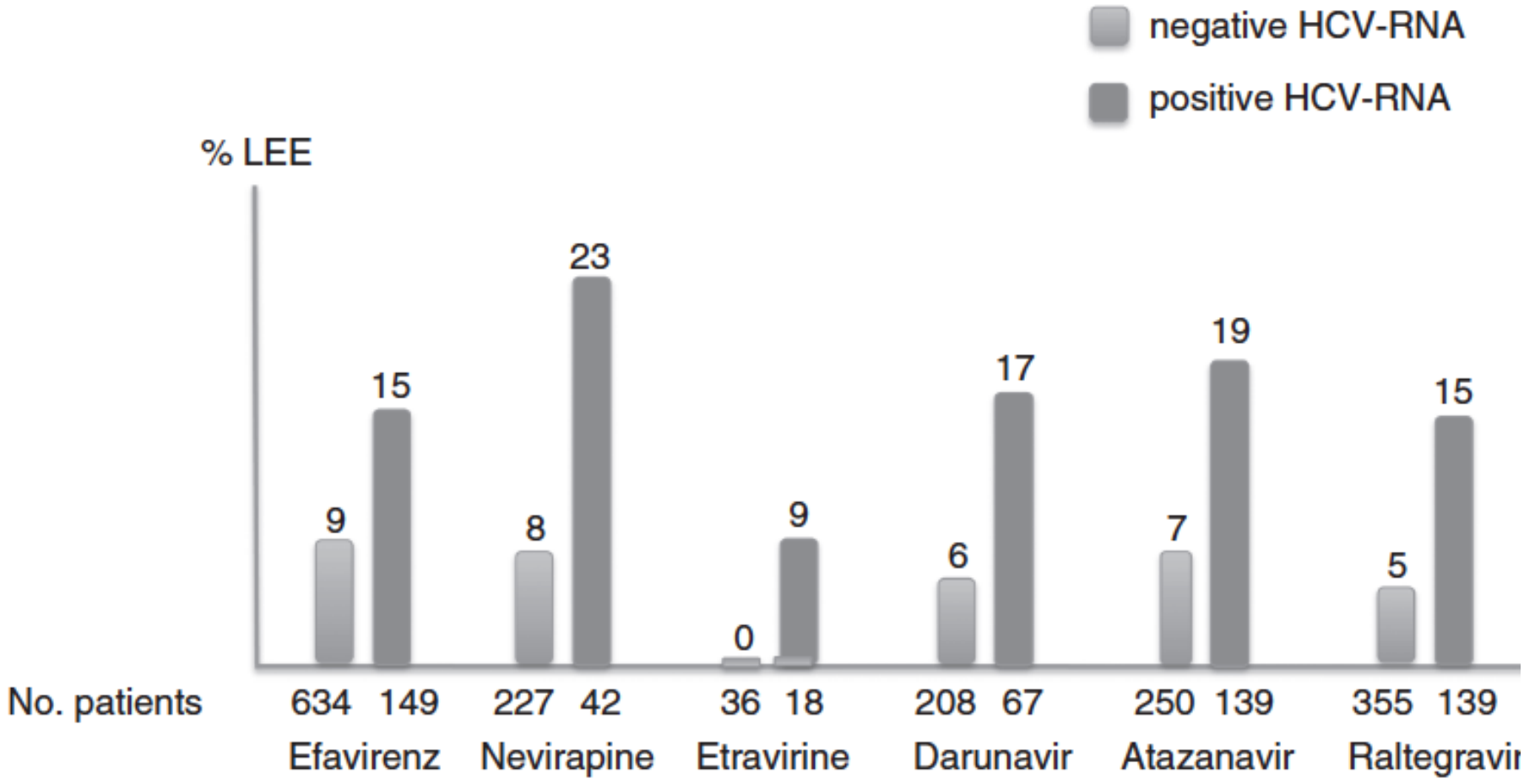
- Rare, severe form of HBV (also HCV)
- Often fulminant course
- Cholestasis and rapid progression to failure
- Associated with severe immunosuppression
- Features: Severe cholestasis, ground glass appearance, ballooning hepatocytes, fibrosis extending from portal tracts, scant inflammatory infiltrate
- Treatment: response to nucleoside analogues

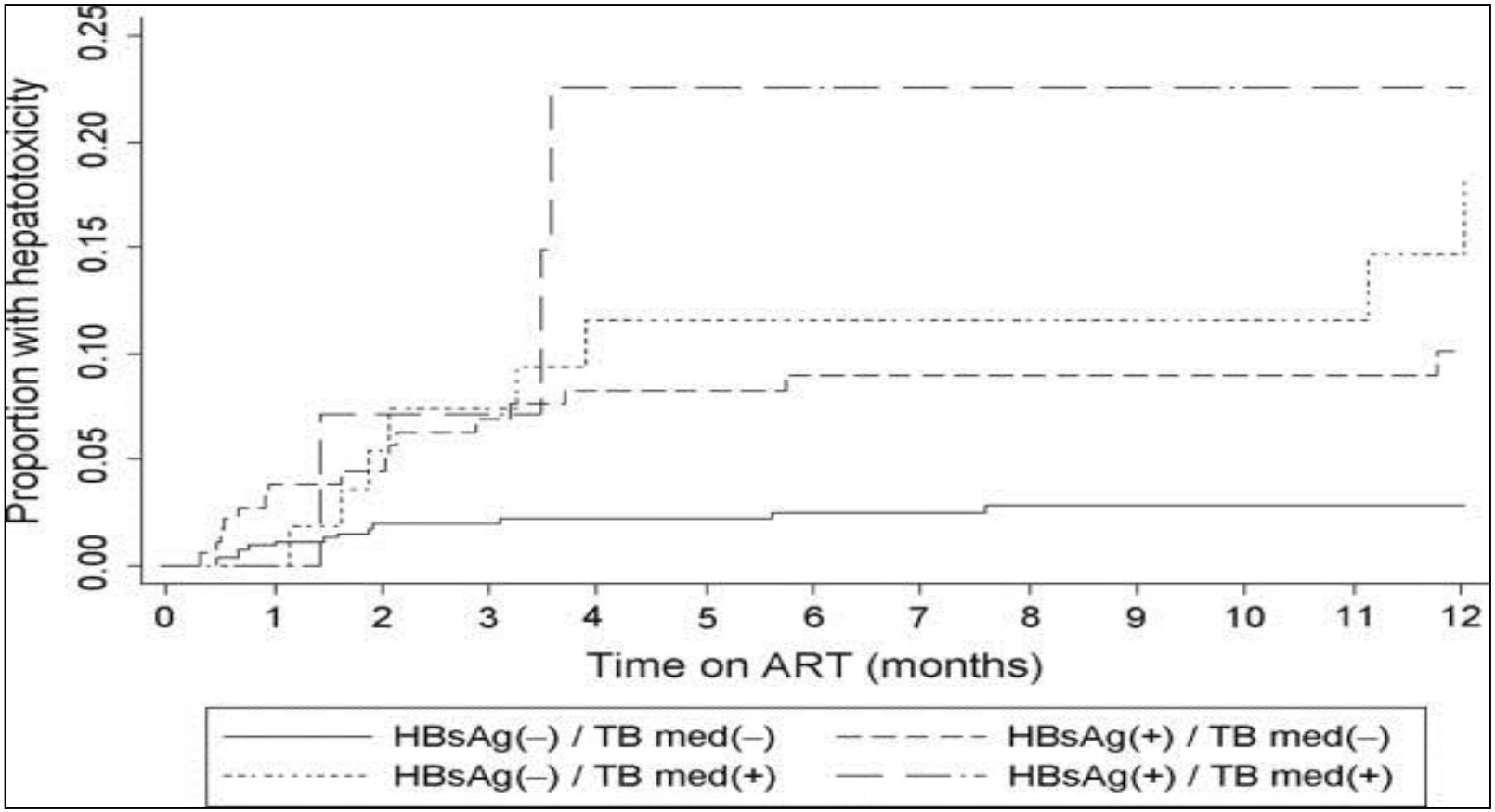
DILI

- Incidence of liver elevation around 5-10% in first 12 weeks
- Risks: HCV, advanced liver fibrosis, male sex[1]

- SA setting: HBV and TB medication[2]

1. AIDS 2013:27(7)1187
2. AIDS.2007: 21(10):1301-1308, .


negative HCV-RNA
positive HCV-RNA
% LEE
9
15
8
23
0
9
6
17
7
19
5
15
No. patients
634 149
227 42
36 18
208 67
250 139
355 139
Efavirenz
Nevirapine
Etravirine
Darunavir
Atazanavir
Raltegravir



AIDS. 21(10):1301-1308, June 2007.
DOI: 10.1097/QAD.0b013e32814e6b08

Course…

- Liver tests worsened with T Bili rising to 286, ALT 447
- No evidence of progression clinically

What would you do next?

A. Continue to watch her for 7 days
B. Stop all her ARVs and monitor LFTs
C. Perform a liver biopsy
D. Re-check her HBV Viral load

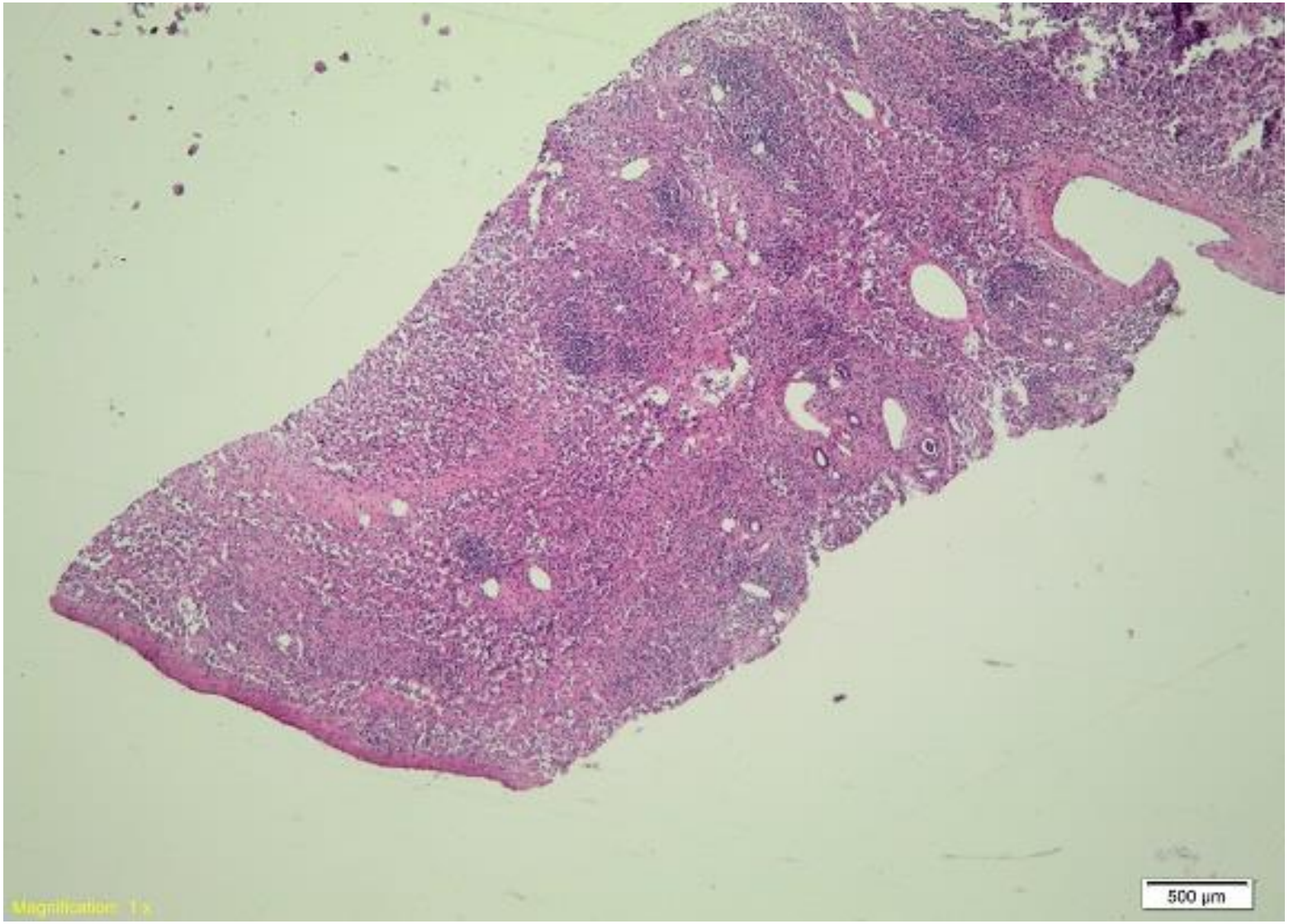
Q2

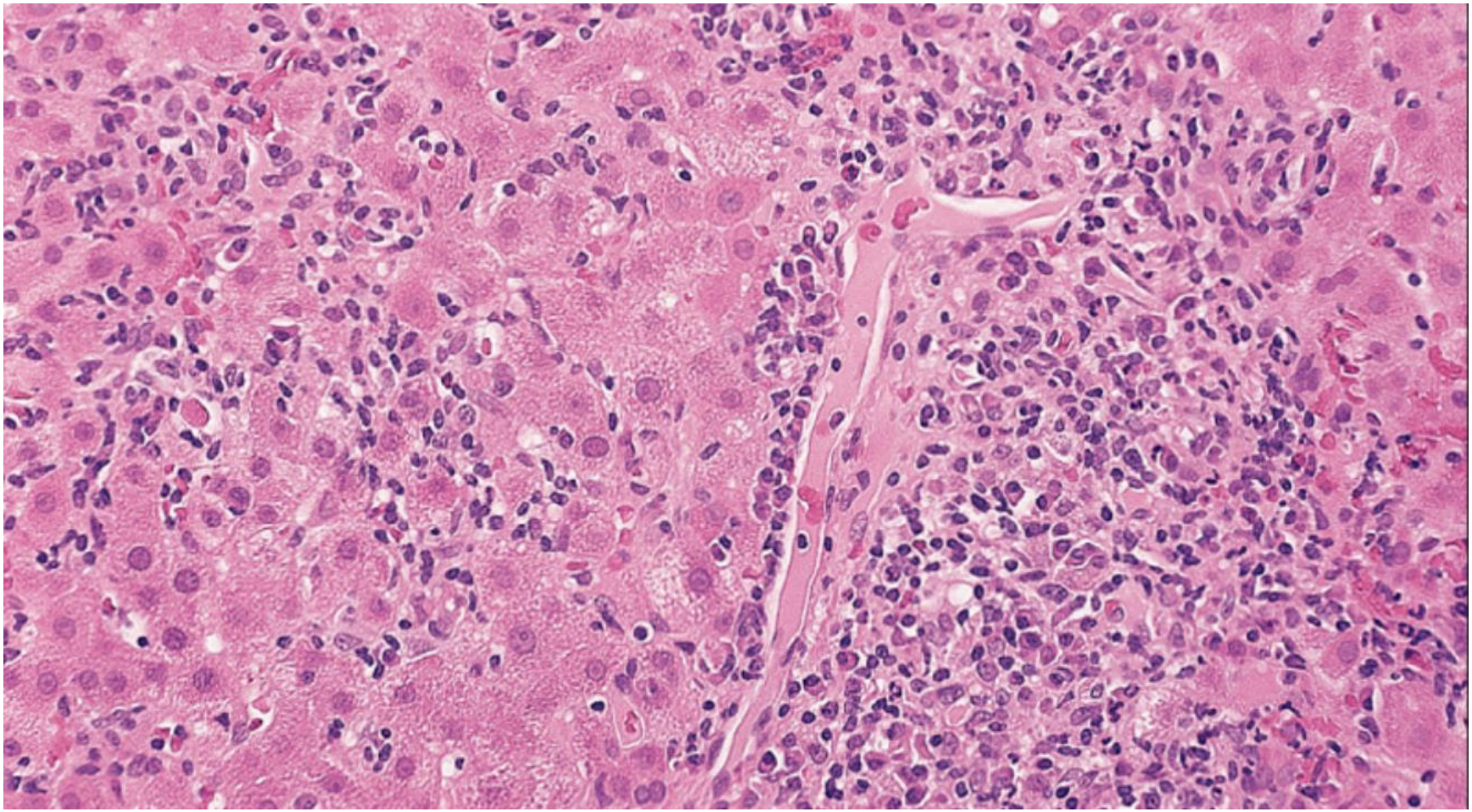
- Answer C

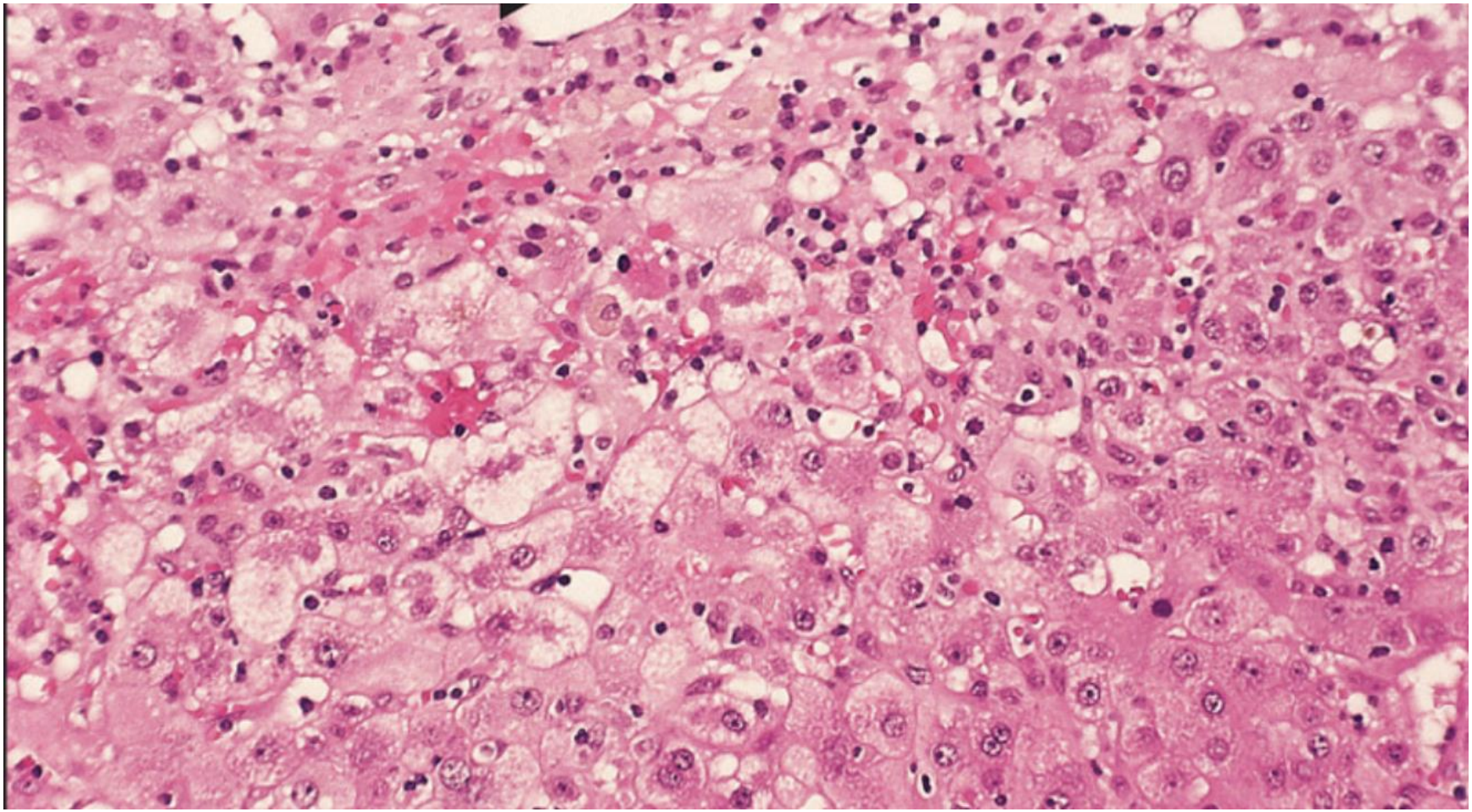
Case 1

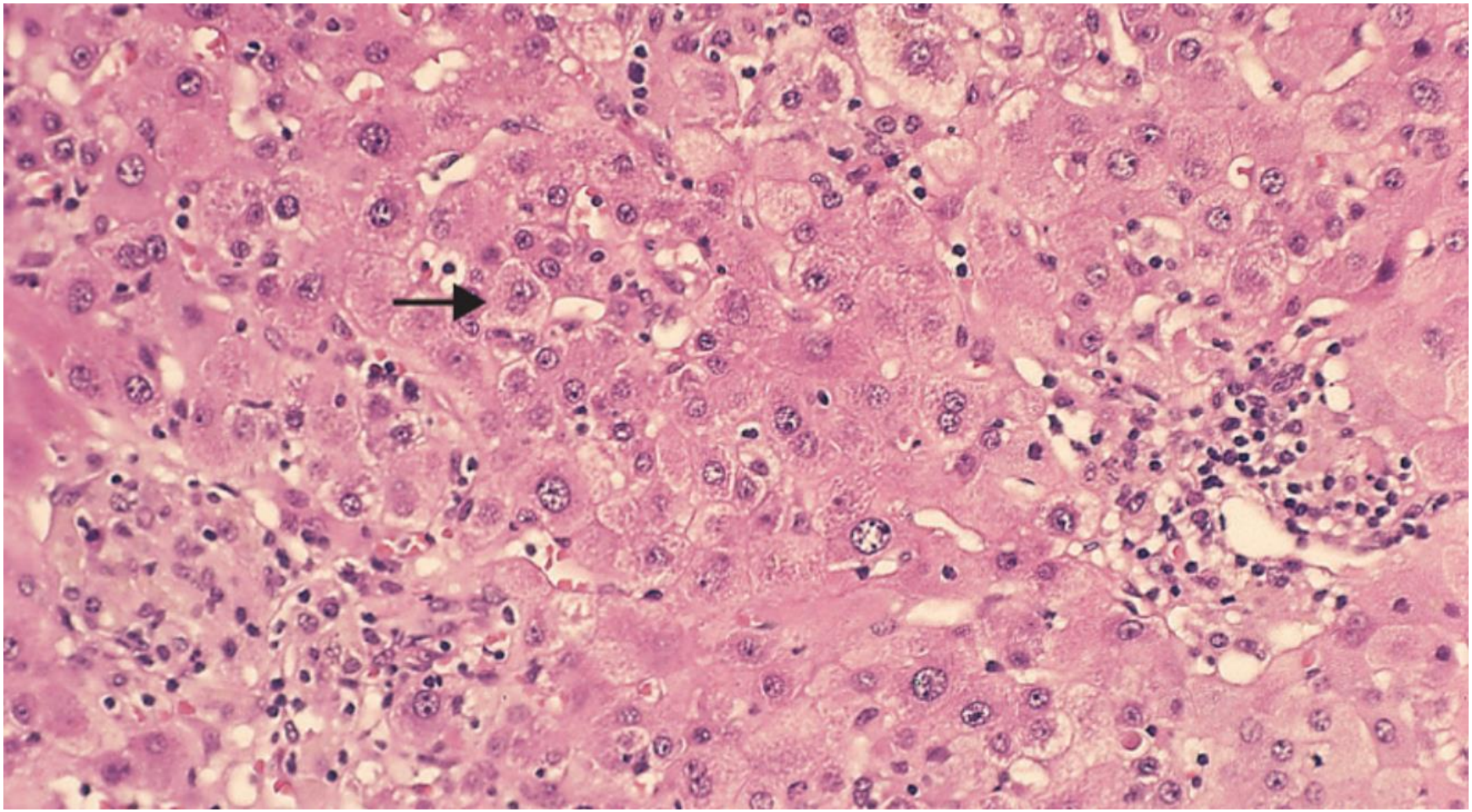
- She has a diagnostic procedure performed

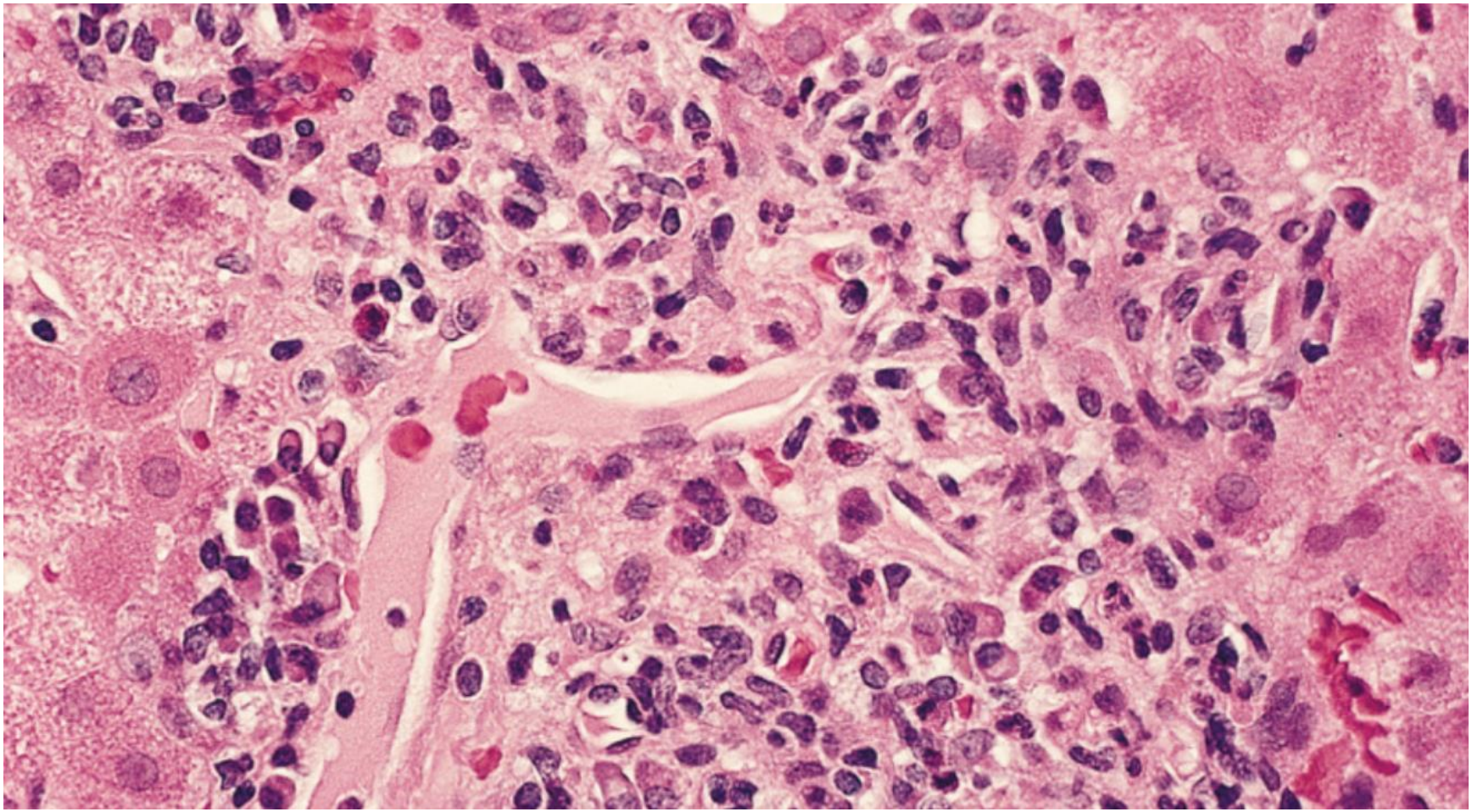
Liver biopsy











Liver biopsy report:

- Moderate portal inflammation, mostly lymphocytes, occasional plasma cells. Eosinophils present.
- Moderate interface hepatitis.
- Bridging necrosis.
- Bridging fibrosis, regenerating nodules.
- Ballooning hepatocytes, rosettes.
- Mild cholestasis.

AIH Simplified Scoring Criteria 2008

Hepatology 2008;48:169-176

Variable	Cutoff	Points
ANA or SMA	1:40	1
ANA or SMA	1:80	
or LKM	1:40	2
or SLA	Positive	
IgG	Upper normal limit	1
	>1.10 times normal limit	2
Liver histology[a]	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
Definite H: ≥7	Probable AIH: ≥6	

Our patient…

- ANA positive at 1:160 = 2 points
- IgG is 25.5 (>1.104ULN) = 2 point
- Histology is typical = 2 points
- No viral hepatitis = 0 points

Total is 6 points: Probable AIH

	Type 1	Type 2
Characteristic autoantibodies	Antinuclear antibody (20% of patients are negative for all conventional autoantibodies) Anti-smooth-muscle antibody Anti-actin antibody Anti-soluble-liver-antigen or anti-liver-pancreas-antigen antibodies	Anti-liver-kidney microsomal antibody type 1 (rarely detected in North America)* Anti-liver-cytosol antibody type 1 antibody Anti-liver-kidney microsomal antibody type 3
Geographical variation	Worldwide	Worldwide
Age at presentation	All ages	Usually childhood and young adulthood
Female-to-male ratio	4:1	10:1
Clinical phenotype	Variable	Generally severe
Histopathological features at presentation	Broad range: mild disease to cirrhosis	Generally advanced: inflammation and cirrhosis common
Treatment failure	Rare	Common
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	About 100%

*Although immunofluorescence is the most appropriate method to measure conventional autoantibodies in autoimmune hepatitis, many laboratories (especially those in the USA) are increasingly using ELISA-based methods to detect these antibody profiles. The profiles of anti-liver-kidney microsomal antibody type 1 can be erroneously reported as detectable antimitochondrial antibodies.[41]

Table 1: **Classification of autoimmune hepatitis on the basis of autoantibody profiles**

	Standard treatment	Alternative treatment*
Induction	Prednis(ol)one 40–60 mg/day (taper to 10 mg/day in 6–12 weeks); add azathioprine† when aspartate aminotransferase decreased to 2–3 times normal range Alternative 1: prednis(ol)one 20 mg/day; azathioprine† 1 mg/kg/day Alternative 2 (for patients without cirrhosis): budesonide 9 mg/day (taper over 6-18 weeks); azathioprine 1 mg/kg/day	Alternative 1: mycophenolate mofetil 1g twice a day; ciclosporin to achieve trough concentrations of the drugs of 150–250 ng/mL
Maintenance of remission	Increase azathioprine to 2 mg/kg per day; steroid withdrawal during 3 months Alternative: steroid monotherapy	Tacrolimus to achieve trough concentrations of the drugs of 6–10 ng/m
Cholestatic features	Addition of 12–15 mg/kg per day ursodeoxycholic acid in divided doses	Cyclophosphamide, methotrexate, sirolimus
Relapse	Prednis(ol)one 40–60 mg/day (slow taper to 15 mg/day); institute azathioprine when not previously used	..
Treatment failure of fulminant disease	Orthotopic liver transplantation	..

*When standard treatment fails or when there are contraindications to steroids (severe osteoporosis, psychosis, morbid obesity, and severe diabetes mellitus). †Check *TPMT* genotype: if homozygous, no azathioprine; if heterozygous, begin azathioprine at dose of 0·5 mg/kg/day and monitor white cell count every week.

Table 4: **Treatment options**

Course…

- Patient was started on ursodeoxycholic acid and prednisone.
- Symptoms improved
- LFTs improved
- Continued on ARVs.

LFT results

	15/1/14	9/4/14	14/5/14	28/5/14	11/6/14	9/7/14	6/8/14
T Bili	72	286		215	150	70	44
ALP	1198	1075	1013		571	413	400
GGT	3369	2371		1189	1322	1021	1281
ALT	249	447	266	171	192	106	119

What was the correct diagnosis?

- Autoimmune hepatitis on background of chronic HBV infection and past ETOH misuse?
- Role of DILI?
- Role or IRIS?

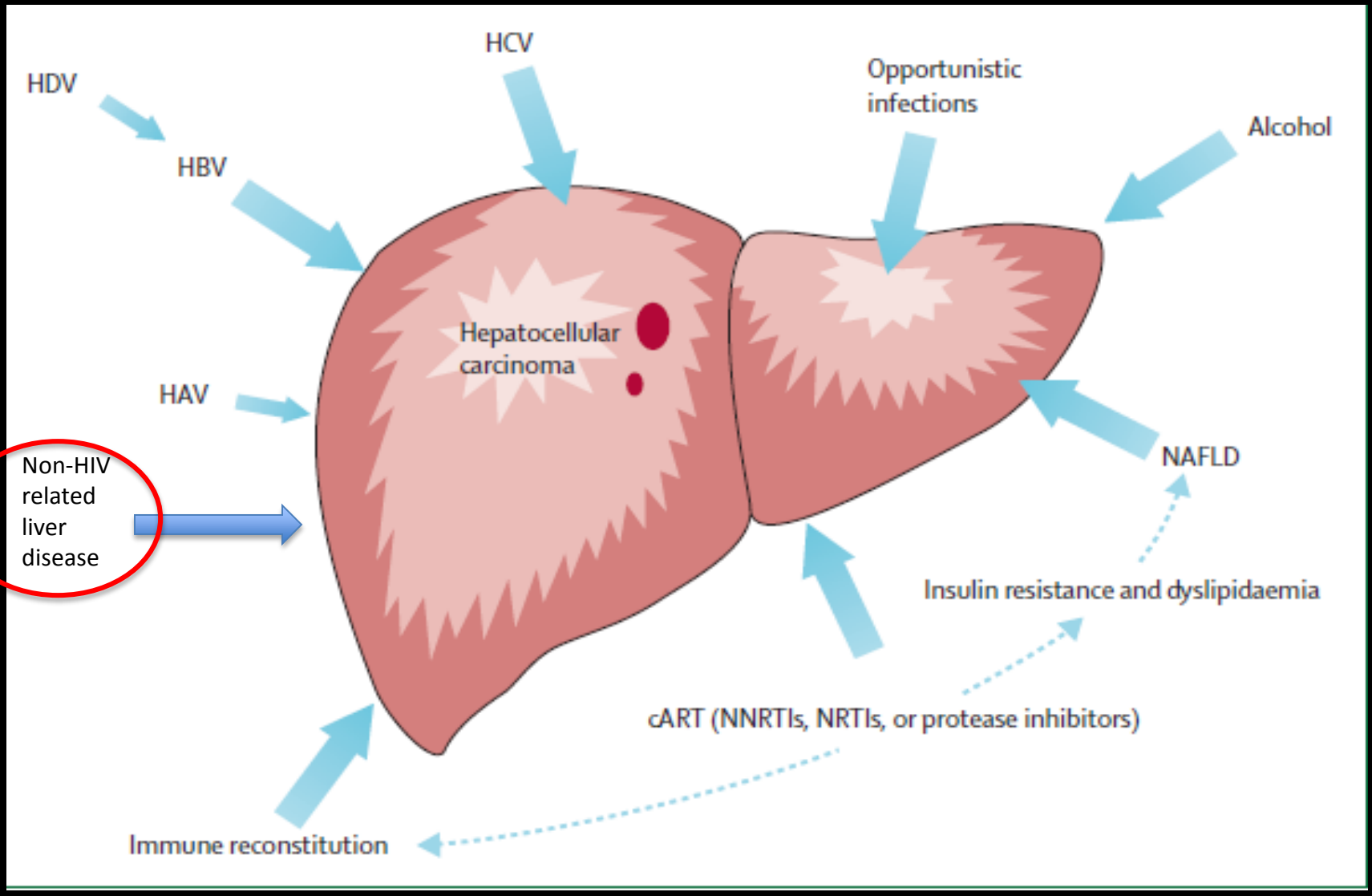
“What is the student but a lover courting a fickle mistress who ever eludes his grasp?”

William Osler

AIH from IRIS

- IRIS has been reported to have led to sarcoidosis, autoimmune thyroid disease and autoimmune arthritis.
- 44 YO F, CD4 269, started TDF, FTC, EFV. 5 months later (Sept 2005) CD4 526. Jan 2006 ALT 245. ANA + (1:160), ASMA +, IgG elevated. ARVs stopped.
- Bx: Hepatitis, bridging necrosis. Predominant lymphocytes. Also plasma cells and few eosinophils.
- Score: Definite AIH. Responded to prednisone.
- ARVs restarted without event.

De novo autoimmune hepatitis during Immune reconstitution. Clin Infect Dis 2008;46:e12-14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Non-HIV related liver disease
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Immune reconstitution

THM

- Differential can be broad in jaundiced patient
- Multidisciplinary input key
- Think about HBV (and HCV and HEV!)

Thank you

Acknowledgements

Dr Eric Murunga

Professor Christo van Rensburg

Dr Jantjie Taljaard