Dr Ed Wilkins

North Manchester General Hospital

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Ed Wilkins	Ed Wilkins has received lecture honoraria, speaker fees, and travel/registration reimbursement from Abbott, BMS, Gilead, Janssen, MSD, and ViiV
Date	**April 2013**

British HIV Association (BHIVA) Guideline Development Manual

- **BHIVA have received NHS accreditation for the process undertaken in Guideline development**

NHS Evidence
accredited provider
NHS Evidence - provided by NICE
www.evidence.nhs.uk

NHS Evidence has accredited the process used by the British HIV Association (BHIVA) to produce guidelines. Accreditation is valid for five years from July 2012 and is applicable to guidance produced using the processes described in the British HIV Association (BHIVA) Guideline Development Manual. More information on accreditation can be viewed at www.evidence.nhs.uk

Appendix 4

Summary of steps involved in producing a guideline

1. √	Title suggestion approved by the BHIVA Guidelines Subcommittee and agreed by the BHIVA Executive Committee.
2. √	Lead author/chair and co-chair identified by BHIVA Guidelines Subcommittee and writing group members nominated by lead author and co-chair. Initial conflict of interest declaration.
3. √	Initial meeting to identify questions, and to produce a scope, a search strategy and selection criteria. Allocation of sections/tasks to writing group members. Timeline and date of second meeting agreed.
4. √	Scope and questions approved by the writing group.
5. √	Data extraction: literature search performed by BHIVA Guidelines Co-ordinator (GC) and identified titles and abstracts forwarded to relevant section author.
6. √	Authors, with assistance of GC, systematically sift and discard those that are irrelevant and scrutinize remaining papers to assess if they meet selection criteria. GC to document the selection process.
7. √	Critical appraisal of the quality of remaining studies by members of writing group
8. √	Section authors write draft review, concise guideline and identify potential audit points and educational tools.
9. √	Second meeting to present a synthesis of data, review draft recommendations and establish consensus and implications for practice. GC will summarize recommendations.
10. √	Draft documents collated by authors and GC and finalised.
11. √	Review by BHIVA Guidelines Subcommittee using checklist (Appendix 8), comments fed back to authors and amendments made.
12.	Publication on BHIVA website for public consultation and sent for external peer review.
13.	Third meeting: consideration of consultation feedback and redrafting, if necessary, in light of received comments.
14.	Review of checklist (Appendix 8) by BHIVA Guidelines Subcommittee.
15	Redrafting in light of received comments if necessary.
16.	Review by BHIVA Guidelines Subcommittee.
17.	Review by BHIVA Executive Committee.
18.	Publication on BHIVA website/ *HIV Medicine* or other journal with final conflict of interest statement.
19.	Periodic review: lead authors contacted by guidelines group prior to expiry of guidelines. Literature search re-run by GC. If needed, updated guideline subjected to usual peer review process. If no update needed, renew web-based document with new expiry date.

Writing committee members

- Dola Awoyemi
- Ellie Barnes
- Sanjay Bhagani
- Gary Brook
- Sheen Castelino
- Graham Cooke
- Martin Fisher
- Anna-Maria Geretti
- **Robert James (UK-CAB)**
- Ranjababu Kulasegaram
- Clifford Leen
- David Mutimer
- **Mark Nelson (Vice Chair)**
- Chloe Orkin
- Padmasayee Papineni
- Emma Page
- Alison Roger
- William Tong
- Ed Wilkins (Chair)

Grade of recommendations: assessment, development and evaluation

- Quality of evidence:
  - Extent to which confidence in estimate of effect adequate to support decision
  - High (A), Moderate (B), Low (C), Very low (D)
- Strength of recommendation:
- Strong (1) or Conditional (2)
  - Quality of evidence
  - Balance of desirable/undesirable outcomes
  - Values and preferences
  - Resource use

Good practice points

- Recommendations based on the clinical judgment and experience of the working group.
- Emphasise important clinical practice for which there is no/ likely to be, any significant research evidence.
- It must be emphasised that GPPs are not an alternative to evidence-based recommendations

Scope

- Guidance on diagnostic and fibrosis screening
- Preventative measures including behaviour modification and immunisation
- ARV therapy and toxicity in co-infection
- Management of acute and chronic HBV and HCV
- Monitoring and management of co-infection related ESLD including transplantation
- Discussion on the role of HDV/HIV and HEV/HIV

Methodology

- Selected & open invite to join writing committee
- COI declared and GRADE training completion
- Scope, purpose and topics agreed
- Key questions drafted in a PICO framework
- Critical outcomes decided
- Systematic literature review undertaken
- GRADE system used throughout
- Guidelines and recommendations formulated

Priority questions and critical outcomes agreed

Chapter	Type of review	Review questions	Outcomes
3	Interventional	Should HCV screening be performed six or twelve monthly	- Missed HCV cases - Cost - Transmission rates
3	Diagnostic	Should the screening test be antibody, NAAT, or antigen	- Missed HCV cases - Cost - Transmission rates
3	Diagnostic	Is liver biopsy or hepatic elastometry the investigation of choice in screening for fibrosis	- Distinction of mild/normal vs. moderate/severe disease - Distinction of cirrhotics from non-cirrhotics - Adverse events - Cost - Patient satisfaction

Jason

- Jason 31 is a reformed (!?!) drug user
- Plans to go to Afghanistan in 2d for a fortnight on ‘peace brigade’ initiative
- Peripatetic lifestyle with fragmented care
  - Recent accommodation

Jason 2

- Taken many drugs but nothing legal

- Remembers being yellow once
  - Believes needle exchange is for sissies
- Vague recollection of hepatitis immunisation in HMP

Jason 2

- Told he had HIV and hepatitis C when screened in prison 2 years ago

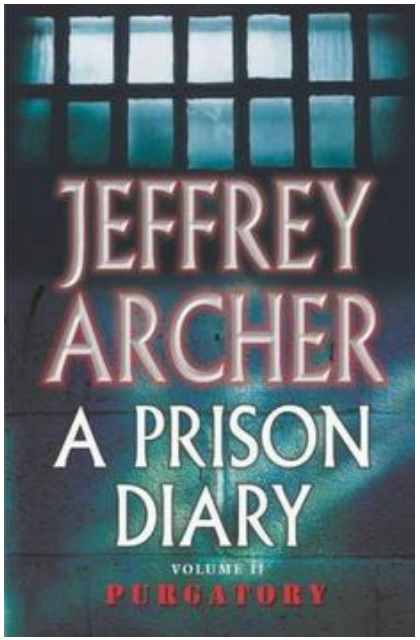
- Results from bloods checked at HMP prior to release:
  - CD4 146
  - Viral load 86,000
  - HBsAg –ve, anti-HBc –ve
  - Hepatitis B surface antibody <10 IU/l
  - Hepatitis C antibody +ve

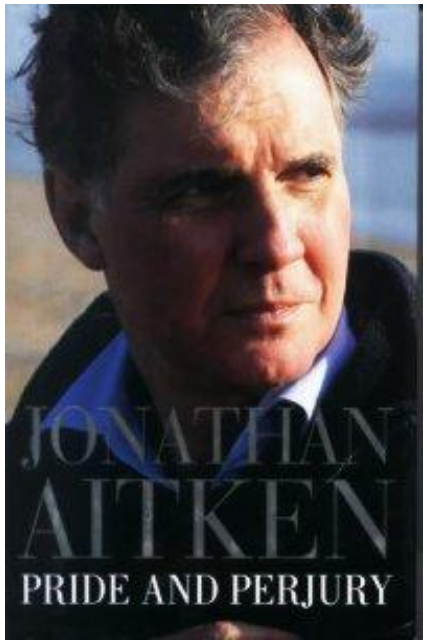
Jason 3

- You start him on Co-trimoxazole
- Check bloods:
  - HIV resistance, HLAB57
  - HCV-PCR, HCV genotype
  - You briefly discuss ARVs and anti-hepatitis treatment
  - You implore him of the need to be followed up in clinic
  - Suspicious this may be goodbye..

Jason 3

- Returns 1w later having found enlightenment in Hackney (not Afghanistan) and some good books





He says he is now a reformed man!

Jason 3

- Results from previous month:
  - Hepatitis B core antibody –ve (surface antigen –ve and surface antibody <10IU/l)
  - CD4 146, VL 86,000,
  - **Wild type HIV, HLAB57 +ve**
  - HCVAb +ve**, HCV-VL Log 6.2, genotype 1**
  - **ALT 64**
  - **Albumin, platelets, AST normal**

- Wants to know what next

What key additional investigation would you recommend?

- HCV GT1 subtype
- Adherence assessment
- *IL28B* genotype
- Fibrosis assessment
- Ultrasound scan
- Other…

Recommendations

- We suggest against routine IL28B testing when considering anti-HCV treatment in HCV/HIV coinfection(2C)
- We recommend staging of liver disease should be performed in those with chronic HCV/HIV and HBV/HIV infections (1B)

How would you assess fibrosis?

- Liver biopsy
- Non-invasive biochemical panel (e.g., APRI)
- Hepatic elastometry (FibroScan)
- Ultrasound scan
- MR scan
- Hepatic vein Doppler
- Child-Pugh score

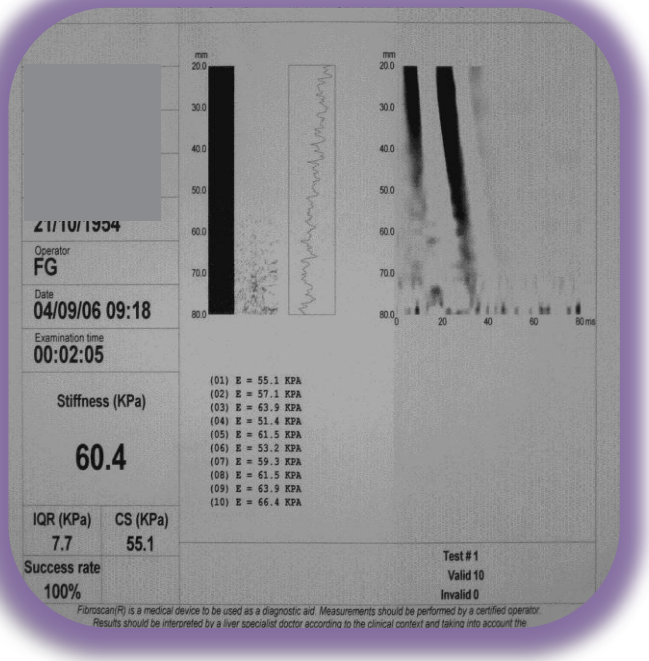
How best to assess fibrosis?

- We suggest in patients with chronic hepatitis/HIV infection a non-invasive test is the investigation of choice (2B).
- We suggest hepatic transient elastography (TE) (FibroScan™)as the non-invasive investigation of choice (2B)

How best to assess fibrosis?

- We recommend TE readings suggestive of cirrhosis (Metavir >F4) using recommended disease-specific cut-offs (>11.0kpA for HBV, >14.5kPA for HCV), should lead to appropriate monitoring for complications of portal hypertension and HCC screening (1B)
- We recommend when the aetiology of underlying liver disease is in doubt, liver biopsy remains the investigation of choice for assessment (GPP)

Transient elastography (Fibroscan®, Echosens, Paris)



Result Jason – TE 11.2kPa
= Significant fibrosis F3/F4

Jason

- Results from previous month:
  - CD4 146, VL 86,000, Wild type HIV, HLAB57 +ve
  - ALT 62
  - HCVAb +ve, HCV-VL Log 6.2, genotype 1
  - Albumin, platelets, AST normal

- KEEN FOR TREATMENT

HCV or HIV treatment first?
CD4 146 viral load 86,000

- Initiate ART and HCV therapy concurrently
- Initiate ART prior to HCV therapy
- Initiate HCV therapy prior to ART
- Initiate ART only
- Read the BHIVA guidelines (again)
- Phone for help

Recommendations

- We recommend commencing ART before HCV therapy is initiated when the CD4 count is less than 350 cells/µl **(GPP)**
- We recommend commencing HAART before HCV therapy is initiated when the CD4 count is 350-500 cells/µl unless there is an urgent indication for anti-HCV treatment when ART should be commenced once stabilised on HCV therapy **(GPP)**

Jason – nine months on

- Starts DAR/r/TDF/FTC
- HIV well controlled:
  - CD4 507, VL <40 c/ml
- HCV recap:
  - GT1a, HCV-VL Log 6.2
  - TE 11.2kPa
  - HBsAg –ve, anti-HBc –ve
  - Anti-HBs <10IU/l
- Up for treatment

How would you manage his HCV?

- Start PEG-IF/RBV and plan for 48w
- Start triple therapy with PEG-IF/RBV and telaprevir and plan for 48w
- Start triple therapy with PEG-IF/RBV and after 4w lead-in boceprevir and plan for 48w
- Advise defer until newer therapies
- Start triple therapy with PEG-IF/RBV and after 4w lead-in telaprevir and plan for 48w

How would you manage his HCV?

- We recommend where there is a current clinical need for treatment or if the patient wishes to be treated, the standard of care should be with triple therapy consisting of pegylated interferon, ribavirin, and either telaprevir or boceprevir **(1C)**
- We recommend for patients with GT 1 infection and non-cirrhotic disease, treatment should be either within a clinical trial or deferred until newer therapies become available **(GPP).**

How would you manage his HCV?

- We recommend the duration of treatment should be guided by virological response and severity of liver disease (1B)
- We recommend a lead in of 4w treatment with PEG-IF/RBV only be considered for all patients commencing therapy with a boceprevir or telaprevir based regimen where the results in HCV decline at 4w will influence whether the DAA will be added (GPP)

Switch or stay on current ART?

- Stay on DAR/r
- Switch to ATAZ/r
- Switch to EFV and increasing TPV dose
- Switch to RAL
- Switch to etravirine

Recommendations

- We recommend when DAA's are to be used there is careful consideration of possible DDIs (1C) and current or archived HIV resistance
- We recommend if boceprevir is to be used, raltegravir (RAL) with TDF/FTC should be the treatment of choice for those with wild-type HIV (1C)
- We recommend if telaprevir is to be used either RAL or standard dose ritonavir-boosted atazanavir should be used: efavirenz may be used but the telaprevir dose then needs to be increased to 1125mg tds (1C).

Jason

- Specialist adherence nurse has concerns over adherence

Jason

- Specialist adherence nurse has concerns over adherence
- Starts PEG-IF, ribavirin and telaprevir
- HCV PCR –ve at 12 and 24w post treatment completion

Jason

- Now has close links with business enterprises in Afghanistan
- He has a better car than you

Jason

- But still has anti-HBs <10 IU/l
  - Thinks he has been immunised
- Still injecting
- Still sharing

- What would you advise for his HBV

Regarding hepatitis B, what would you do? HBsAb <10IU/l

- Assume previous hepatitis B immunisation and give booster standard dose
- Assume previous hepatitis B immunisation and give booster 40μg dose
- Give full course of HBV immunisation standard dose at 0, 1, and 6 months
- Give full course of HBV immunisation 40μg dose at 0, 1, and 6 months
- Give full course of HBV immunisation 40μg dose at 0, 1, 2, and 6 months

How best to HB immunise?

- We recommend the 40µg strength of HBV vaccine should be used in HIV-infected patients **(1A)** and given at months 0, 1, 2 and 6 **(1B)**
- We recommend a booster dose of 40µg vaccine should be offered to those whose anti-HBs levels have declined to <10 IU/l **(1C)**

Also remains at risk for HCV

Which test & how often?

- 3-6 monthly HCV antibody
- Annual HCV-PCR with additional test for HCV-PCR if ALT increases
- 3-6 monthly HCV-PCR
- Annual HCV antibody with additional test for HCV-PCR if ALT increases
- Something totally different!

Recommendations

- We recommend those that have been successfully treated for HCV or who have spontaneously cleared infection and are HCVAb +ve, the diagnostic test should to be **HCV-PCR (1C)**
- We recommend patients who have repeated high-risk exposures but persistently normal transaminases are screened with HCV Ab and HCV-PCR at **3-6 monthly intervals** or HCV-PCR alone if previously successfully treated or spontaneously cleared infection **(GPP)**

Progress 4

- CD4 increases to 507, VL undetectable for >9m
- Has booster 40µg hepatitis B vaccine
- Returns home

Jason

- Whoops, but no anti-HBs levels post-booster
  - Back into prison
  - Stops ART in protest
  - Becomes mildly jaundiced as inmate 12m before review
  - ALT, HBsAg +ve, anti-HBeAg –ve, anti-HBeAb +ve
  - HBV DNA Log 7.4
  - HCV RNA –ve
  - ALT 64

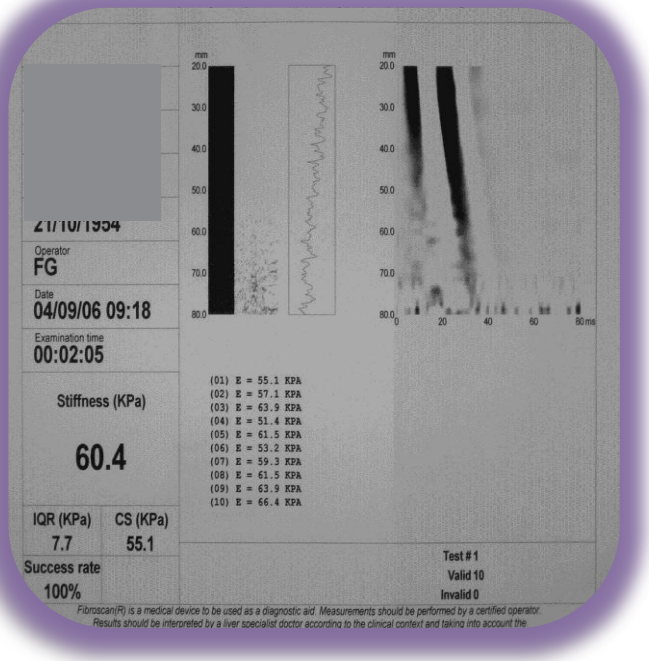
What additional tests are indicated?

- HBV resistance
- HBV genotype
- Ultrasound scan
- Assessment of fibrosis
- AFP

What additional tests are indicated?

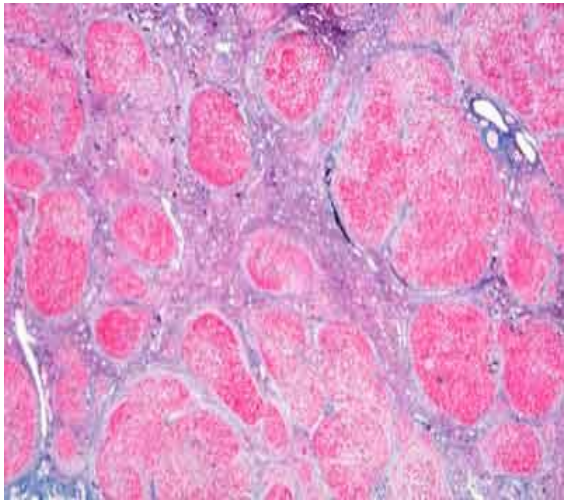
- We recommend against HBV resistance testing at baseline in those previously unexposed to antivirals **(1C)**
- We suggest testing for HBV genotype should be considered prior to a decision to initiate PEG-IF treatment **(2C)**
- We recommend staging of liver disease should be performed in those with chronic HBV/HIV infection **(1B)**

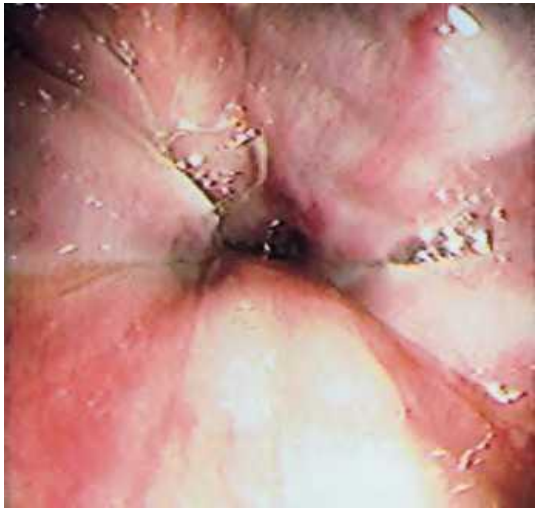
Transient elastography (Fibroscan®, Echosens, Paris)

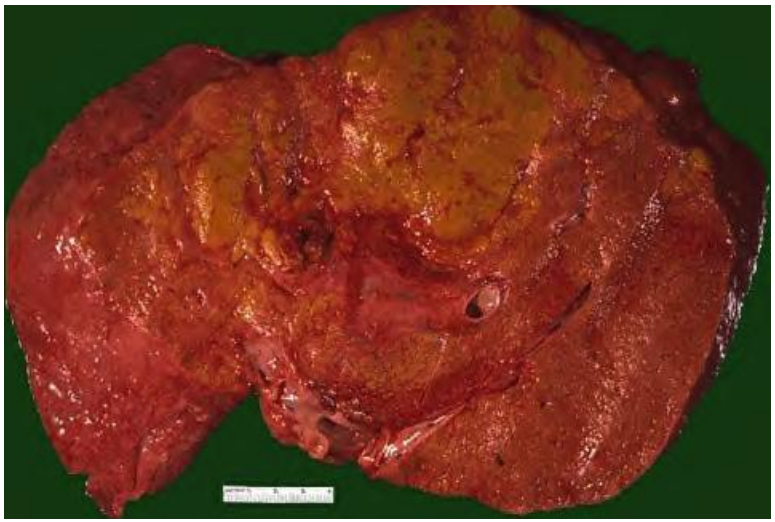


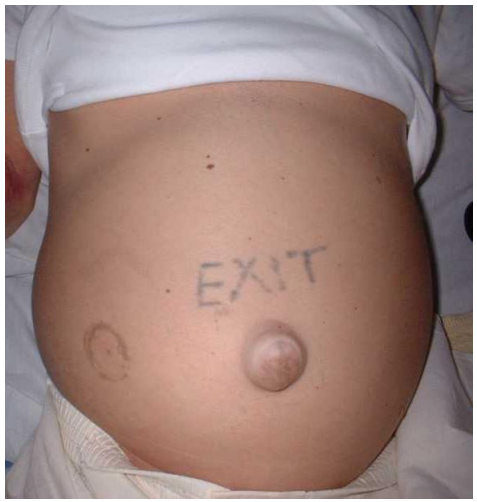
Result Jason – TE 17.2kPa

Increased Risk and more rapid cirrhosis and liver cancer









What screening for HCC would you initiate?

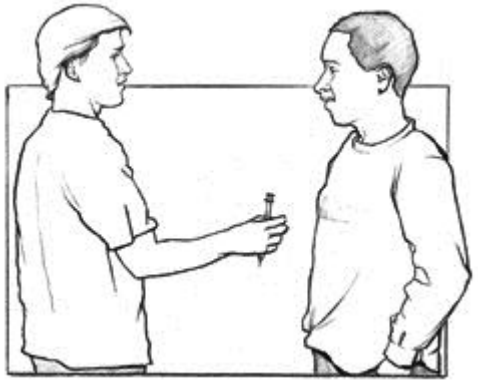
- USS yearly
- USS six monthly
- AFP yearly
- AFP six monthly
- USS yearly and AFP six monthly
- Await symptoms/signs

Recommendations

- We recommend HCC screening with 6 monthly ultrasound **(1A)** and serum alpha-fetoprotein (AFP) **(2C)** should be offered to all cirrhotic patients with HBV/HIV and HCV/HIV coinfection
- We suggest all non-cirrhotic patients with HBV/HIV co-infection should be screened for HCC **(GPP)**

What anti –HBV treatment would you start?

- HIV
  - CD4 507, VL 82000, WT virus
- HBV
  - HBV ALT, HBsAg +ve, anti-HBeAg –ve, anti-HBeAb +ve
  - ALT 64
- HCV-PCR –ve
- HDV antibody -ve

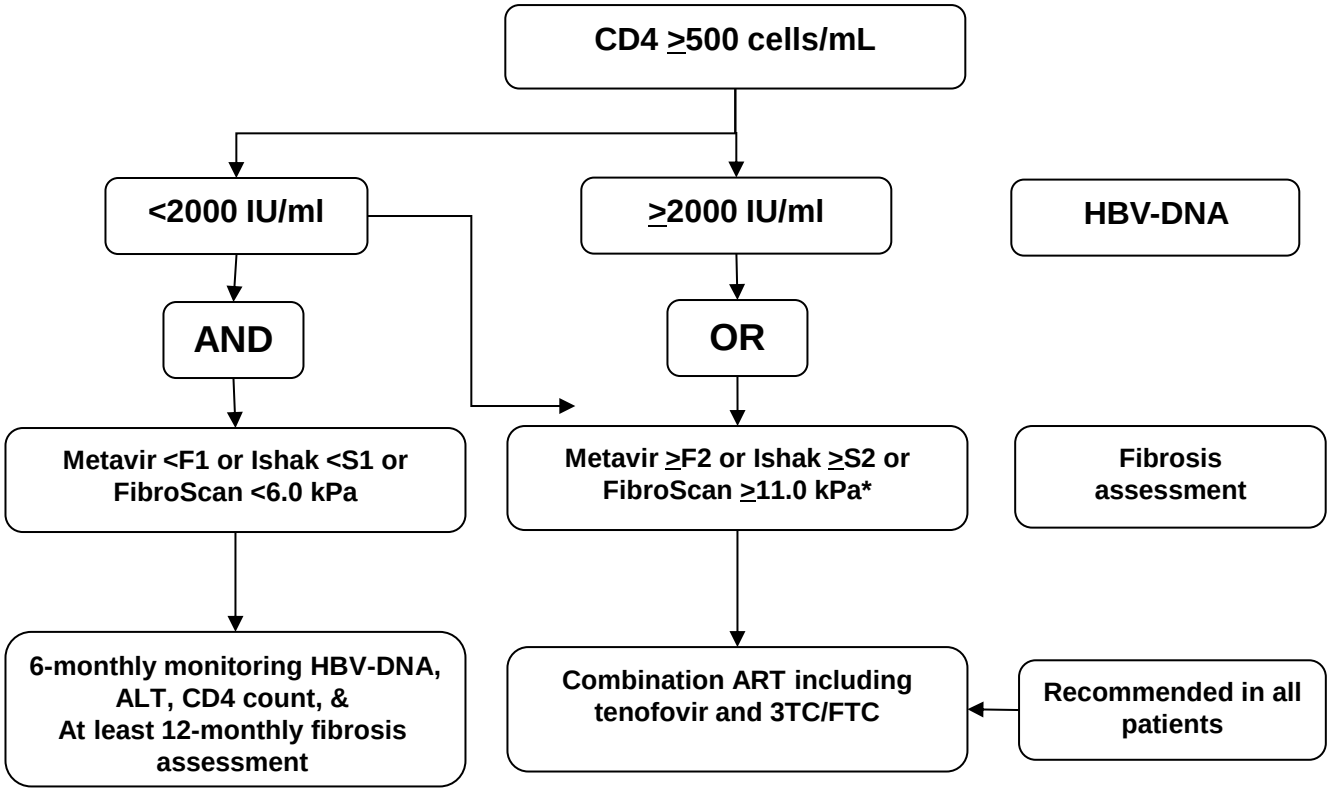


What anti-HBV treatment would you start?

- Entecavir monotherapy
- PEG-IF
- Adefovir
- Restart TDF/FTC containing ART
- Defer therapy as CD4 >500

What ART treatment would you start?

- We recommend all those with an HBV DNA ≥2000 IU/mL should be treated **(1C)**
- We recommend all those with more than minimal fibrosis (Metavir ≥F2 or Ishak ≥S2 or FibroScan ≥7.2kPa) should be treated **(1C)**



* Recommend liver biopsy recommended if FibroScan 6kPa - <11kPa

What ART/HBV treatment would you start?

- ATAZ/r/TDF/FTC
- ATAZ/r/TDF/ZDV
- ATAZ/r/RAL/FTC
- RPV/TDF/FTC
- EFV/ABC/3TC

What ART/HBV treatment would you start?

- We recommend TDF/FTC as part of a fully suppressive combination HAART regimen be used in those with confirmed or presumed sensitive HBV **(1B)**
- We recommend where tenofovir is not currently being given as a component of HAART it should be added or substituted for another agent **(1C)**
- We recommend 3TC and FTC should not be used as the sole active drug against HBV in HAART due to the rapid emergence of HBV resistant to these agents **(1B)**

Jason

- HBV
  - DNA falls over 9m to <10IU/l
  - Remains HBsAg +ve
  - OGD, no varices
  - USS cirrhosis, portal hypertension but mild splenomegaly (15cms)
- HCV-RNA -ve
- Under joint ID/hepatology care
- Regular HCC screening

Scope

- Guidance on diagnostic and fibrosis screening
- Preventative measures including behaviour modification and immunisation
- ARV therapy and toxicity in co-infection
- Management of acute and chronic HBV and HCV
- Monitoring and management of co-infection related ESLD including transplantation
- Discussion on the role of HDV/HIV and HEV/HIV

British HIV Association

BHIVA

19th Annual Conference of the British HIV Association (BHIVA)

16–19 April 2013

Manchester Central Convention Complex