Dr Ed Wilkins
North Manchester General Hospital

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ed Wilkins</td>
<td>Dr Wilkins has received educational grants and unrestricted travel support from Gilead, BMS, BI, MSD, Janssen, J&amp;J</td>
</tr>
<tr>
<td>Date</td>
<td>November 2013</td>
</tr>
</tbody>
</table>
Guidelines needed updating....

British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010

G Brook, J Main, M Nelson, S Bhagani, E Wilkins, C Leen, M Fisher, Y Gilleece, R Gilson, A Freedman, R Kulasegaram, K Agarwal, C Sabin and C Deacon-Adams on behalf of the BHIVA Viral Hepatitis Working Group*

British HIV Association (BHIVA), BHIVA Secretariat, Mediscript Ltd, London, UK

Keywords: HIV, hepatitis B, hepatitis C, guidelines, treatment

Accepted 27 August 2009

- Full rewrite decided
- Along NICE framework
- Establish platform to regularly update from
Decided scope – best clinical practice

• Diagnostic and fibrosis screening
• Preventative measures
• ARV therapy and toxicity
• Management of chronic (and acute) HBV and HCV
• Monitoring and management of co-infection related ESLD
• Discussion of HDV/HIV and HEV/HIV
Agreed focussed and answerable questions
Used PICO framework

<table>
<thead>
<tr>
<th>PICO</th>
<th>Example Key Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>HIV/hepatitis virus co-infected</td>
</tr>
<tr>
<td>Investigation</td>
<td>Fibrosis screening with TE</td>
</tr>
<tr>
<td>Comparator</td>
<td>Liver biopsy</td>
</tr>
<tr>
<td>Outcome</td>
<td>Fibrosis detection</td>
</tr>
</tbody>
</table>

11 key questions identified
Best evidence tracked down using defined search criteria

Medical Articles Per Year

- Biomedical
- MEDLINE
- Trials
- Diagnostic?
Evidence critically and statistically appraised
Peer-reviewed recognised not to equate to good quality
Agreed recommendations and GRADE

• Quality of evidence:
  – Extent to which confidence in estimate of effect adequate to support decision
  – High (A), Moderate (B), Low (C), Very low (D)

• Allow for Good Practice
  – GPP

• Then apply strength of recommendation
  – Strong Unanimous (1) or Weaker Consensus (2)
Individual ‘presentation skills’ at the Writing committee meetings ignored.
Because any of these ≠ wisdom ≠ improved knowledge
Other guidelines were consulted but no more!!

They may have got it wrong
Today

Assessing level of fibrosis

Management
For today, Guidelines compared with..
HCV
Patient

• Borek, 34yr old ex-IDU from Eastern Europe
• Prison screening test anti-HCV +ve and HIV antibody +ve

<table>
<thead>
<tr>
<th>HCV results</th>
<th>HIV results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT1a</td>
<td>VL 47,000</td>
</tr>
<tr>
<td>VL 680,000</td>
<td>WT virus</td>
</tr>
<tr>
<td>HAV/HBV immune</td>
<td>CD4 401</td>
</tr>
<tr>
<td>ALT 54</td>
<td></td>
</tr>
</tbody>
</table>
Fibrosis staging recommended in all patients (1B)/Non-invasive test suggested first (2B)
Assessing level of fibrosis

Newly diagnosed chronic HBV/HIV or HCV/HIV

Perform TE
(Biochemical panel if TE unavailable)

F0/F1
HCV <7.2

?F2/F3
If decision on treatment to be made

F4
HCV >14.5

Perform 2nd test (TE or biochemical panel or liver biopsy)

- if non-concordance between TE and panel perform LB

If decision on treatment to be made
Assessing level of fibrosis

Newly diagnosed chronic HBV/HIV or HCV/HIV

Perform TE (Biochemical panel if TE unavailable)

- F0/F1
  - HCV < 7.2

- ?F2/F3
  - If decision on treatment to be made

- F4
  - HCV > 14.5

F2 or F3
Management Borek

F0/F1
- Naive
- Deferral/Triple therapy/Offer trial

F2
- Deferral/Triple therapy/Offer trial

F3
- Deferral/Triple therapy/Offer trial
- Liver biopsy – F3

F4
- Triple therapy
- TE 15.2kPa

Indicative – F0/1
- TE 6.2kPa
GT1 naive recommendations

• We recommend where there is a current clinical need for treatment (F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with PEG-IFN/RBV, and either telaprevir or boceprevir (1C).
GT1 naive recommendations

• We suggest for patients with non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with TE or alternative non-invasive testing at least annually. Where there is confirmed progression of fibrosis, treatment initiation should be reconsidered.
## HCV GT1: guidelines comparison – naïve?

EACS Guidelines 2013; French Guidelines 2013 - accessed on line

<table>
<thead>
<tr>
<th>F0/F1</th>
<th>BHIVA</th>
<th>EACS</th>
<th>French</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defer/Triple therapy/Offer trial</td>
<td>Individual decision</td>
<td>Defer</td>
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<table>
<thead>
<tr>
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<th>BHIVA</th>
<th>EACS</th>
<th>French</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defer/Triple therapy/Offer trial</td>
<td>Triple therapy</td>
<td>PEG-RBV*/Triple therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F3</th>
<th>BHIVA</th>
<th>EACS</th>
<th>French</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defer/Triple therapy/Offer trial</td>
<td>Triple therapy</td>
<td>Triple therapy</td>
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</table>

<table>
<thead>
<tr>
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<th>BHIVA</th>
<th>EACS</th>
<th>French</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple therapy</td>
<td>Triple therapy</td>
<td>Triple therapy</td>
<td></td>
</tr>
</tbody>
</table>
Management Borek

- **F0/F1**
  - Non-responder
  - Defefer/Triple therapy/ Offer trial

- **F2**
  - Defefer/Triple therapy/ Offer trial

- **F3**
  - Liver biopsy – F3
  - Defer/Triple therapy/ Offer trial

- **F4**
  - Triple therapy
  - TE 15.2kPa
  - Indicative – F4

- **TE 6.2kPa**
  - Indicative – F0/1
GT1 non-responder recommendations

• We suggest non-cirrhotic patients who were previously null responders, partial responders or who experienced breakthrough should, wherever possible, wait for the availability of interferon-sparing regimens or interferon-based regimens including at least two new agents.
HCV GT1: guidelines comparison – non-responder?

<table>
<thead>
<tr>
<th></th>
<th>BHIVA</th>
<th>EACS</th>
<th>French</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>F0/F1</strong></td>
<td>Defer/Triple therapy/Offer trial</td>
<td>Defer</td>
<td>Defer</td>
</tr>
<tr>
<td><strong>F2</strong></td>
<td>Defer/Triple therapy/Offer trial</td>
<td>Defer</td>
<td>Triple therapy/Offer trial</td>
</tr>
<tr>
<td><strong>F3</strong></td>
<td>Defer/Triple therapy/Offer trial</td>
<td>Defer</td>
<td>Triple therapy/Offer trial</td>
</tr>
<tr>
<td><strong>F4</strong></td>
<td>Triple therapy</td>
<td>Triple therapy on case-by-case basis</td>
<td>Triple therapy/Offer trial</td>
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</tbody>
</table>
Factors influencing recommendations on HCV treatment

• Likelihood of SVR with current treatment
SVR12 with TVR or BOC + PEG-IF/RBV vs. PEG-IF/RBV alone in HIV/HCV infection

Primary endpoint = Sustained Virological Response (SVR) at 12 weeks; interim analysis presented; TVR = telaprevir

*Pegylated interferon-α-2a; **Pegylated interferon-α-2b.

Virological response in cirrhotic non-responders

**Telaprevir**

- W4: 60% (12/20)
- W12: 67% (10/15)
- W24: 60% (6/10)

**Boceprevir**

- W4: 50% (0/4)
- W12: 50% (2/4)
- W24: 50% (2/4)

IAS Kuala Lumpur 2013
Factors influencing recommendations on HCV treatment

- Likelihood of SVR with current treatment
- Risk of significant progression/≥F4 without current treatment
**Risk of significant progression/≥F4 without current treatment**

Risk of liver decompensation among HIV/HCV co-infected individuals with advanced fibrosis: implications for the timing of therapy

<table>
<thead>
<tr>
<th>Period</th>
<th>No. Entering Each Period</th>
<th>No. of Liver Decompensations</th>
<th>Probability of Remaining Free of Decompensation (95% CI)</th>
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<tbody>
<tr>
<td><strong>F3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>149</td>
<td>1</td>
<td>99% (95%–100%)</td>
</tr>
<tr>
<td>3 y</td>
<td>128</td>
<td>1</td>
<td>98% (94%–100%)</td>
</tr>
<tr>
<td>5 y</td>
<td>112</td>
<td>3</td>
<td>95% (89%–98%)</td>
</tr>
<tr>
<td>&gt;5 y</td>
<td>81</td>
<td>7</td>
<td>80% (67%–89%)</td>
</tr>
<tr>
<td><strong>F4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>168</td>
<td>3</td>
<td>96% (91%–98%)</td>
</tr>
<tr>
<td>3 y</td>
<td>150</td>
<td>8</td>
<td>87% (81%–92%)</td>
</tr>
<tr>
<td>5 y</td>
<td>116</td>
<td>8</td>
<td>77% (69%–83%)</td>
</tr>
<tr>
<td>&gt;5 y</td>
<td>77</td>
<td>9</td>
<td>56% (44%–67%)</td>
</tr>
<tr>
<td><strong>Fibrosis staged by biopsy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.5 kPa–14.5 kPa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>275</td>
<td>3</td>
<td>99% (96%–100%)</td>
</tr>
<tr>
<td>3 y</td>
<td>194</td>
<td>2</td>
<td>97% (94%–99%)</td>
</tr>
<tr>
<td>5 y</td>
<td>94</td>
<td>1</td>
<td>96% (90%–98%)</td>
</tr>
<tr>
<td>&gt;5 y</td>
<td>34</td>
<td>0</td>
<td>96% (90%–98%)</td>
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<tr>
<td>≥14.6 kPa</td>
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<td></td>
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<tr>
<td>1 y</td>
<td>300</td>
<td>18</td>
<td>93% (89%–96%)</td>
</tr>
<tr>
<td>3 y</td>
<td>209</td>
<td>19</td>
<td>83% (77%–87%)</td>
</tr>
<tr>
<td>5 y</td>
<td>104</td>
<td>8</td>
<td>73% (64%–80%)</td>
</tr>
<tr>
<td>&gt;5 y</td>
<td>27</td>
<td>2</td>
<td>63% (47%–76%)</td>
</tr>
</tbody>
</table>

Macias J. Clinical Infectious Diseases 2013;57(10):1401–8
Factors influencing recommendations on HCV treatment

- Likelihood of SVR with current treatment
- Risk of significant progression/≥F4 without current treatment
- Licensing date and likely availability of DAA(s) with benefits (SVR rate/AE/adherence etc.)
Licensing date and likely availability of DAA(s) with benefits

<table>
<thead>
<tr>
<th>1st wave PEG/RIB - based</th>
<th>2nd wave PEG/RIB - based</th>
<th>1st wave PEG/RIB - free</th>
<th>2nd wave PEG/RIB - free</th>
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<tbody>
<tr>
<td>Boceprevir</td>
<td>Simeprevir</td>
<td>3 DAA</td>
<td>Abbvie</td>
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<tr>
<td>Telaprevir</td>
<td>Sofosbuvir</td>
<td>SOF/LDV</td>
<td>Gilead</td>
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<tr>
<td></td>
<td>Faldaprevir</td>
<td>FDV + DBV</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCV + ASV</td>
<td>Bristol-Myers Squibb Co.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MSD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Janssen</td>
</tr>
</tbody>
</table>

- 2011: Boceprevir
- 2012: Telaprevir
- 2013: 
- 2014: Simeprevir, Sofosbuvir, Faldaprevir
- 2015: 3 DAA, SOF/LDV, FDV + DBV
- 2016: 4 DAA, DCV + ASV
Faldaprevir in GT1: STARTVerso 4 - Overall SVR 4 in naïve patients and relapsers

Results for total population

- **Treatment-naive**: 71% (169/239)
- **Relapsers**: 87% (60/69)

Denominator = patients with ETS

Rockstroh JK et al. AASLD 2013 WASHINGTON DC POSTER NO 1099

Simeprevir in GT 1: Phase III C212 study in HIV co-infected patients (N = 106)

• 87% of treatment naïve (88%, n=41) and relapser (85%, n=13) patients met the criteria for 24 week RGT

• On HAART (93/106): 99% on NRTI, 87% on raltegravir, 15% on rilpivirine (efavirenz excluded)

Sofosbuvir in GT1: SVR 12 non-cirrhotic (n = 23)

- 23 non-cirrhotic, HIV co-infected patients with HCV GT-1-4, naïve to HCV treatment
- SOF 400 mg QD + PegIFN/RBV for 12 weeks

**SVR12 by HCV GT**

- GT1: 89% (17/19)
- GT1a: 87% (13/15)
- GT1b: 100% (4/4)
- GT2: 100% (1/1)
- GT3: 100% (2/2)
- GT4: 100% (1/1)

**SVR12 by ARV Regimen**

- Protease inhibitor: 93% (13/14)
- NNRTI: 91% (10/11)
- Raltegravir: 100% (7/7)

NNRTI, non-nucleoside reverse transcriptase inhibitor

Maribel Rodriguez-Torres et al.  IDWeek 2013, October 2-6, 2013, San Francisco, CA
Factors influencing recommendations on HCV treatment

- Likelihood of SVR with current treatment
- Risk of significant progression/≥F4 without current treatment
- Licensing date and likely availability of DAA(s) with benefits (SVR rate/AE/adherence etc.)
- Accuracy of monitoring for worsening fibrosis
Accuracy of monitoring for worsening fibrosis
So for discussion in naives and PEG-IFN/RBV experienced..

• Can we accept current triple therapy and level of SVR in naives with F3?
• Is the risk of decompensation too high/too unpredictable with F3 to wait?
• Does the reduction in SVR with new DAAs if progression to F4 occurs argue to treat now?
• Are we being too optimistic about DAA availability and what restrictions are likely to apply?
• Is monitoring progression to F4 with TE accurate/safe?
Patient

- Borek, 34yr old ex-IDU from Eastern Europe
- Prison screening test anti-HCV +ve and HIV antibody +ve

<table>
<thead>
<tr>
<th>HCV results</th>
<th>HIV results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT3</td>
<td>VL 47,000</td>
</tr>
<tr>
<td>VL 680,000</td>
<td>WT virus</td>
</tr>
<tr>
<td>HAV/HBV immune</td>
<td>CD4 401</td>
</tr>
<tr>
<td>ALT 54</td>
<td></td>
</tr>
</tbody>
</table>
Management Borek

- **Naive**
  - **F0/F1**
    - Defer/PEG-RBV/Offer trial
  - **F2**
    - Defer/PEG-RBV/Offer trial
  - **F3**
    - Defer/PEG-RBV/Offer trial
  - **F4**
    - PEG-RBV

- **TE 6.2kPa**
  - Indicative – F0/1

- **TE 11.2kPa**
  - Liver biopsy – F3

- **TE 15.2kPa**
  - Indicative – F4
Management HCV/HIV GT 1: 13/08/13

- **F0/F1**
  - TE 6.2kPa
  - Indicative – F0/1
  - Offer trial

- **F2**
  - TE 11.2kPa
  - Liver biopsy – F3
  - Offer trial

- **F3**
  - TE 15.2kPa
  - Indicative – F4
  - Offer trial

- **F4**
  - Non-responder
  - Defer/PEG-RBV*/Offer trial
GT2/3 non-responder recommendations

• We recommend where there is a current clinical need for treatment (F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with PEG-IFN/RBV (1C).

• We suggest for patients with non-cirrhotic disease there is the option to defer treatment until newer therapies or a suitable trial become available.
### HCV GT 2/3: guidelines comparison – naïve?

<table>
<thead>
<tr>
<th>Grade</th>
<th>BHIVA</th>
<th>EACS</th>
<th>French</th>
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<tbody>
<tr>
<td>F0/F1</td>
<td>Defer/PEG-RBV/Offer trial</td>
<td>PEG-RBV</td>
<td>PEG-RBV</td>
</tr>
<tr>
<td>F2</td>
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<td>PEG-RBV</td>
<td>PEG-RBV</td>
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<tr>
<td>F3</td>
<td>Defer/PEG-RBV/Offer trial</td>
<td>PEG-RBV</td>
<td>PEG-RBV</td>
</tr>
<tr>
<td>F4</td>
<td>PEG-RBV</td>
<td>PEG-RBV</td>
<td>PEG-RBV</td>
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HCV GT 2/3: guidelines comparison – non-responders?

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</tr>
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<tbody>
<tr>
<td>F0/F1</td>
<td>Defer/PEG-RBV*/Offer trial</td>
<td>Defer</td>
<td>Case by case decision</td>
</tr>
<tr>
<td>F2</td>
<td>Defer/PEG-RBV*/Offer trial</td>
<td>Defer</td>
<td>Case by case decision</td>
</tr>
<tr>
<td>F3</td>
<td>Defer/PEG-RBV*/Offer trial</td>
<td>Defer</td>
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<tr>
<td>F4</td>
<td>Defer/PEG-RBV*/Offer trial</td>
<td>Defer</td>
<td>Case by case decision</td>
</tr>
</tbody>
</table>
So for discussion in HCV treatment naïve patients..

- Should we be recommending PEG-IFN/RBV naives (44-73% SVR) for all naïve patients? (or maybe just GT3)
- Is the risk of decompensation too high/too unpredictable with F3 to wait?
- Does the reduction in SVR with new DAAs if progression to F4 occurs argue to treat now?
- Are we being too optimistic about DAA availability and what restrictions are likely to apply?
HBV
Patient

- Precious, 34yr old from Zimbabwe
- Screened HIV antibody +ve and HBsAg +ve after routine in-patient screen

<table>
<thead>
<tr>
<th>HBV results</th>
<th>HIV results</th>
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<tbody>
<tr>
<td>HBeAg -ve, anti-HBe +ve</td>
<td>VL 47,000</td>
</tr>
<tr>
<td>VL 628</td>
<td>WT virus</td>
</tr>
<tr>
<td>HAV immune/HCV -ve</td>
<td>CD4 602</td>
</tr>
<tr>
<td>ALT 24</td>
<td></td>
</tr>
<tr>
<td>TE – 4.8 kPa</td>
<td></td>
</tr>
</tbody>
</table>
Management HBV/HIV by CD4 count, fibrosis level and HBV-DNA

- **F0/F1**
  - TE = 4.8kPa
  - CD4 ≥500 ART happy
  - Monitor/ART with TDF/FTC
  - Monitor

- **>F2**

- **DNA <2000**
  - DNA = 628
  - Monitor/ART with TDF/FTC
  - Monitor

- **DNA ≥2000**
HBV recommendations where CD4 >500 & no HBV treatment indication

- We suggest those with a CD4 ≥500 cells/μL, an HBV DNA of <2000 IU/mL, minimal or no evidence of fibrosis (Metavir ≤F1 or FibroScan <6.0 kPa) and a repeatedly normal ALT should be given the option to commence treatment or to be monitored not less than 6-monthly with HBV DNA and ALT and at least yearly for evidence of fibrosis (2C).
Patient

- Precious, 34yr old from Zimbabwe
- Screened HIV antibody +ve and HBsAg +ve after routine in-patient screen

**HBV results**
- HBeAg +ve, anti-HBe -ve
- VL Log 7.8
- HAV immune/HCV -ve
- ALT 24
- TE – 10.8 kPa

**HIV results**
- VL 47,000
- WT virus
- CD4 602
Management HBV/HIV by CD4 count, fibrosis level and HBV-DNA

- **F0/F1**
  - CD4 $\geq 500$
  - ART happy

- **>F2**
  - TE = 10.8 kPa
  - ART with TDF/FTC
  - Adefovir/48w PEG-IF

- **DNA <2000**
  - Log 7.8
  - ART with TDF/FTC

- **DNA $\geq 2000$**
  - CD4 $\geq 500$
  - ART unhappy
HBV recommendations where CD4 >500 & HBV treatment indication

• We recommend all those with an HBV DNA ≥2000 IU/mL should be treated, regardless of fibrosis score (1C).

• We recommend all those with more than minimal fibrosis (Metavir ≥F2 or FibroScan ≥9.0 kPa) should be treated, regardless of HBV DNA level (1C)
HBV recommendations where CD4 >500 & HBV treatment indication but declines ART

- We suggest adefovir or 48 weeks of PEG-IFN are alternative options in patients unwilling or unable to receive TDF/FTC as part of a fully suppressive ART combination but requiring HBV therapy (2C).
- We suggest PEG-IFN is only used in HBsAg-positive patients with a repeatedly raised ALT, low HBV DNA (<2 × 106 IU/mL), and minimal fibrosis, irrespective of HBeAg antigen status (2D).
Management HBV/HIV by CD4 count, fibrosis level and HBV-DNA

- **CD4 <500**
  - **F0/F1**: ART with TDF/FTC
  - **＞F2**: ART with TDF/FTC
  - **DNA <2000**: ART with TDF/FTC
  - **DNA ≥2000**: ART with TDF/FTC
HBV: guidelines comparison?

EACS Guidelines 2013; - accessed on line

<table>
<thead>
<tr>
<th>CD4 &gt;500</th>
<th>ART</th>
<th>BHIVA</th>
<th>CD4 &gt;500</th>
<th>no ART - EACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor/ ART with TDF/FTC</td>
<td>Monitor</td>
<td>Monitor</td>
<td>Monitor</td>
<td></td>
</tr>
<tr>
<td>ART with TDF/FTC</td>
<td>ART with TDF + FTC/3TC</td>
<td>Adefovir/ 48w PEG-IF</td>
<td>Telbivudine /Adefovir/ 48w PEG-IF</td>
<td></td>
</tr>
<tr>
<td>Monitor/ ART with TDF/FTC</td>
<td>Monitor</td>
<td>Monitor</td>
<td>Monitor</td>
<td></td>
</tr>
<tr>
<td>ART with TDF/FTC</td>
<td>ART with TDF/FTC or 48w PEG-IF</td>
<td>Adefovir/ 48w PEG-IF</td>
<td>Telbivudine /Adefovir/ 48w PEG-IF</td>
<td></td>
</tr>
</tbody>
</table>

- F0/F1
- >F2
- DNA <2000
- DNA >2000
The one known is that in 6m time it will have changed

There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

(Donald Rumsfeld)

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