Dr Ed Wilkins

North Manchester General Hospital

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr Ed Wilkins	Dr Wilkins has received educational grants and unrestricted travel support from Gilead, BMS, BI, MSD, Janssen, J&J
Date	**November 2013**

Guidelines needed updating….

DOI: 10.1111/j.1468-1293.2009.00781.x

HIV Medicine (2010), 11, 1–30

BRITISH HIV ASSOCIATION GUIDELINES

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

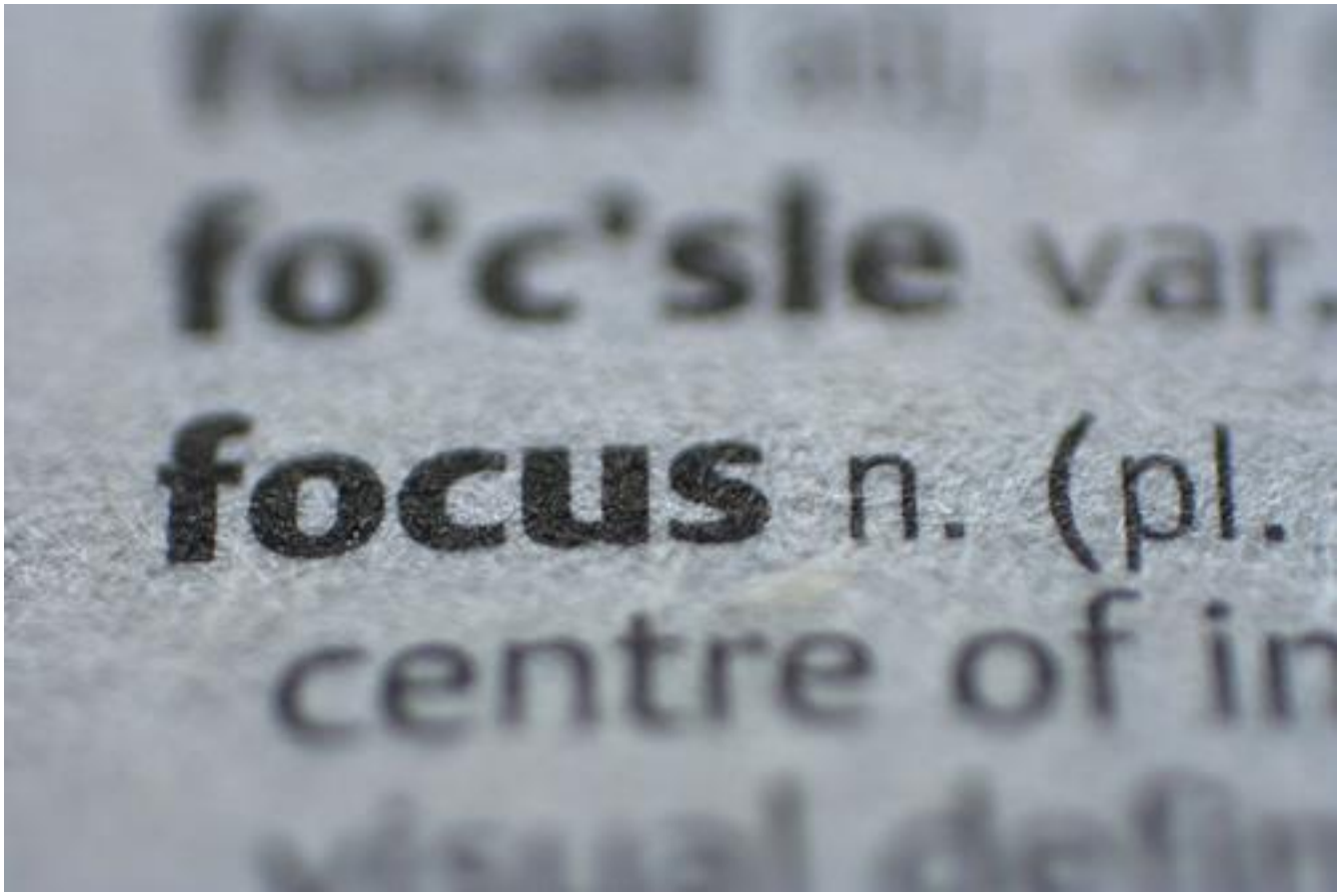
Accepted 27 August 2009

- 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

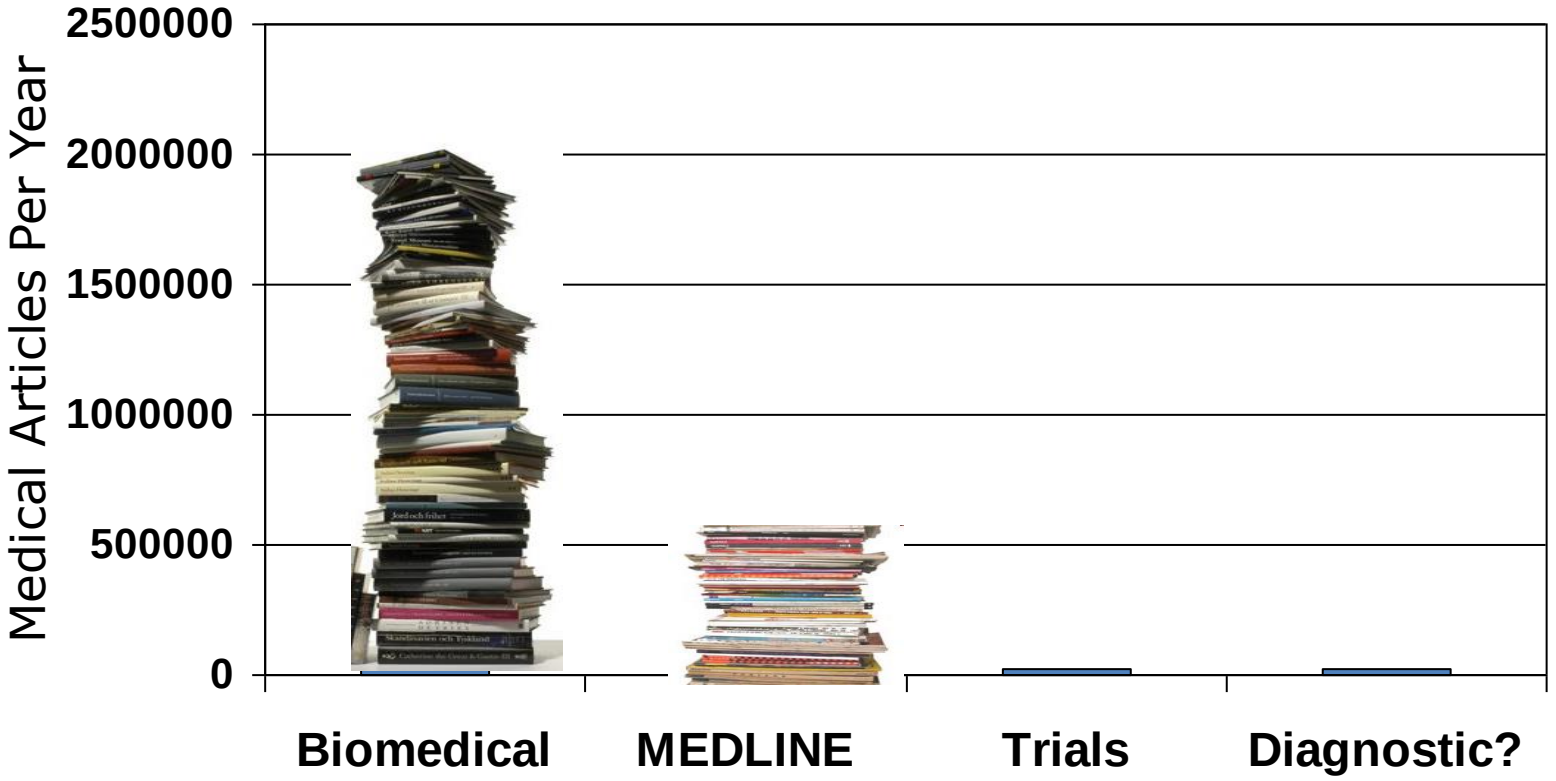


Used PICO framework

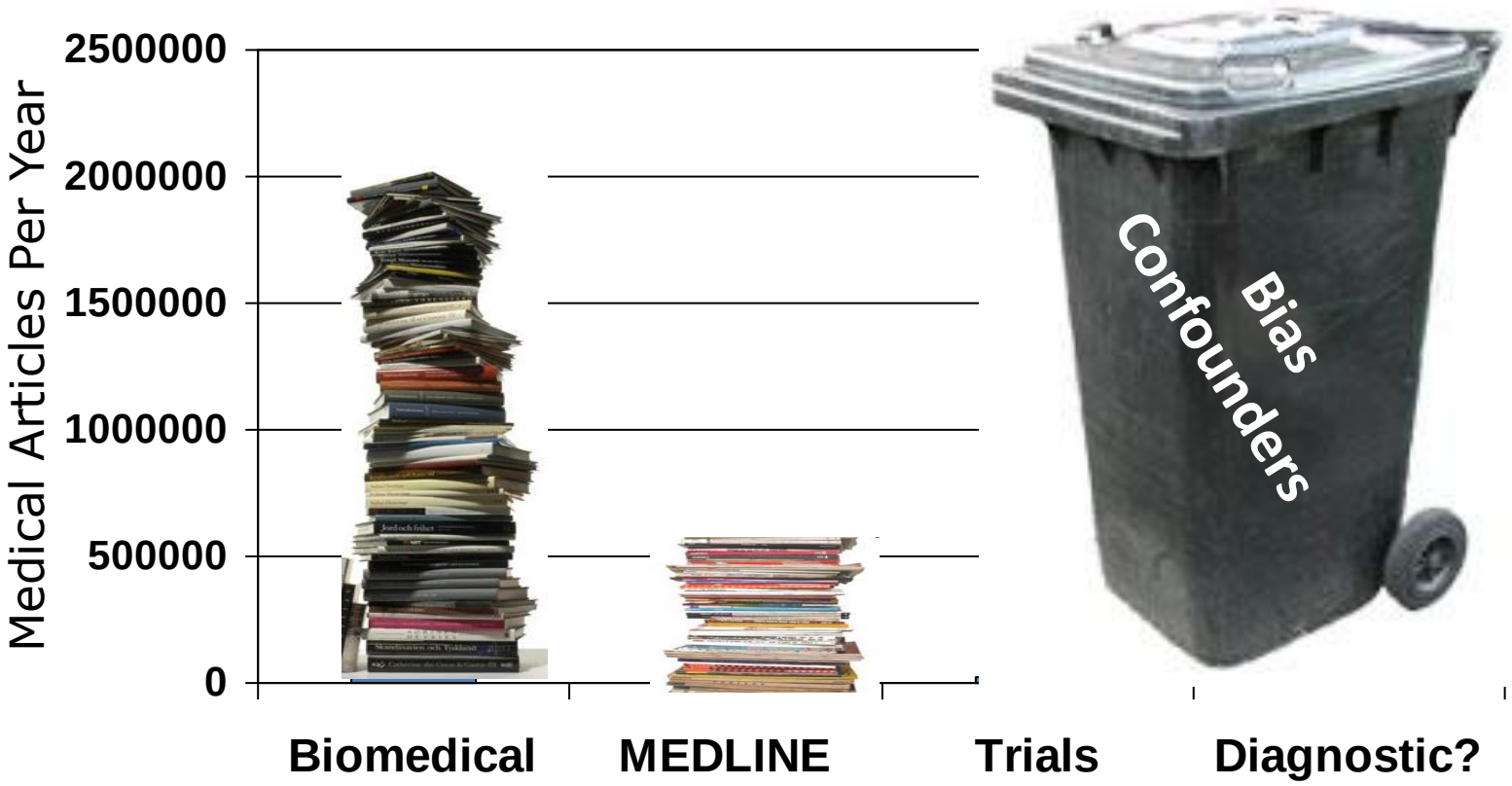
PICO	Example Key Question
Population	HIV/hepatitis virus co-infected
Investigation	Fibrosis screening with TE
Comparator	Liver biopsy
Outcome	Fibrosis detection

11 key questions identified

Best evidence tracked down using defined search criteria



Evidence critically and statistically appraised

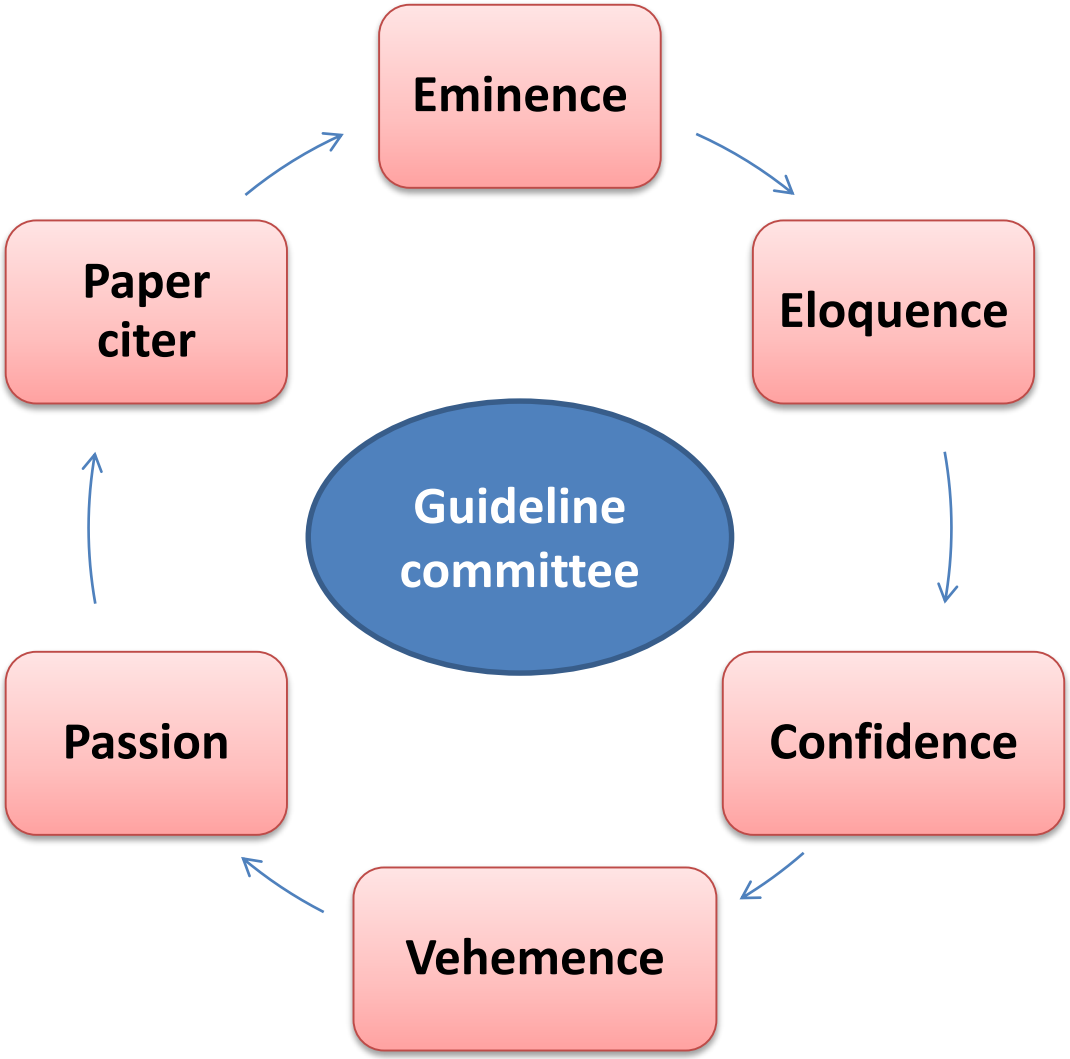


Peer-reviewed recognised not to equate to good quality

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

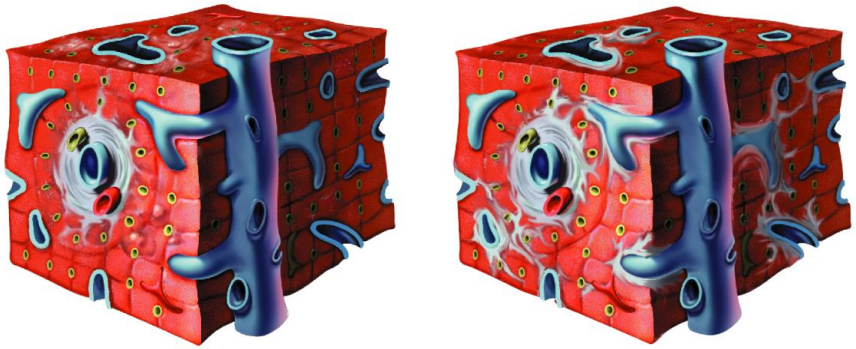


Because any of these ≠ wisdom ≠ improved knowledge

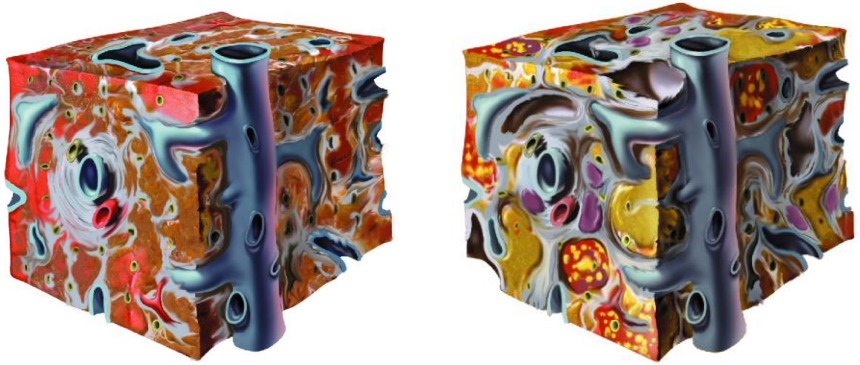
Other guidelines were consulted but no more!!

They may have got it wrong

Today

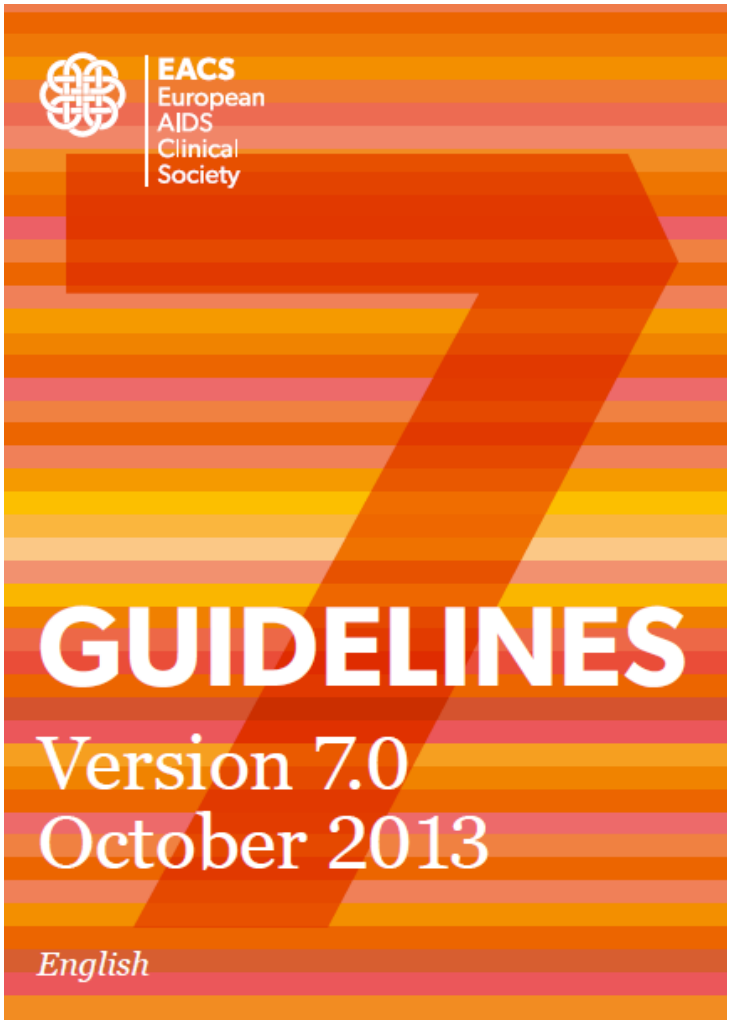


Assessing level of fibrosis



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

HCV results

GT1a

VL 680,000

HAV/HBV immune

ALT 54

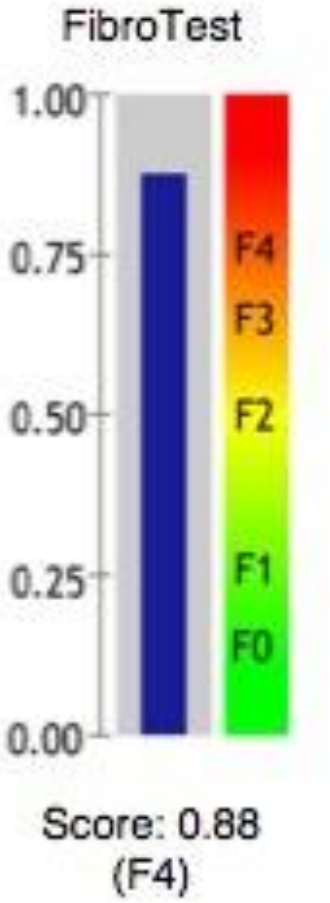
HIV results

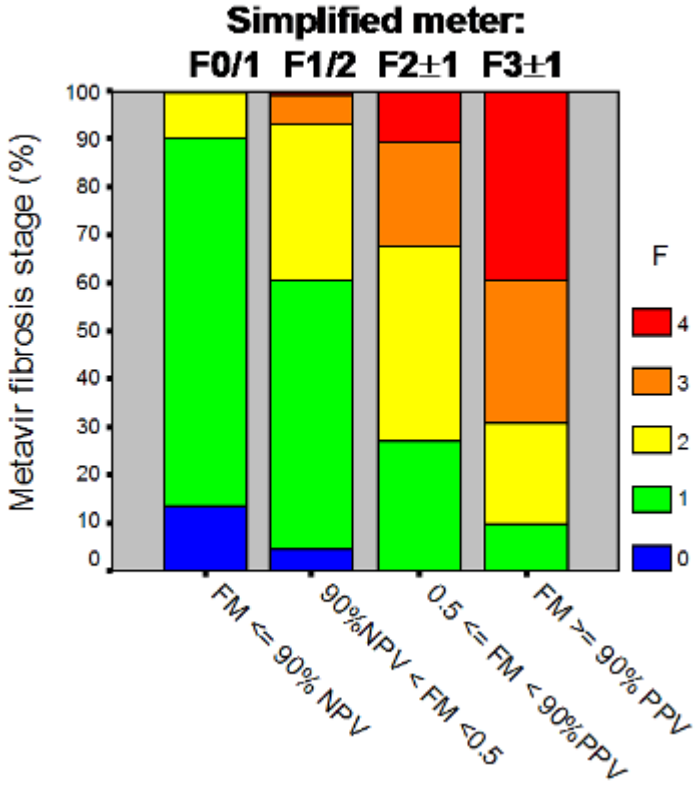
VL 47,000

WT virus

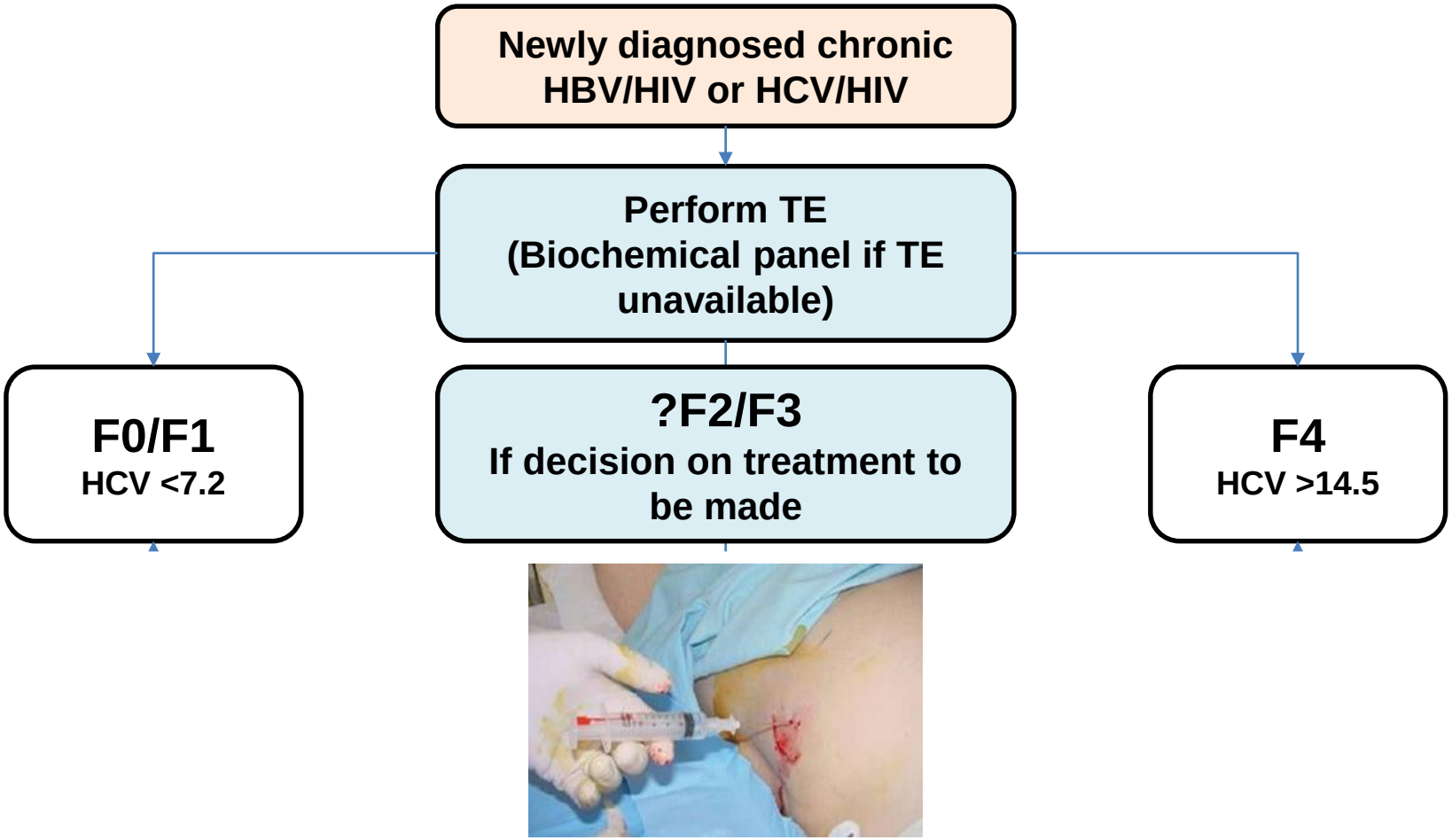
CD4 401

Fibrosis staging recommended in all patients (1B)/Non-invasive test suggested first (2B)

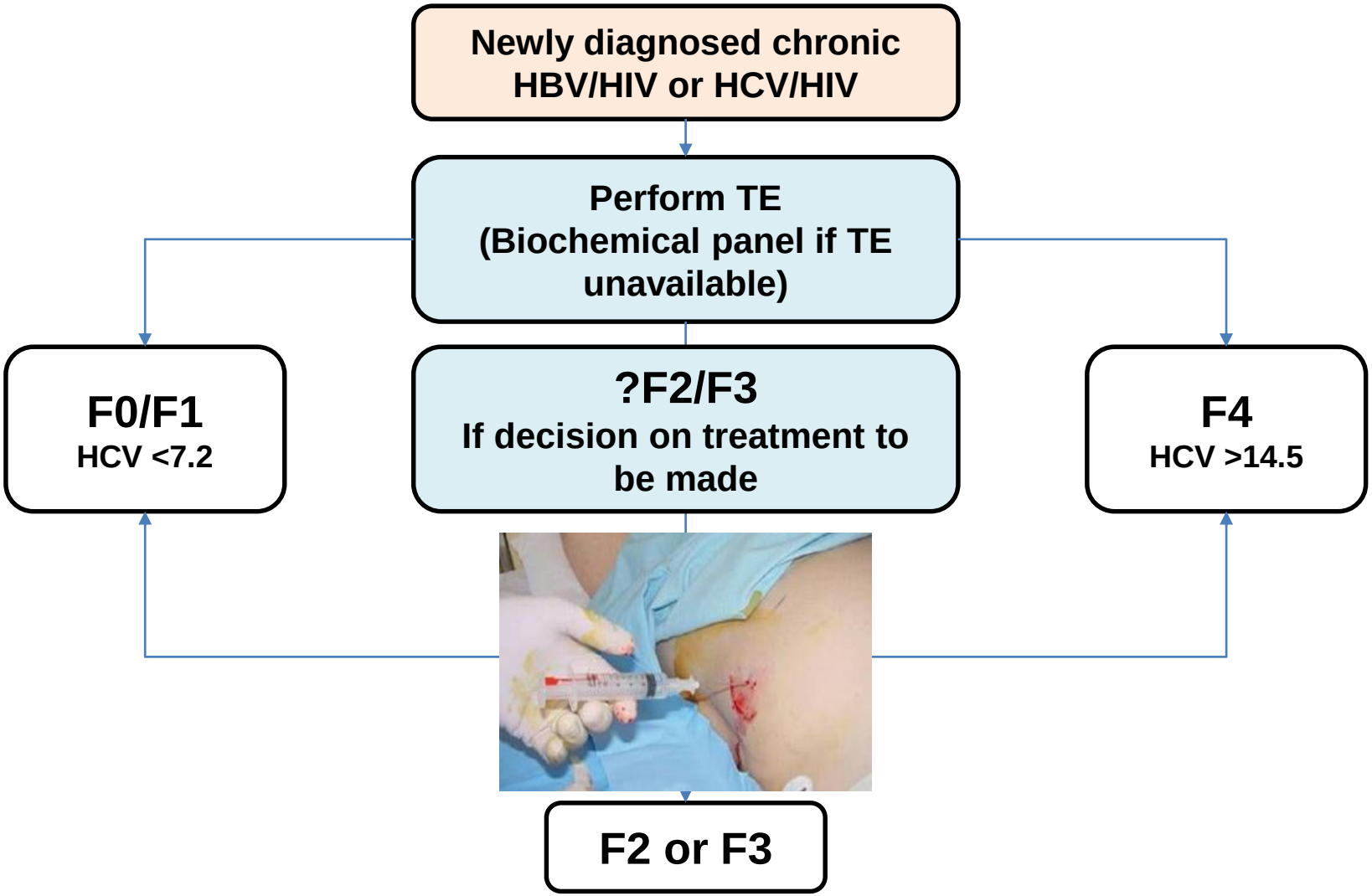




Assessing level of fibrosis



Assessing level of fibrosis



Management Borek

	Naive	
F0/F1	Defer/Triple therapy/ Offer trial	**TE 6.2kPa** **Indicative – F0/1**
F2	Defer/Triple therapy/ Offer trial	
F3	Defer/Triple therapy/ Offer trial	**TE 11.2kPa** **Liver biopsy – F3**
F4	Triple therapy	**TE 15.2kPa** **Indicative – F4**

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

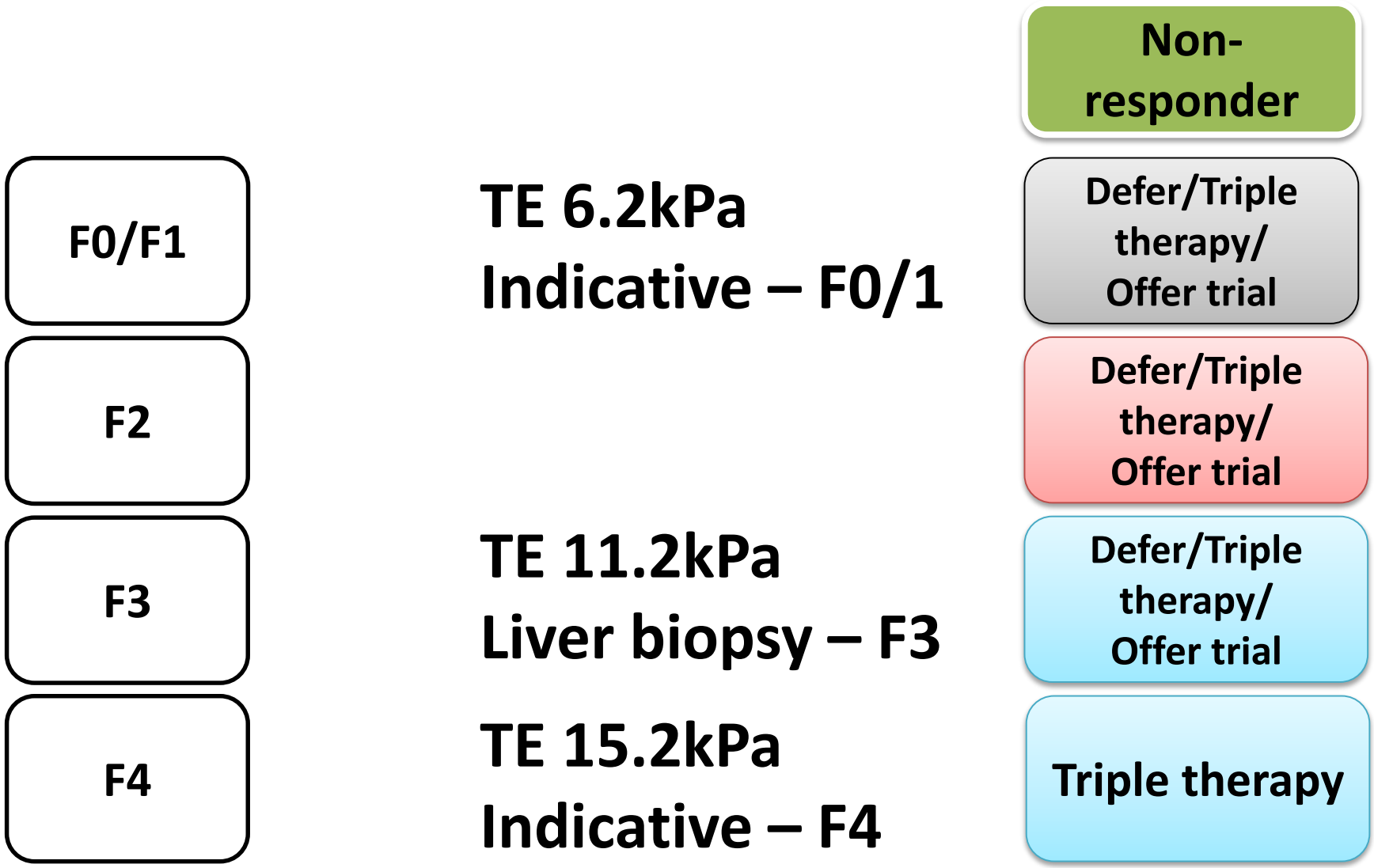
- We **suggest** for patients with non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with TE or alternative non-invasive testing at least annually. Where there is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

HCV GT1: guidelines comparison – naïve?

EACS Guidelines 2013; French Guidelines 2013 - accessed on line

	BHIVA	EACS	French
F0/F1	Defer/Triple therapy/ Offer trial	Individual decision	Defer
F2	Defer/Triple therapy/ Offer trial	Triple therapy	PEG-RBV*/Triple therapy
F3	Defer/Triple therapy/ Offer trial	Triple therapy	Triple therapy
F4	Triple therapy	Triple therapy	Triple therapy

Management Borek



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.

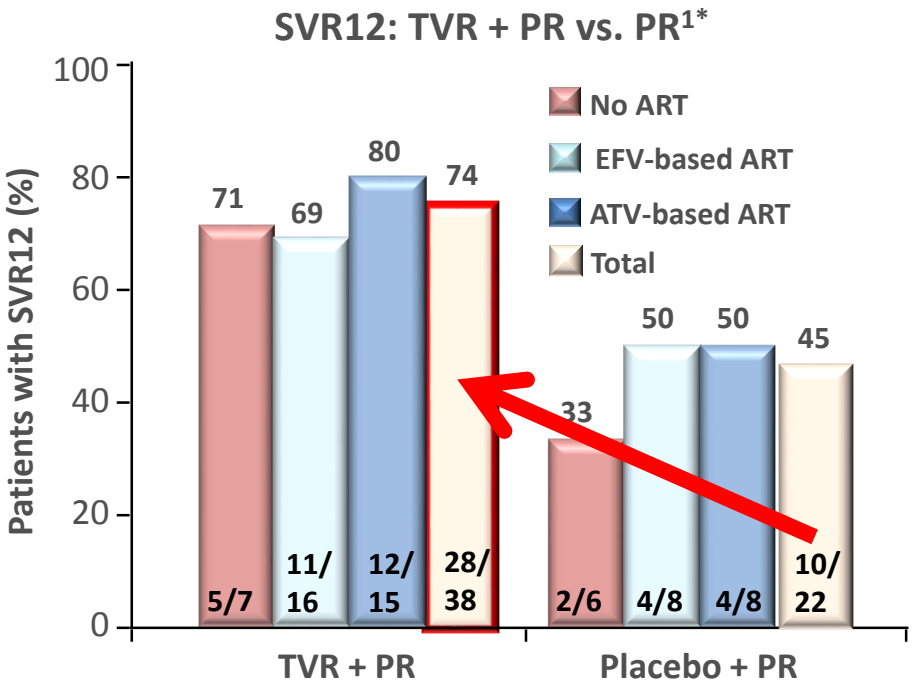
HCV GT1: guidelines comparison – non-responder?

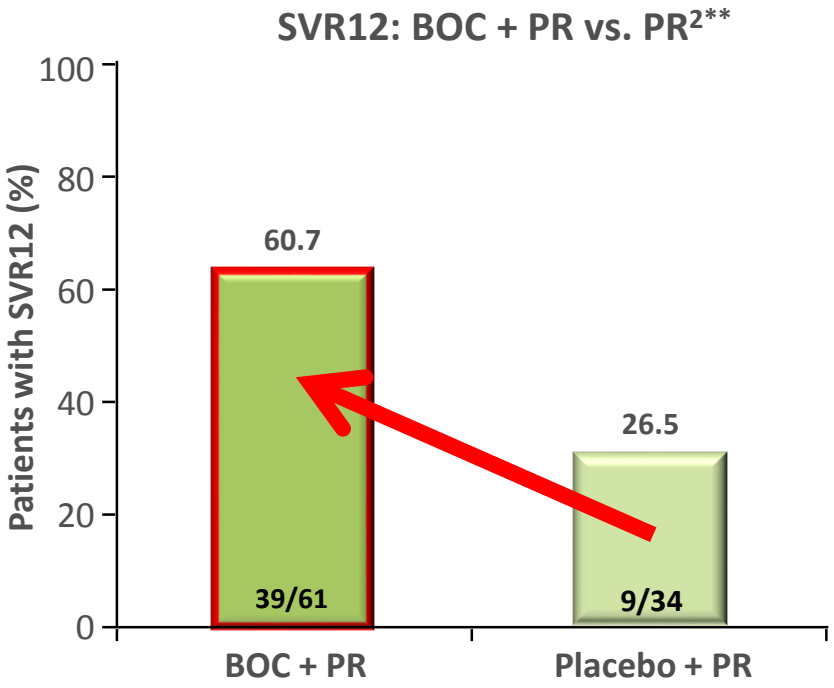
	BHIVA	EACS	French
F0/F1	Defer/Triple therapy/ Offer trial	Defer	Defer
F2	Defer/Triple therapy/ Offer trial	Defer	Triple therapy/Offer trial
F3	Defer/Triple therapy/ Offer trial	Defer	Triple therapy/Offer trial
F4	Triple therapy	Triple therapy on case-by-case basis	Triple therapy/Offer trial

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





- Rebound in HIV-1 RNA not observed in any patient

	DC due to AEs
PR (n=22)	0%
TVR + PR (n=38)	8%

- HIV-1 RNA breakthrough observed in 7 patients

	DC due to AEs
PR (n=34)	9%
BOC + PR (n=64)	20%

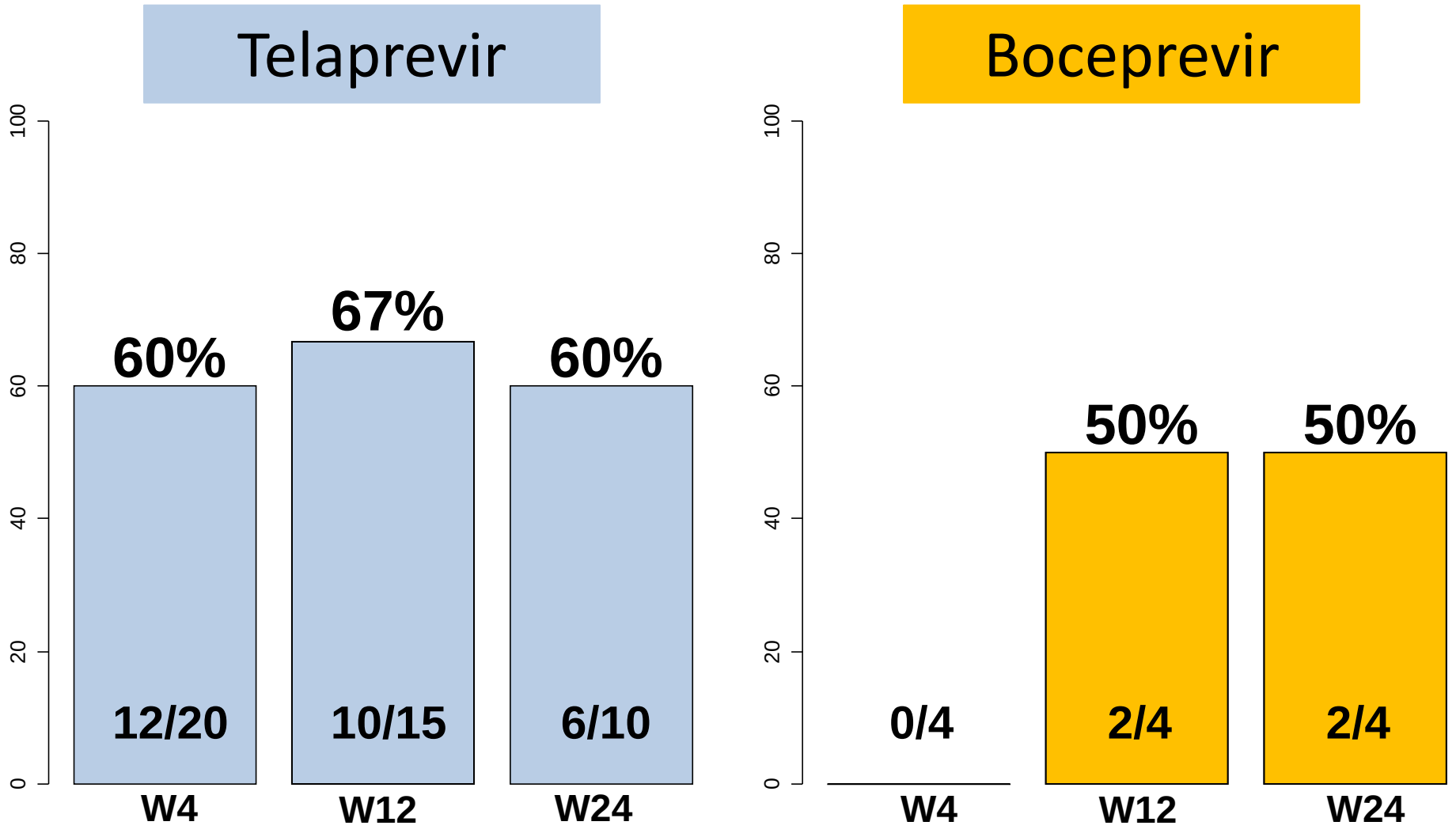
Primary endpoint = Sustained Virological Response (SVR) at 12 weeks; interim analysis presented; TVR = telaprevir

Primary endpoint = Sustained Virological Response (SVR) at 44 weeks; interim analysis presented; BOC = boceprevir

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

Adapted from: 1. Dieterich DT, et al. CROI 2012. Oral Presentation 46; 2. Sulkowski MS, et al. CROI 2012. Oral Presentation 47.

Virological response in cirrhotic non responders



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 de-compensation among HIV/HCV co-infected individuals with advanced fibrosis: implications for the timing of therapy

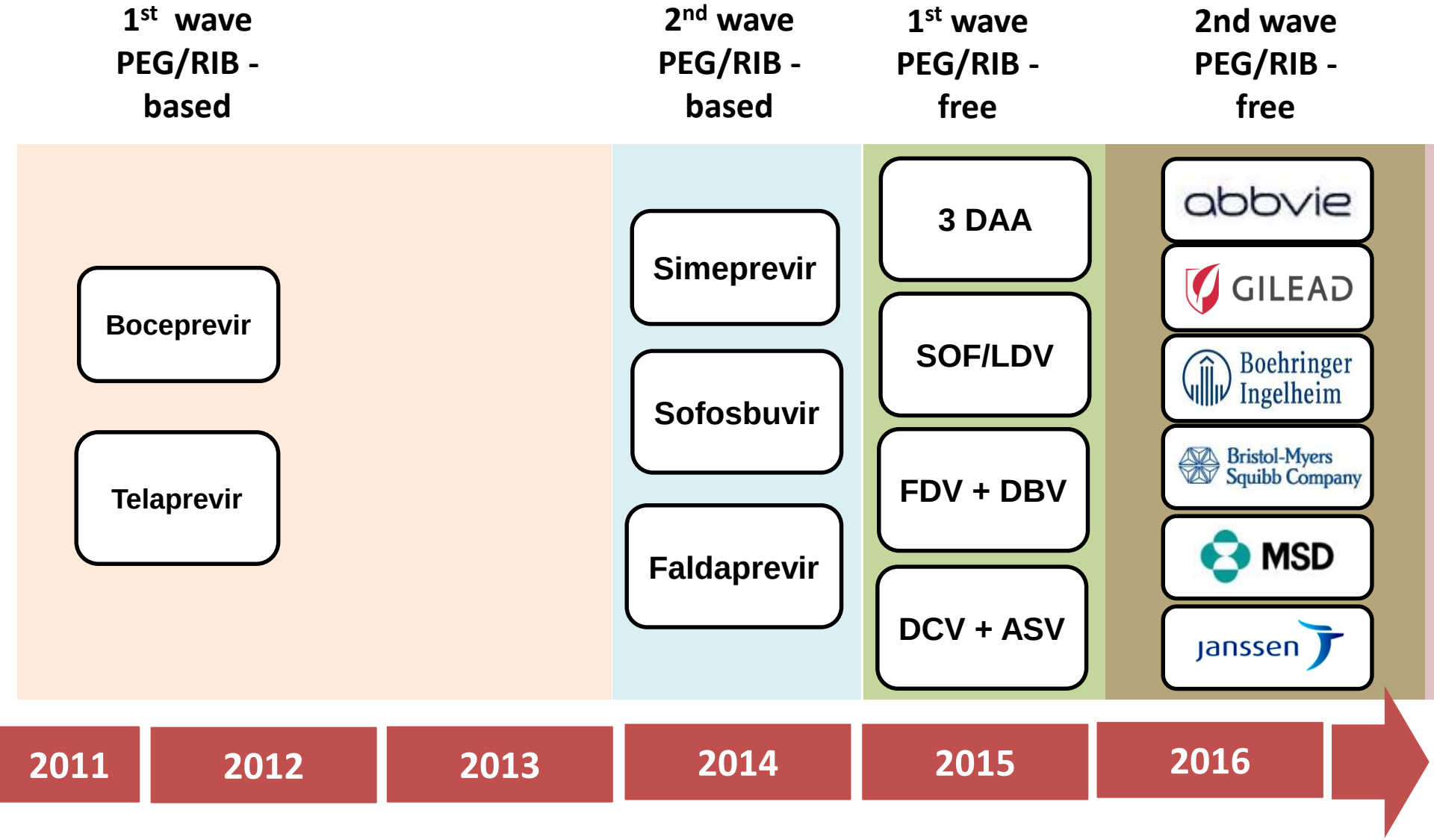
Period	No. Entering Each Period	No. of Liver Decompensations	Probability of Remaining Free of Decompensation (95% CI)
Fibrosis staged by biopsy			
F3			
1 y	149	1	99% (95%–100%)
3 y	128	1	98% (94%–100%)
5 y	112	3	95% (89%–98%)
>5 y	81	7	80% (67%–89%)
F4			
1 y	168	3	96% (91%–98%)
3 y	150	8	87% (81%–92%)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

Macias J. Clinical Infectious Diseases 2013;57(10):1401–8

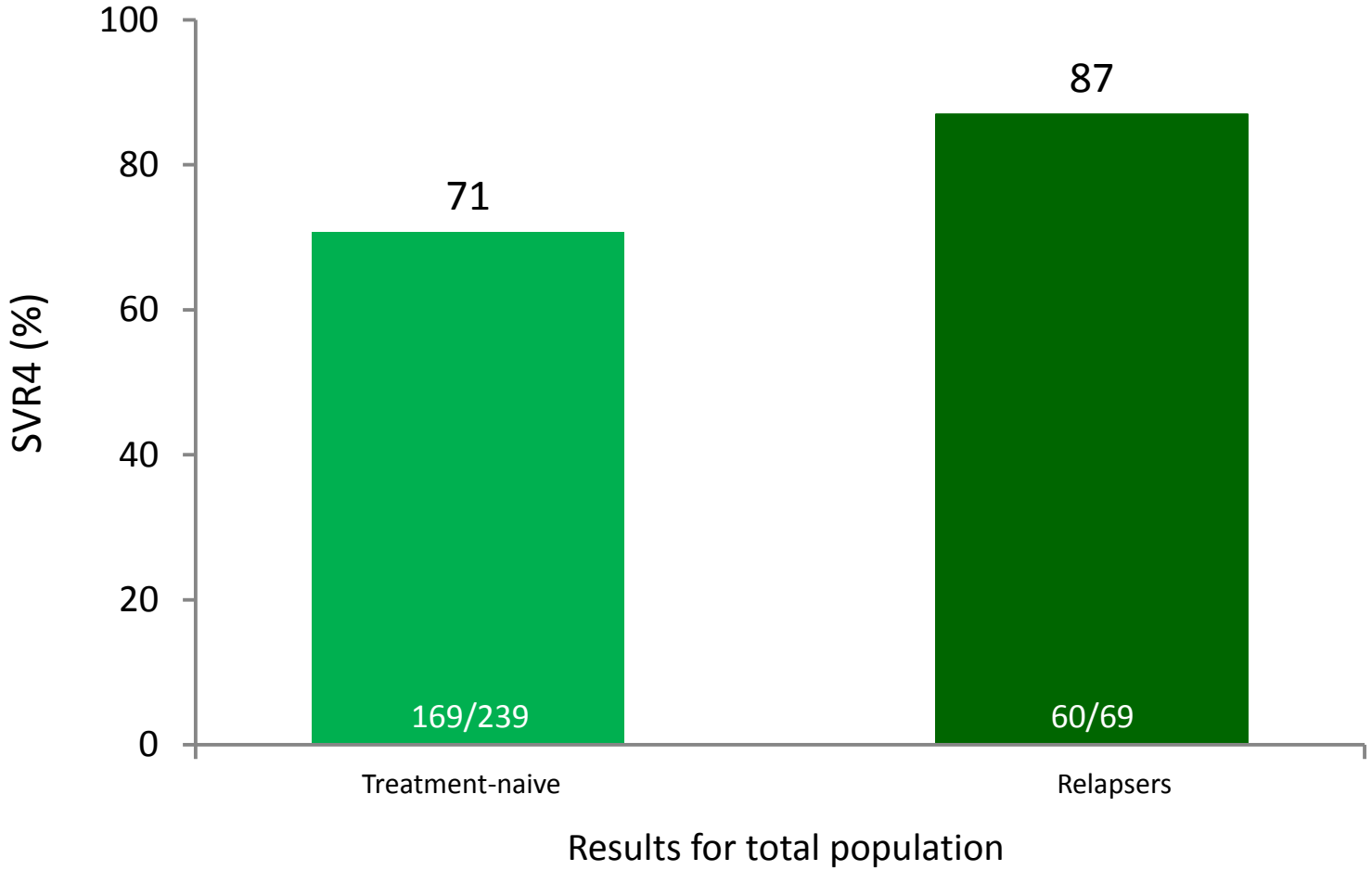
Factors influencing recommendations on HCV treatment

- 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



Faldaprevir in GT1: STARTVerso 4 - Overall SVR 4 in naïve patients and relapsers

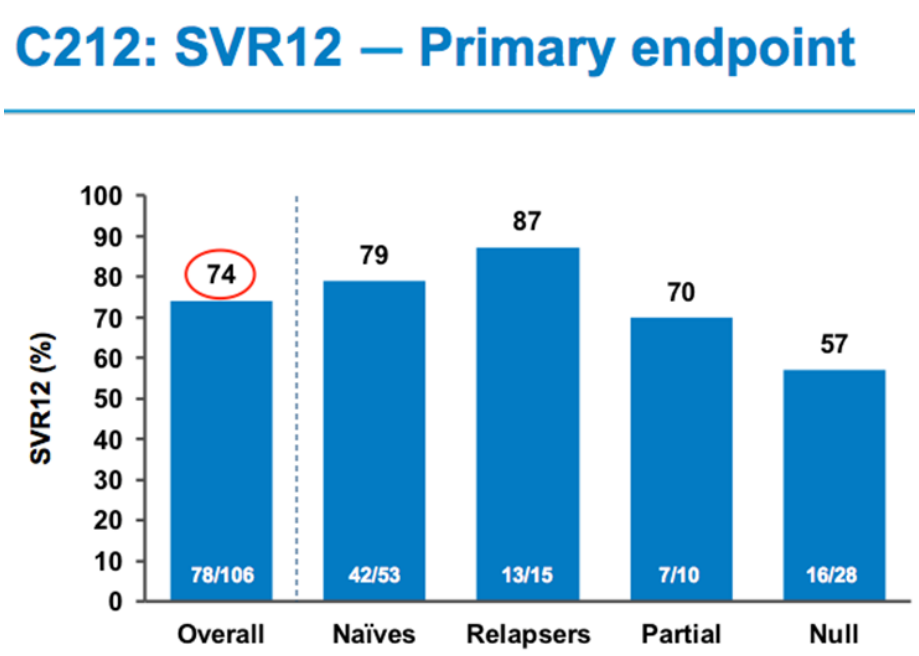


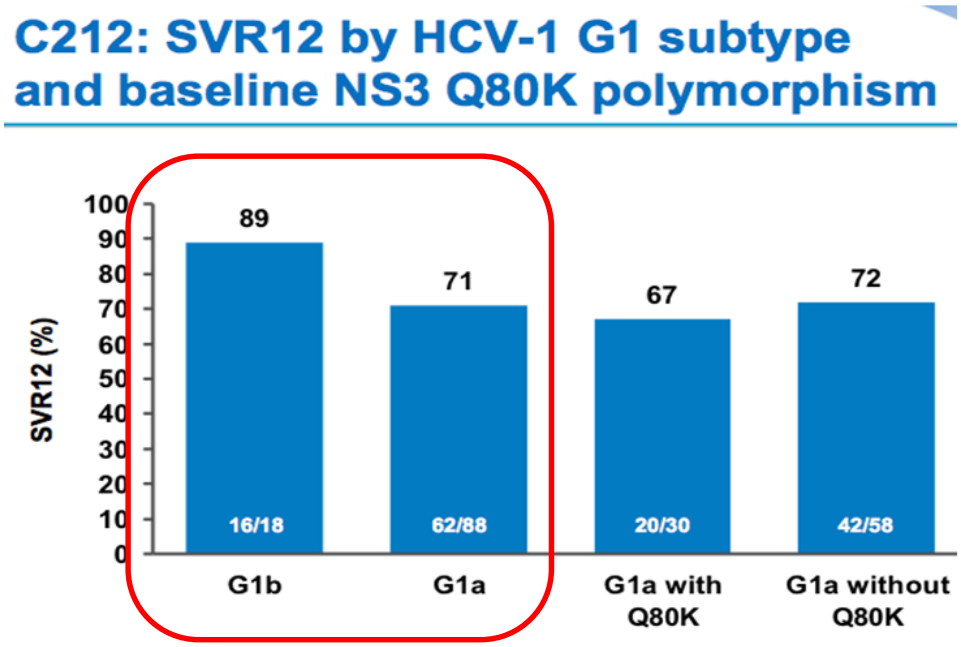
[a]Denominator = patients with ETS

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

Rockstroh J, et al. **14TH EUROPEAN AIDS CONFERENCE, OCTOBER 16–19, 2013, BRUSSELS, BELGIUM. ORAL PS9/7**

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





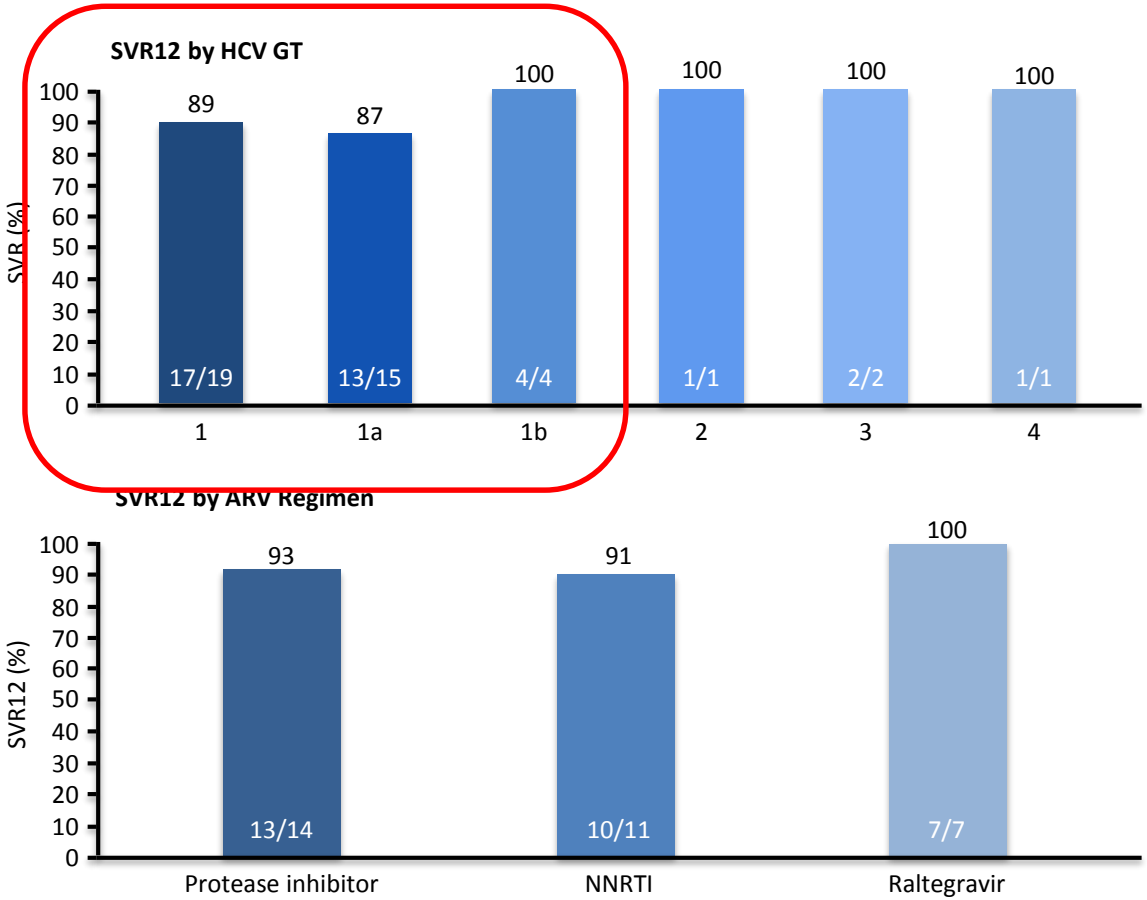
- 87% of treatment naïve (88%, n=41) and relapser (85%, n=13) patients met the criteria for 24 week RGT

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

Dieterich D et al. 14th European AIDs Conference (EACS 2013). Brussels. October 16-19, 2013. Abstratct PS9/5.

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

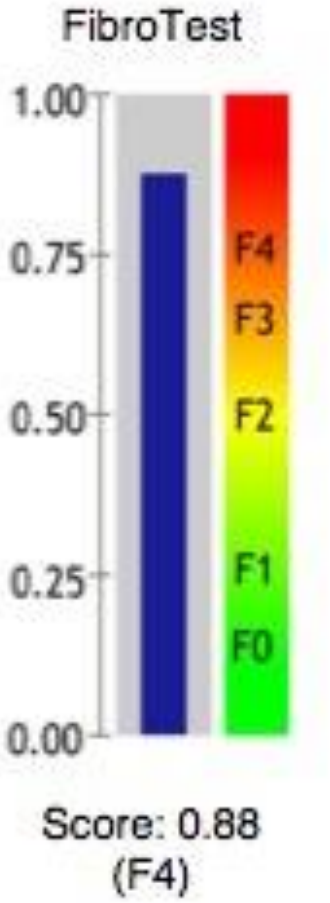


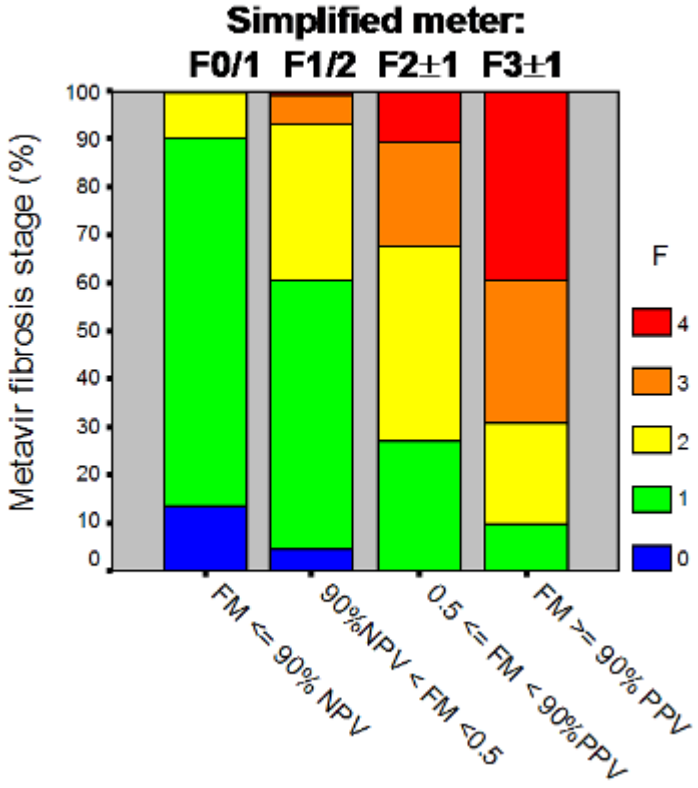
NNRTI, non-nucleoside reverse transcriptase inhibitor

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

HCV results

GT3

VL 680,000

HAV/HBV immune

ALT 54

HIV results

VL 47,000

WT virus

CD4 401

Management Borek

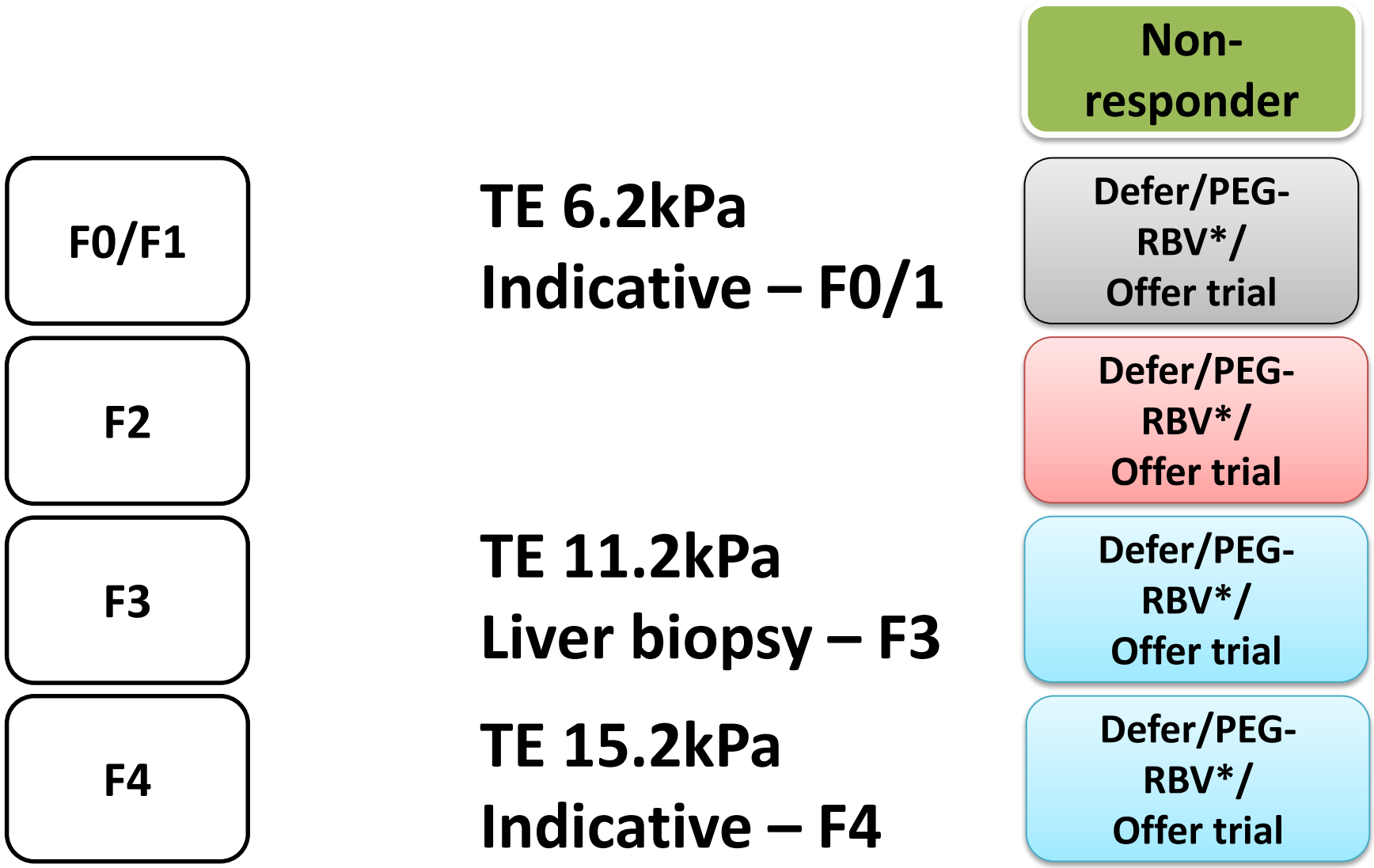
	Naive
F0/F1	**Defer/PEG-RBV/ Offer trial**
F2	**Defer/PEG-RBV/ Offer trial**
F3	**Defer/PEG-RBV/ Offer trial**
F4	**PEG-RBV**

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



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?

	BHIVA	EACS	French
F0/F1	Defer/PEG-RBV/ Offer trial	PEG-RBV	PEG-RBV
F2	Defer/PEG-RBV/ Offer trial	PEG-RBV	PEG-RBV
F3	Defer/PEG-RBV/ Offer trial	PEG-RBV	PEG-RBV
F4	PEG-RBV	PEG-RBV	PEG-RBV

HCV GT 2/3: guidelines comparison – non-responders?

	BHIVA	EACS	French
F0/F1	Defer/PEG-RBV*/ Offer trial	Defer	Case by case decision
F2	Defer/PEG-RBV*/ Offer trial	Defer	Case by case decision
F3	Defer/PEG-RBV*/ Offer trial	Defer	Case by case decision
F4	Defer/PEG-RBV*/ Offer trial	Defer	Case by case decision

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

HBV results

HBeAg -ve, anti-HBe +ve

VL 628

HAV immune/HCV -ve

ALT 24

TE – 4.8 kPa

HIV results

VL 47,000

WT virus

CD4 602

Management HBV/HIV by CD4 count, fibrosis level and HBV-DNA

		CD4 ≥500 ART happy	CD4 ≥500 ART unhappy
F0/F1	TE = 4.8kPa	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

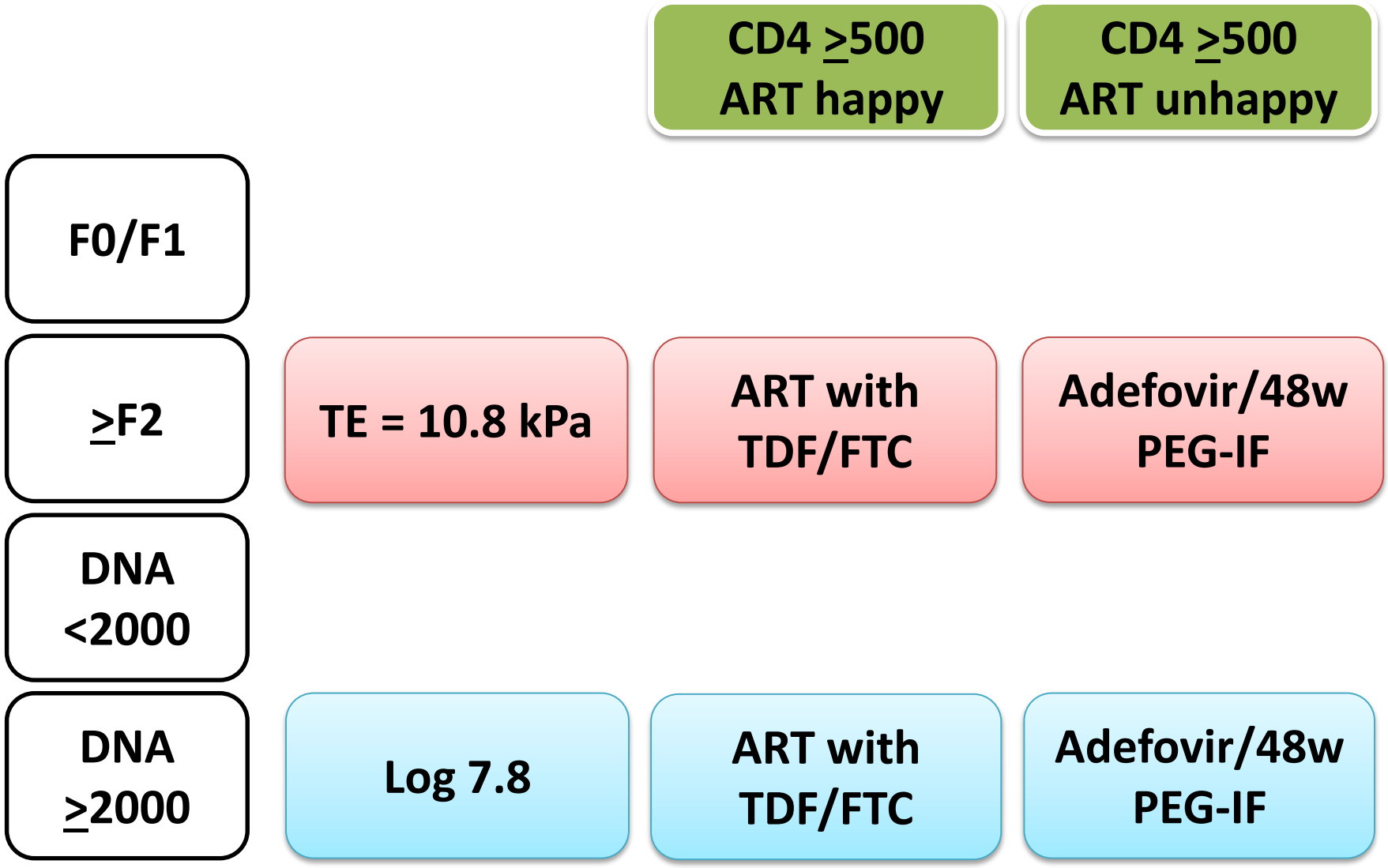
- We suggest those with a CD4 ≥500 cells/μL, an HBV DNA of <2000 IU/mL, minimal or no evidence of fibrosis (Metavir ≤F1 or FibroScan <6.0 kPa) and a repeatedly normal ALT should be given the option to commence treatment or to be monitored not less than 6-monthly with HBV DNA and ALT and at least yearly 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	**HIV results**
HBeAg +ve, anti-HBe -ve	VL 47,000
VL Log 7.8	WT virus
HAV immune/HCV -ve	**CD4 602**
ALT 24	
TE – 10.8 kPa	

Management HBV/HIV by CD4 count, fibrosis level and HBV-DNA



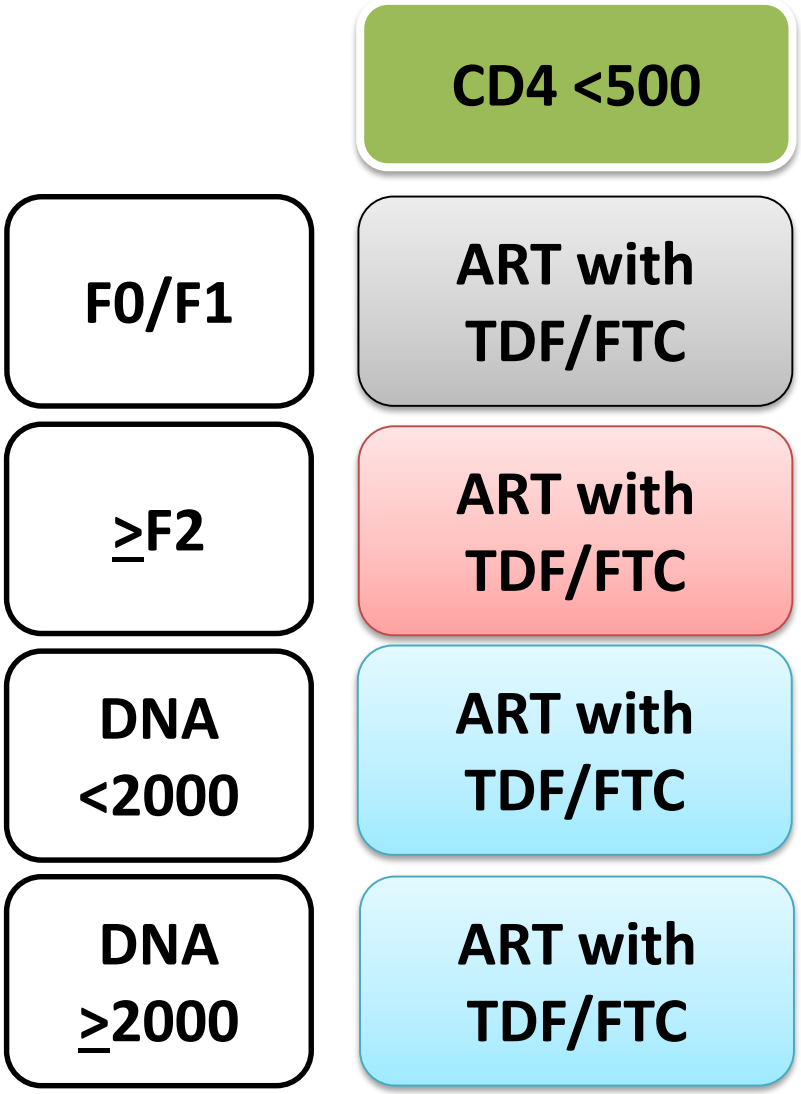
HBV recommendations where CD4 >500 & HBV treatment indication

- 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



HBV: guidelines comparison?

EACS Guidelines 2013; - accessed on line

CD4 ≥500 ART BHIVA

CD4 ≥500 no ART - EACS

F0/F1	**Monitor/ ART with TDF/FTC**	**Monitor**	**Monitor**	**Monitor**
≥F2	**ART with TDF/FTC**	**ART with TDF + FTC/3TC**	**Adefovir/ 48w PEG-IF**	**Telbivudine /Adefovir/ 48w PEG-IF**
DNA <2000	**Monitor/ ART with TDF/FTC**	**Monitor**	**Monitor**	**Monitor**
DNA ≥2000	**ART with TDF/FTC**	**ART with TDF/FTC or 48w PEG-IF**	**Adefovir/ 48w PEG-IF**	**Telbivudine /Adefovir/ 48w PEG-IF**

The one known is that in 6m time it will have changed