

Management and treatment of chronic hepatitis B virus Belgian Guidelines

Belgian Association for the Study of the Liver



October 2007

Conflits d'intérêts éventuels

- **Roche**: bourse de recherche; bourse de congrès; orateur; études cliniques
- **Schering Plough**: bourse de recherche; bourse de congrès; orateur; hepatitis advisory board; études cliniques
- **Gilead/UCB**: advisory board
- **BMS**: advisory board
- **Novartis**: advisory board
- **Innogenetics**: bourse de recherche
- **INAMI**: expert
- **Fonds des Maladies Professionnelles**: expert

Guidelines internationaux

- Guidelines AASLD: Hepatology, Février 2007
- EASL Consensus Conference: J Hepatol , 2003
- Asian-Pacific Consensus Statement. Liver Int 2005

- Management of HBV: panel of experts. Hepatology, Avril 2007
- Treatment algorithm in the US: Clin Gastroenterol Hepatol, Août 2006

- Roadmap for management of oral therapy for HBV: Clin Gastroenterol Hepatol, Août 2007

Belgian guidelines

- Natural history
- Identification of infected persons and screening
- Effect of treatment on natural history and cost-effectiveness of treatment
- Indications for treatment
- Treatment options
- Management of antiviral resistance

Belgian guidelines

- Follow up during and after treatment
- Special groups: HBV/HCV; HBV/HDV
HBV/HIV; acute HBV; compensated and
decompensated cirrhosis; reactivation
during immune suppressive treatment;
HBV and liver transplantation

BASL guidelines

Colle I, Adler M, Brenard R, Henrion J, Langlet P, Michielsen P, Orlent H, Reynaert H, Sprengers D, Starkel P, Van Damme P, Verslype C, Delwaide J

SRBGE octobre 2007

- Grandes lignes
- Les sujets qui fâchent

Importance of HBV DNA level

- Clear relationship between HBV DNA level and prognosis
- High HBV DNA levels are associated with increased progression to cirrhosis, decompensated cirrhosis, need for liver transplantation and development of HCC

ALT not predictor for evolution and severity of disease, but predictor for response to therapy



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Importance of HBV DNA level

HBV DNA	Incidence cirrhosis	Incidence HCC
< 300 copies/mL or < \approx 50 IU/mL	4.5%	1.3%
> 10^6 copies/mL or > \approx 200,000 IU/mL	36.2%	14.9%

Effect of treatment on natural history of HBV

- Chronic HBV is mostly asymptomatic until cirrhosis and HCC arise
- All anti-HBV drugs showed treatment benefit using biochemical, virological and histologic endpoints
- Long term suppression of HBV DNA decreases incidence of decompensation and HCC

GOALS of therapy

- **First major goal of therapy:**
 - suppress HBV DNA as much as possible
 - => prevent disease progression
 - => prevent cirrhosis and decompensation
 - => prevent HCC
 - => prevent liver transplantation and death
- **Second major goal of therapy:** cure HBV
 - in HBeAg positive: HBeAg seroconversion and development of anti-HBeAb (and eventually HBsAg conversion)
 - in HBeAg negative: HBsAg seroconversion and development of anti-HBsAb



Chronic hepatitis B profiles

	Inactive carrier	Immuno-tolerant phase	Active chronic HBV wild type	Active chronic HBV precore mutant
HBsAg	+	+	+	+
HBeAg	-	+	+	-
Anti HBe Ab	+	-	-	+
ALT	normal	normal	elevated	elevated
HBV DNA Copies/ml	$\leq 10^5$	$\geq 10^{5-7}$	$\geq 10^5$	$\geq 10^{4-5}$
HBV DNA IU/ml	≤ 20.000	≥ 20.000	≥ 20.000	$\geq 2.000-20.000$



Chronic hepatitis B profiles

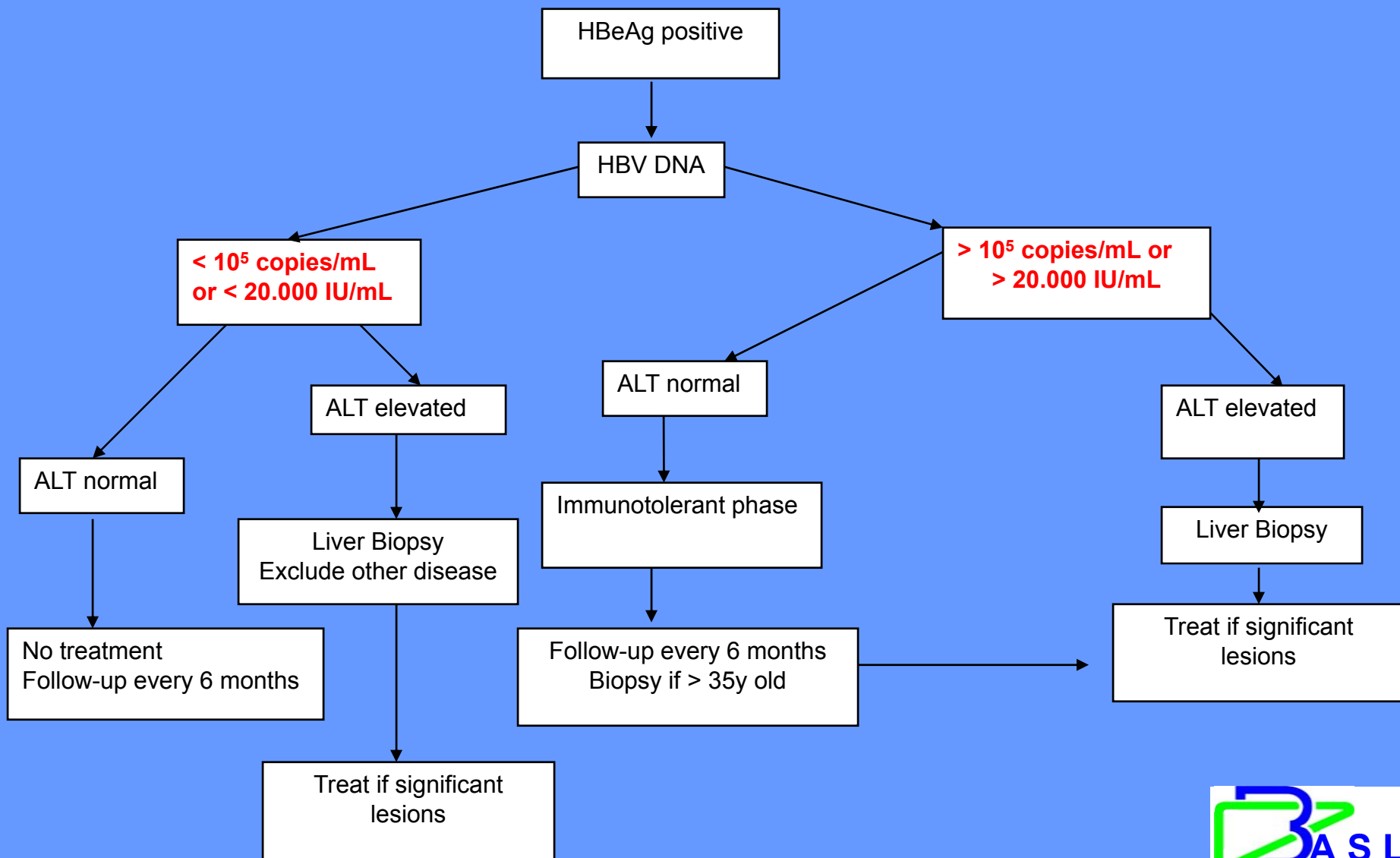
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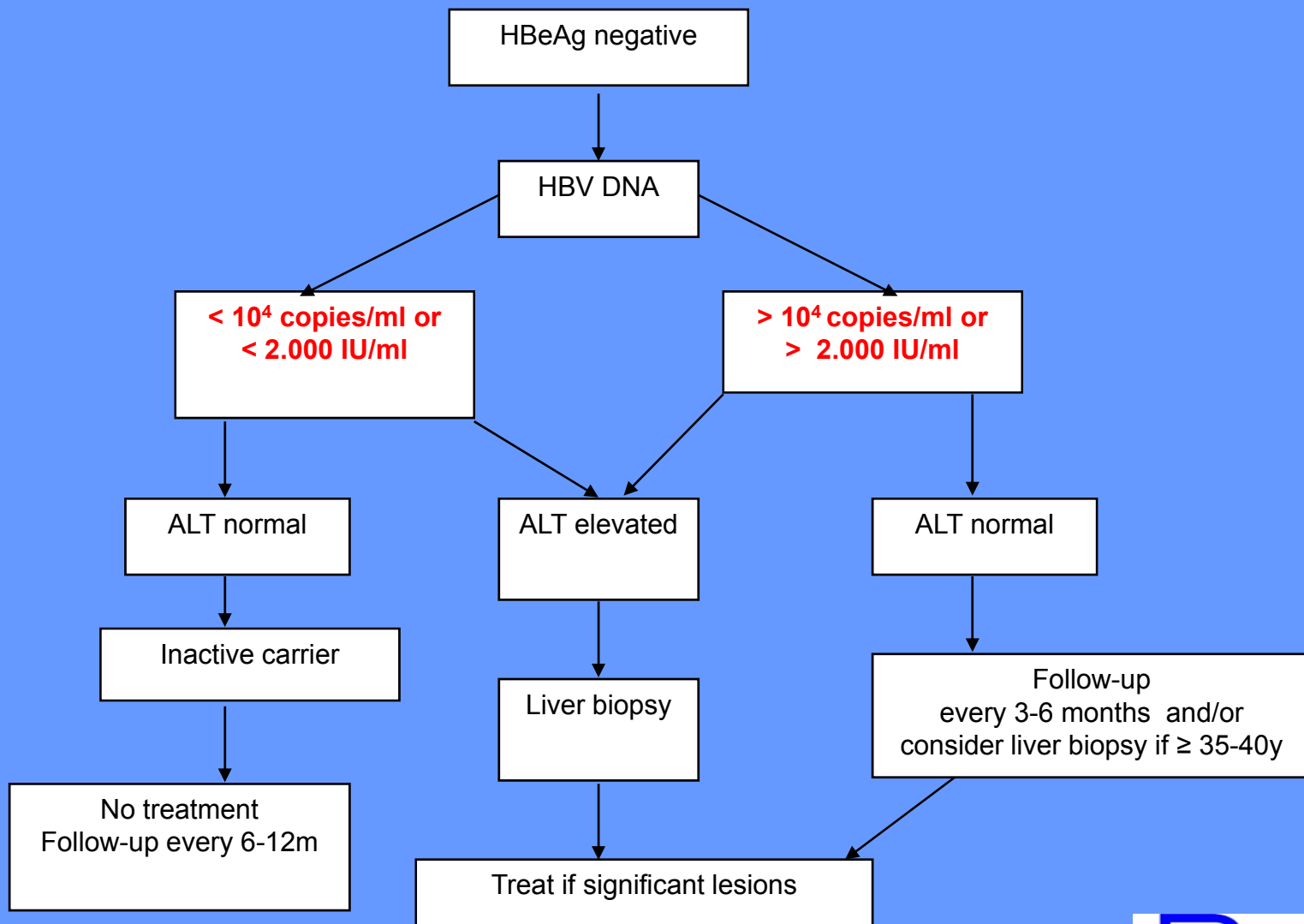
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Management algorithm for patients with HBeAg positive chronic HBV



Management algorithm for patients with HBeAg negative chronic HBV



Traitements

- Immunomodulateurs: interférons et peginterféron
- Antiviraux: lamivudine (Zeffix), adéfovir (Hepsera), entécavir (Baraclude)

Situation actuelle en Belgique

Pegasys (peginterferon alpha 2a)

1ère ligne

- AgHBs + > 6 mois
- AgHBe + ou –
- DNA viral B > 100.000 copies/ml
- TGP > 2 X Nle
- PBH: nécroinflammation modérée à sévère
- Pas de HIV, pas de greffe hépatique
- Pas de pré- ou de cirrhose

Pegasys (2ème ligne)

- Résistant à lamivudine

Lamivudine (Zeffix)

- Hépatite B chronique
- HIV –
- DNA viral élevé
- TGP élevées
- PBH: fibrose ou activité inflammatoire
- Remboursement 5 ans

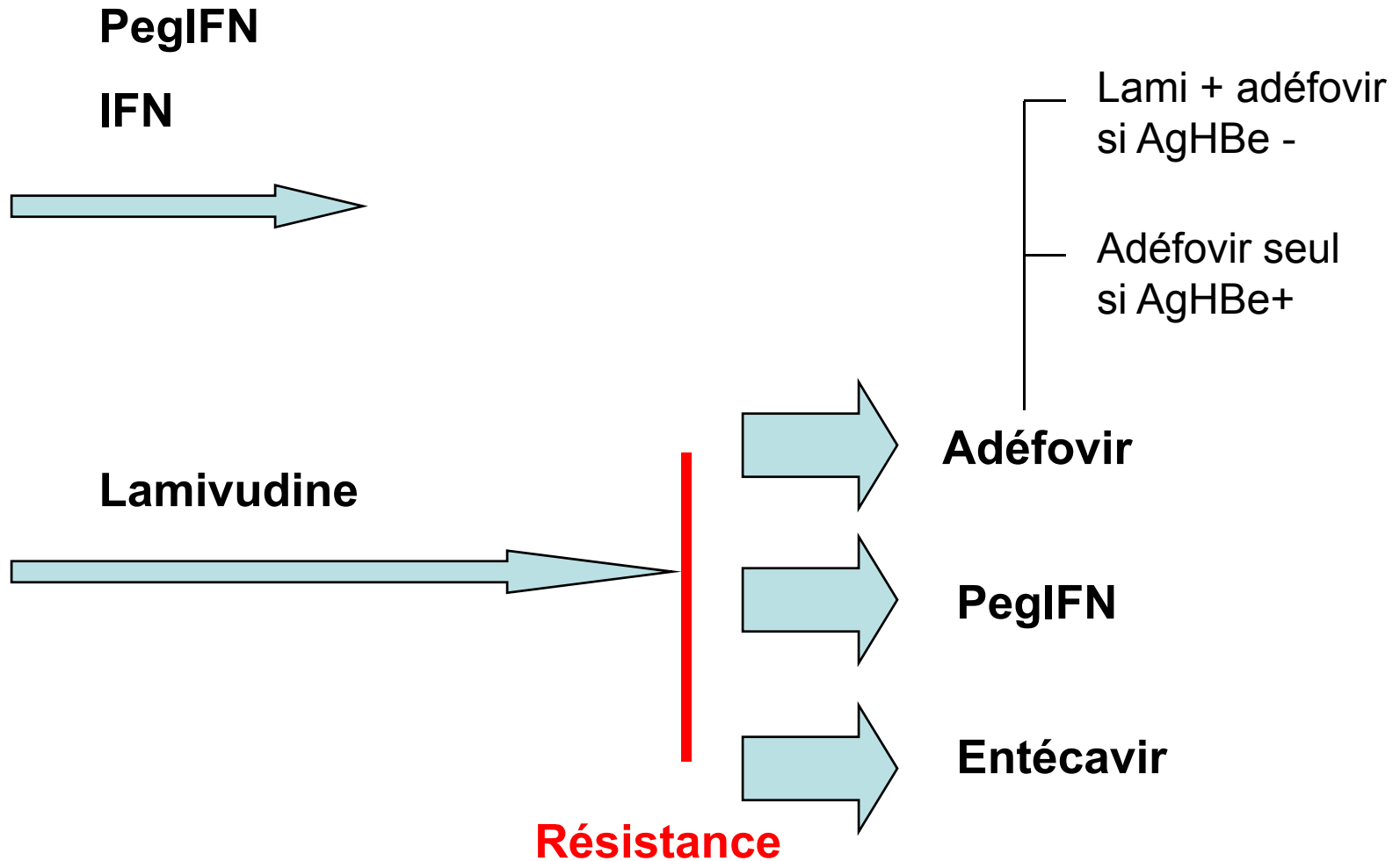
Adéfovir (Hepsera): 2ème ligne

- Hépatite B chronique, DNA élevé, TGP élevé, PBH (fibrose et inflammation)
- Résistant à lamivudine
 - si AgHBe +: adéfovir monothérapie
(si DNA et TGP > à valeurs avant traitement par lamivudine)
 - si AgHBe -: adéfovir + lamivudine
(si DNA > 100.000 UI/ml)

Entecavir (Baraclude): 2ème ligne

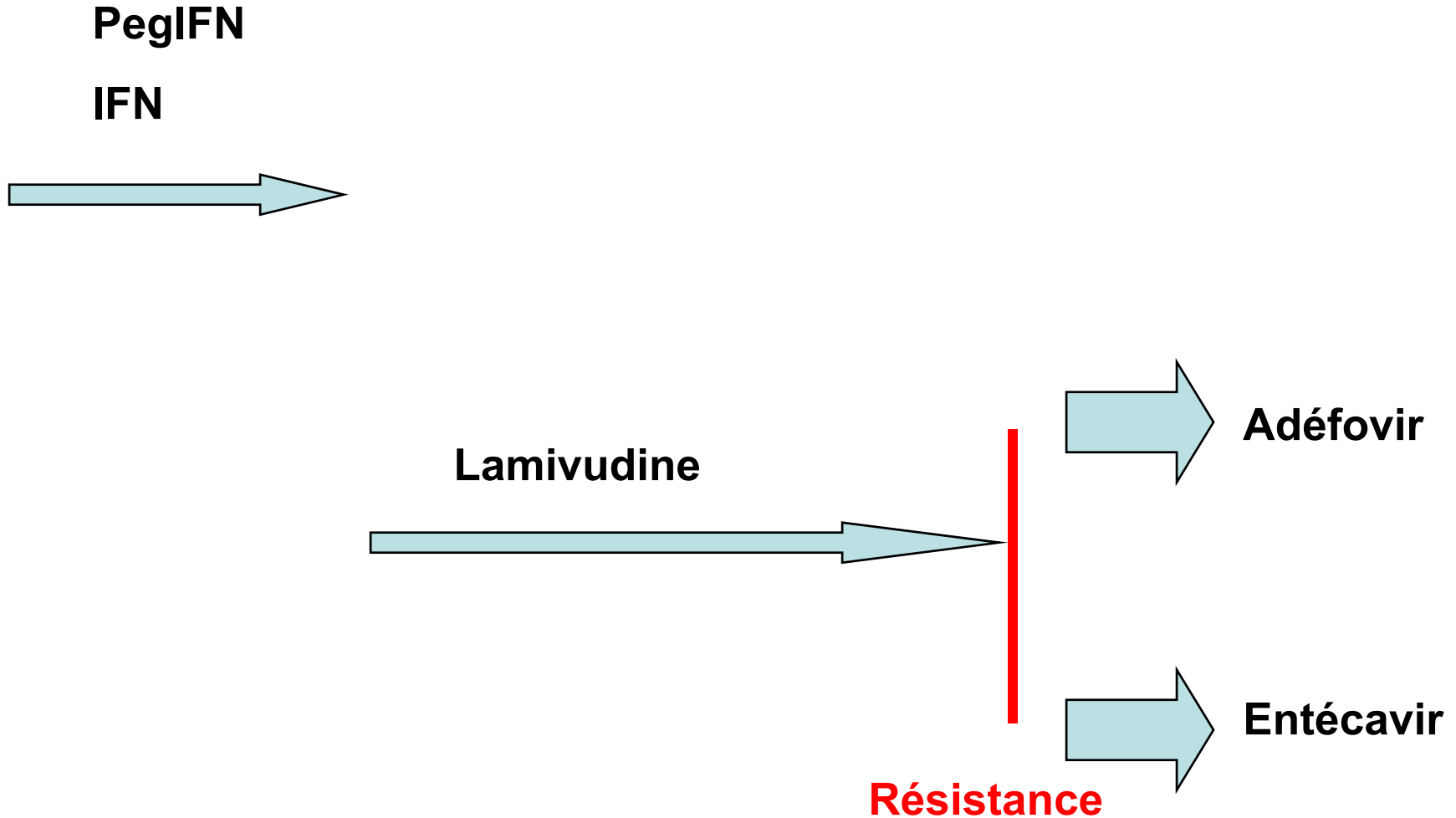
- Hépatite B chronique, TGP élevées, DNA viral +, PBH (fibrose ou activité inflammatoire)
- AgHBe+ ou -
- Résistant à lamivudine
- Absence de cirrhose child B ou C

Situation actuelle



Situation actuelle

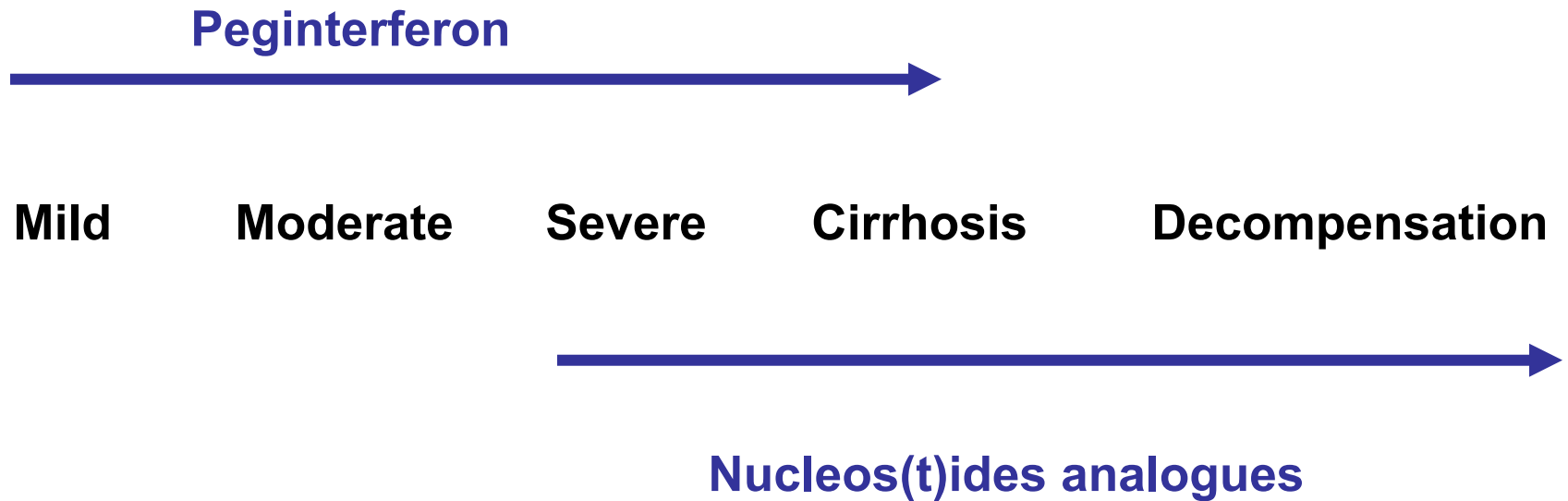
Conseil de bonne pratique



UK recommendations 2007

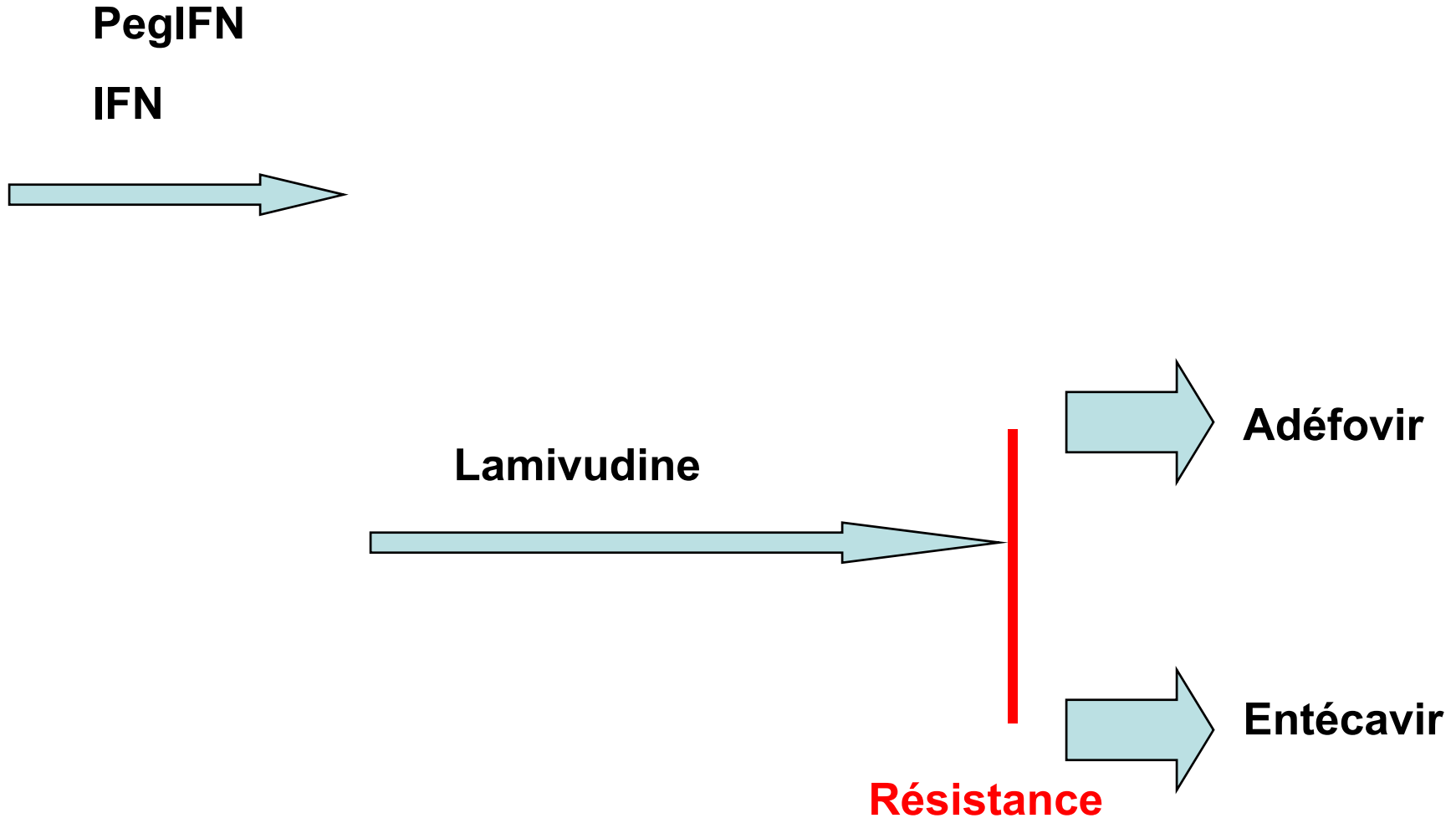
- Peginterferon recommended as first line therapy

Italian Consensus 2007



Situation actuelle

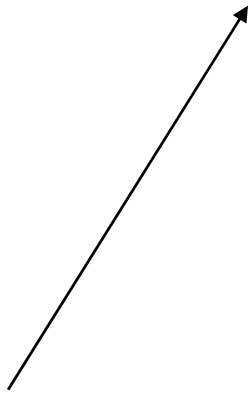
Conseil de bonne pratique



Problèmes en Belgique (1)

PegIFN

IFN

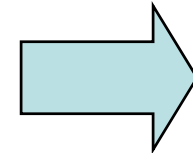


Non remboursement
de PegIFN si cirrhose
compensée

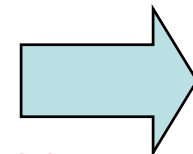
Lamivudine



Résistance



Adéfovir



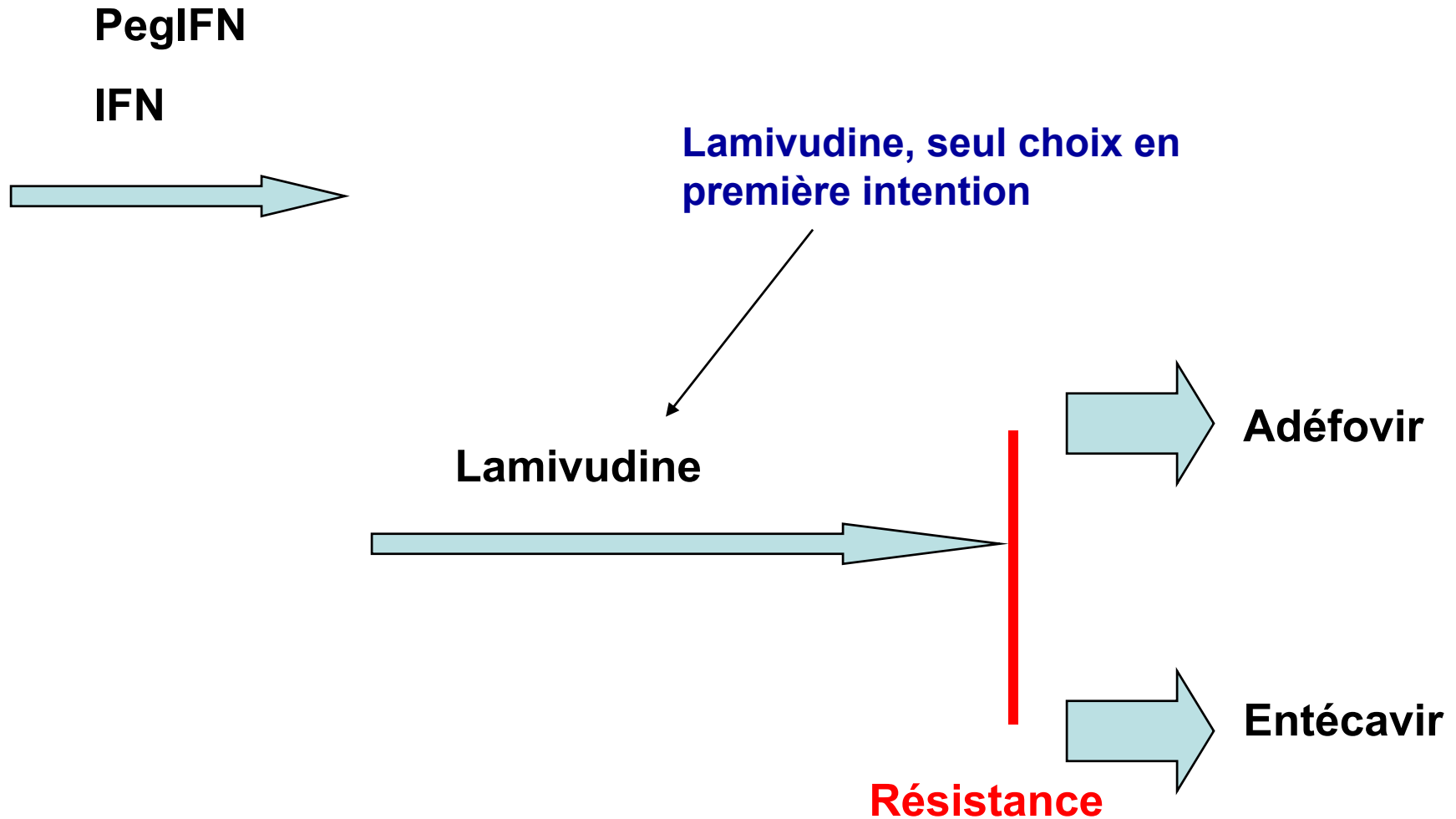
Entécavir

PegIFN is safe and effective in HBeAg + with advanced fibrosis

*Buster E, Hansen B, Buti M, Delwaide J, Niederau C,
Michielsen P et al. Hepatology 2007; 46: 388-394*

Fibrose avancée (n=70)	Fibrose peu avancée (n=169)
• HBeAg seroconversion: 36%	29% (ns)
• HBsAg seroconversion: 9%	4% (ns)
• DNA <400 copies/ml: 13%	7% (ns)
• Virologic response (HBe seroconversion and DNA <10.000 copies/ml): 25%	12% (p=0.02)
• Serious adverse event: 4%	5% (ns)

Problèmes en Belgique (2)



Risk of resistance

	Peg IFN	Lamivudine	Adefovir	Entecavir	Telbivudine
1y	0%	27%	0%	0%	4%
2y	0%	42%	2%	0%	22%
3y	0%	53%	11%	< 1%	
4y	0%	70%	18%		
5y	0%		29%		

Entecavir in lamivudine resistant patients: resistance in 38% after 3 years

Recommendations for the specific current Belgian situation (2):

- *Reimbursement of non L-nucleosides adefovir , entecavir currently - and tenofovir in near future - for use in 1st and 2nd line is needed for optimal long term HBV disease management.*
- *Avoid continued lamivudine 1st line treatment to prevent further cumulative resistance problems. Its use should be restricted to add on therapy in case of resistance to 1st line adefovir therapy and indications with limited duration of therapy such as prevention of reactivation of inactive carriers undergoing chemotherapy.*
- *For current lamivudine resistant patients, adefovir add on therapy should be reimbursed.*

Schéma plus performant

(selon les connaissances actuelles)

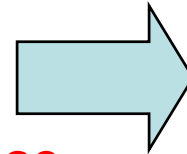
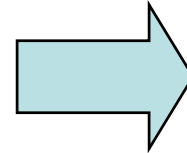
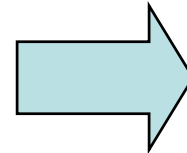
PegIFN

IFN



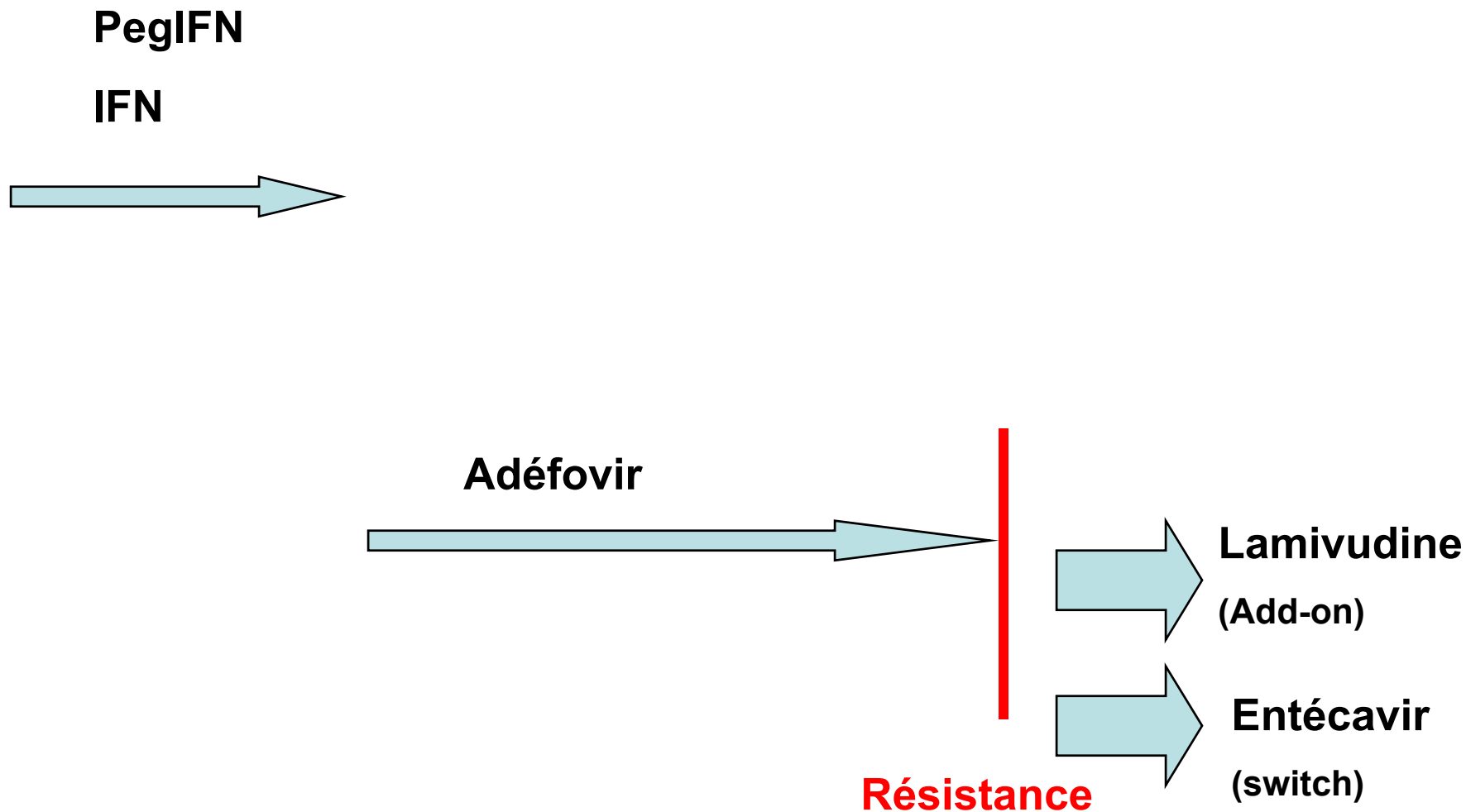
Entécavir

Adéfovir



Résistance

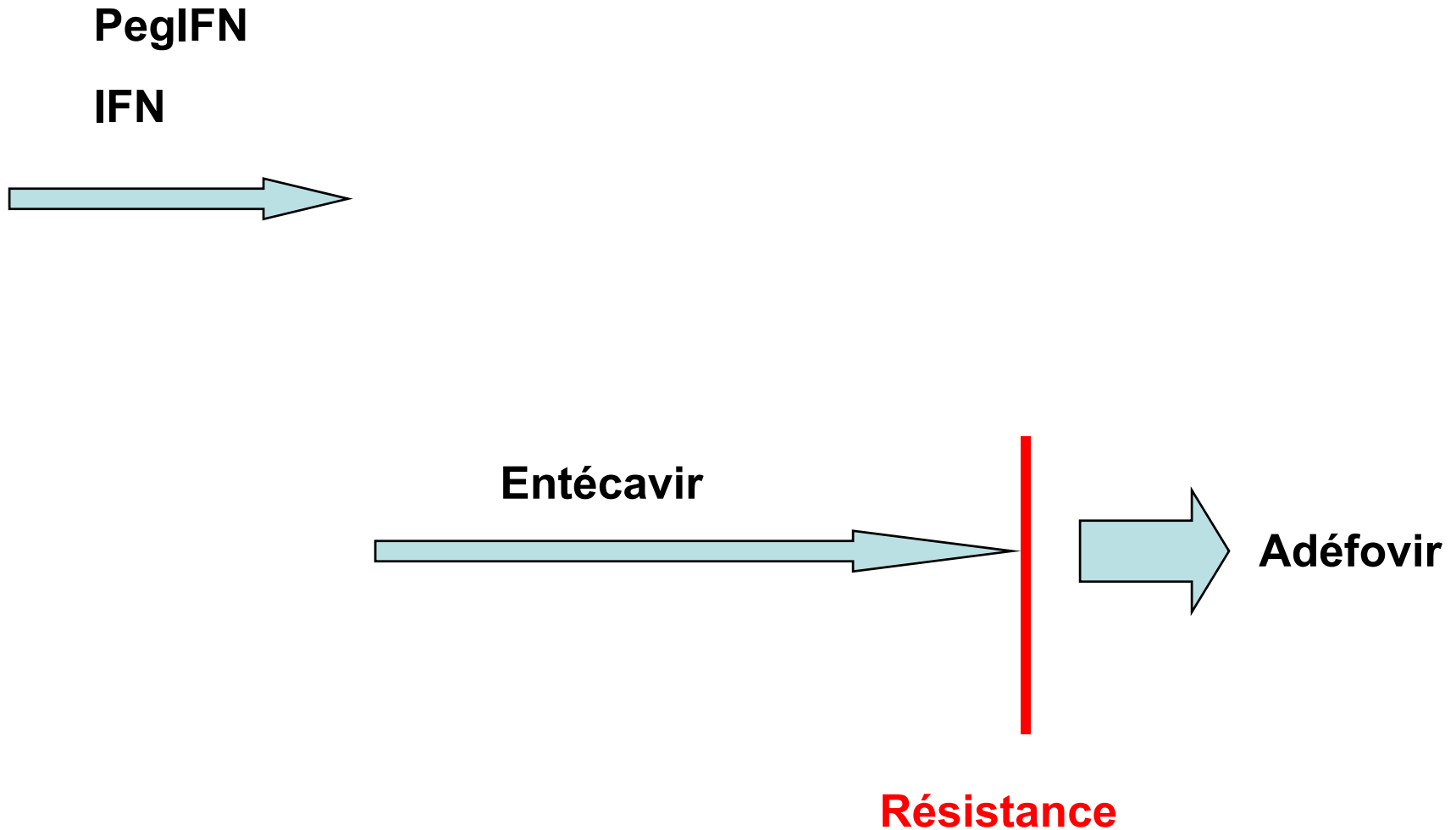
Schéma potentiellement plus performant (selon les connaissances éparses actuelles)



Needs in Belgium

- Second line therapies:
 - **Entecavir switch** for lamivudine resistance (= available), and **for adefovir resistance** (given in lami R pts)
 - Adefovir add on for lamivudine resistance in HBeAg+ and HBeAg – patients (not only for HBeAg-)
 - **Lamivudine add on for adefovir** (given to NA naive pts) resistance
 - Peg-IFN in case of resistance to any NA

Schéma potentiellement plus performant (selon les connaissances très préliminaires actuelles)



Place résiduelle de la lamivudine en première ligne

PegIFN

IFN



Lamivudine

Traitement de courte durée:

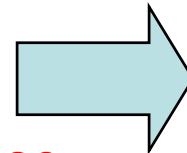
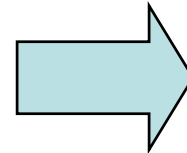
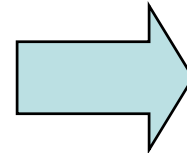
-réactivation HBV sous chimiothérapie

-HBV aigu sévère

-En pré-transplantation si délai d'attente < 6 mois

Entécavir

Adéfovir



Résistance

Recommendations to *prevent HBV reactivation* in immunosuppressed patients

*-All patients who are candidates for **chemo- or immunosuppressive** therapy should be screened for HBV markers and all naïve patients should be immunized against HBV as soon as possible.*

*-Patients who are **HBsAg positive** should be offered **pre-emptive** treatment with **lamivudine** at 100 mg/day **regardless of their HBeAg or HBV DNA status**. In these patients, lamivudine should be **started at least 1 week before** initiation of chemotherapy and should be continued for **at least 3 months after** discontinuation of chemotherapy.*



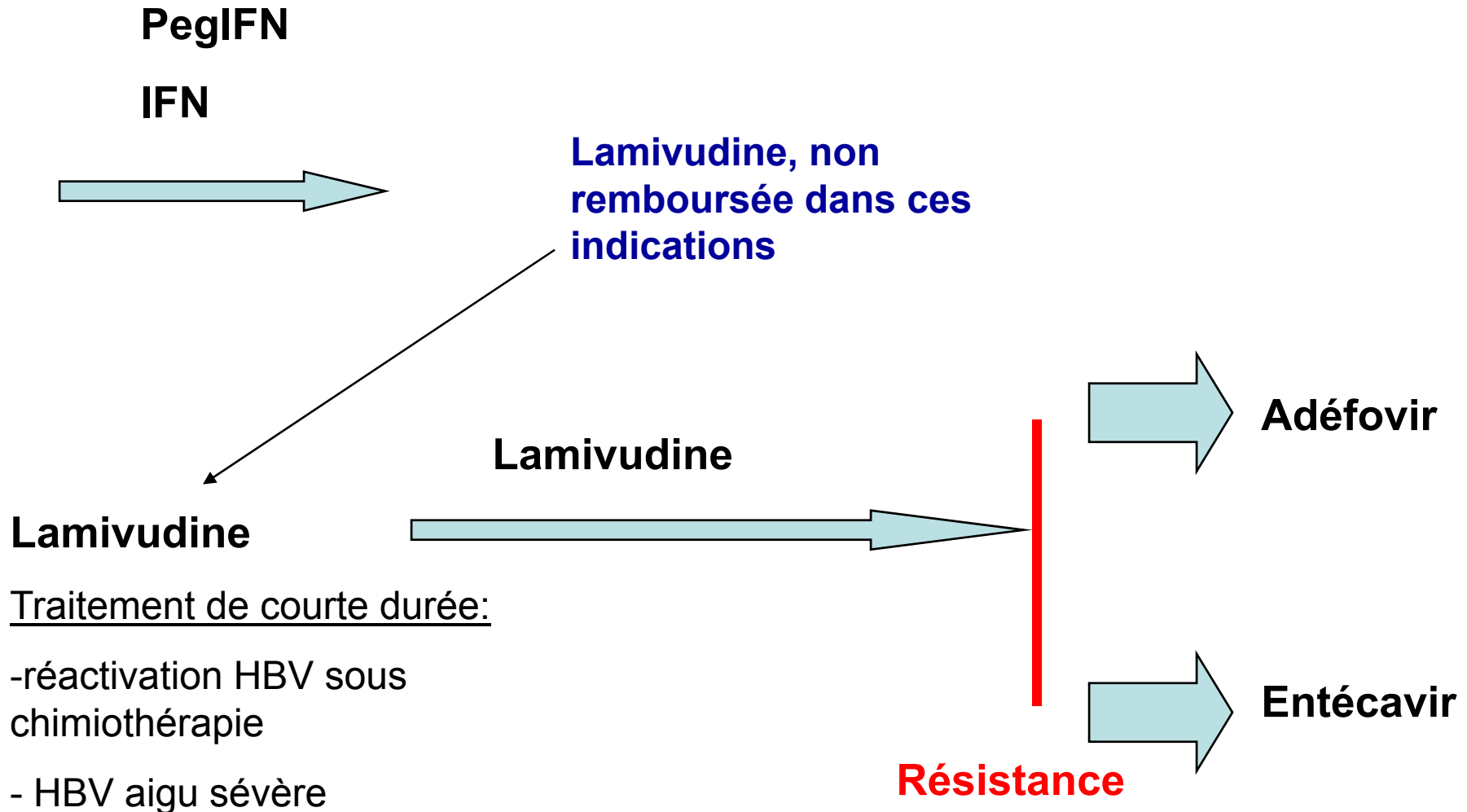
Recommendations to **prevent HBV reactivation** in immunosuppressed patients

- In case of pre-chemotherapy HBV DNA ≥ 2000 IU/ml, immunosuppressive chemotherapy should be preferably started when viral load has declined under 2000 IU/ml and should be continued for at least 1 year.
- Patients who are HBsAg negative but positive for anti-HBc alone with HBV DNA detectable (occult HBV infection) should be treated similarly as patients positive for HBs Ag.
- Patients who are **HBsAg negative, anti-HBc positive, anti-HBs positive (resolved infection)** should not be treated pre-emptively but should be **monitored for ALT elevation and HBV DNA rise** (every 2 or 4 weeks) during chemotherapy and 3 to 6 months after stopping immunosuppressive therapy

Recommendations for **acute HBV**

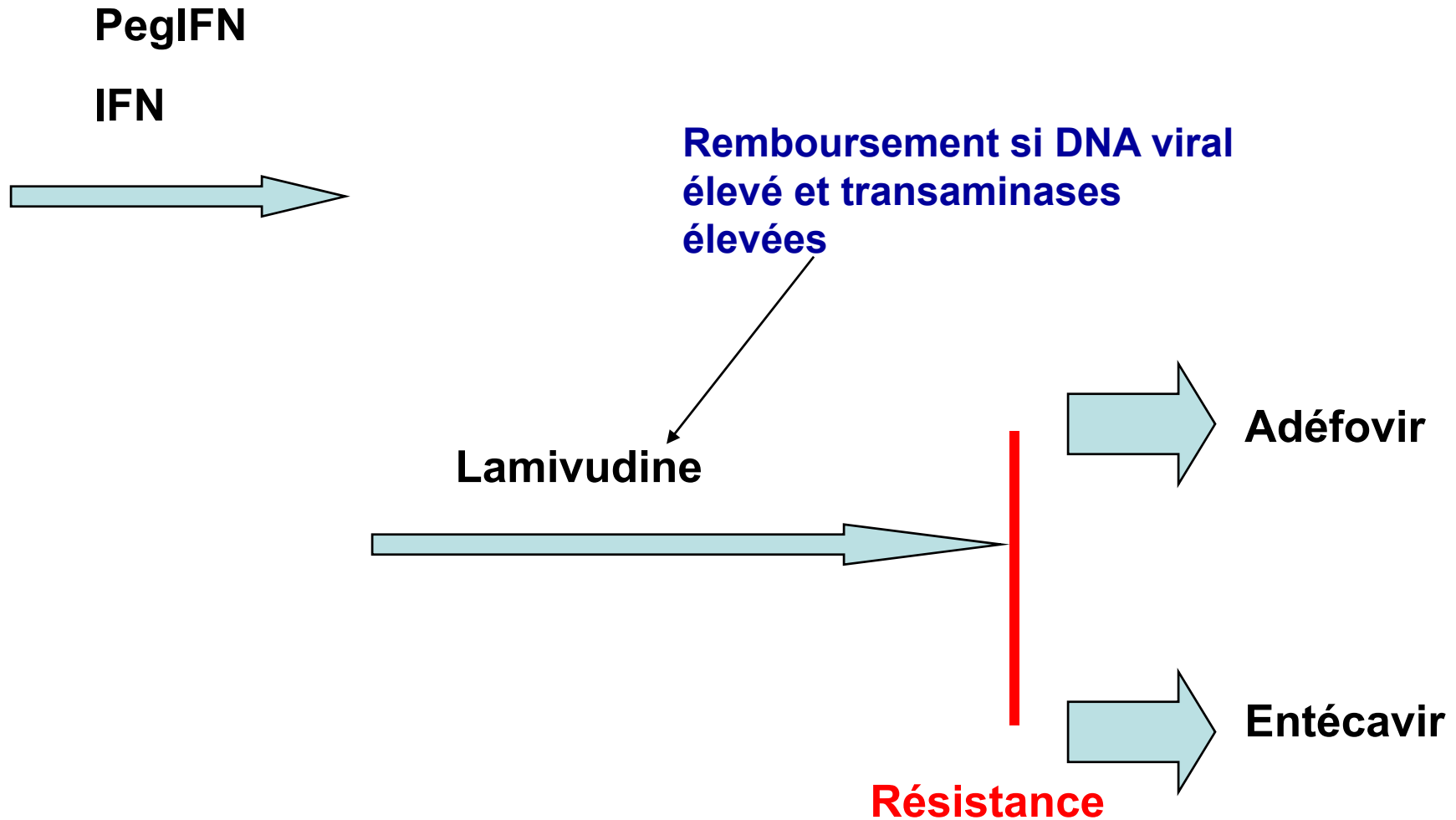
- *Typical acute hepatitis B does not need antiviral therapy.*
- *Patients with severe acute hepatitis B (PT < 50% and/or hepatic encephalopathy) should be treated by nucleot(s)ide analogues (lamivudine, telbivudine or entecavir are preferred) as soon as the first sign of liver failure occurs. In these case the patient should also be considered for liver transplantation.*
- *In patients treated for their acute HBV, should maintain their treatment until HBsAg clearance is observed and confirmed.*
- *If transplanted, therapy should be maintained at least 1y + HBIG.*

Problèmes en Belgique (3)



Problèmes en Belgique (4)

Cirrhose compensée

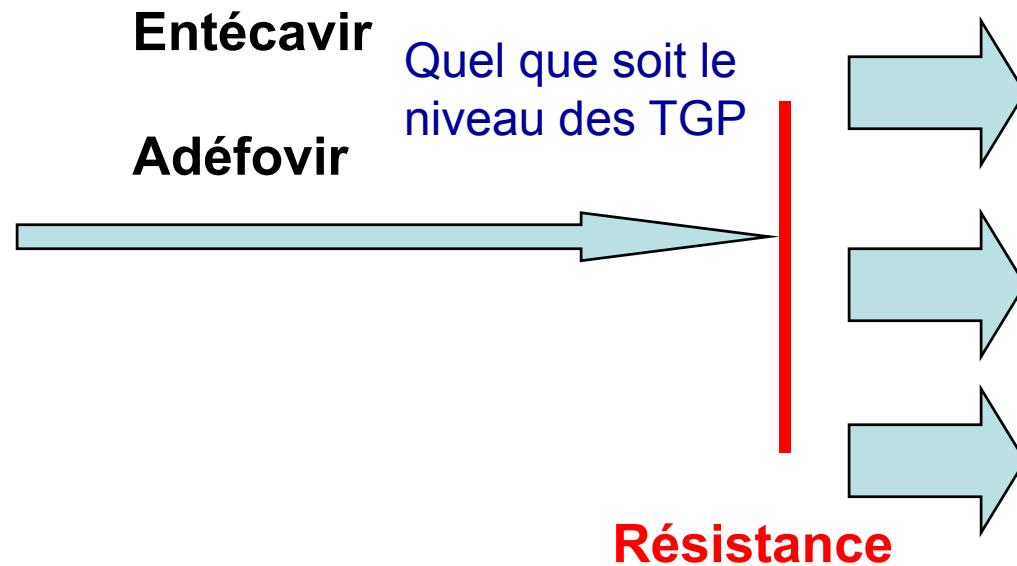


Recommendations for **compensated** cirrhosis

- *Patients with compensated cirrhosis should be considered for treatment if **HBV DNA is ≥ 2000 IU/ml regardless of ALT levels.***
- *Given the risk of Interferon-induced flares, nucleo(t)side analogues should be preferred.*
- *In view of the need for long term therapy and because of the rapid emergence of resistant mutants with lamivudine, **first-line treatment with adefovir or entecavir** should be started.*

Schéma plus performant

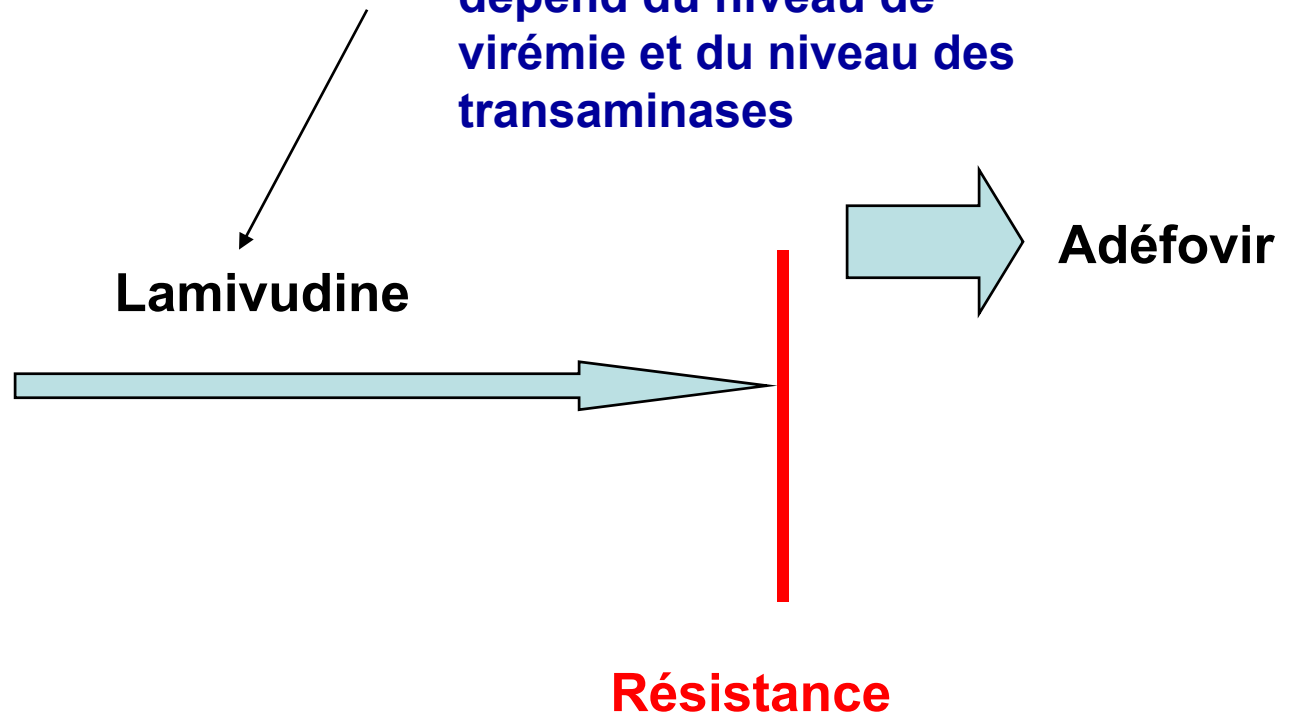
Cirrhose compensée



Problèmes en Belgique (5)

Cirrhose décompensée

- 1) Lamivudine, seul choix en première intention
- 2) Accès au remboursement dépend du niveau de virémie et du niveau des transaminases

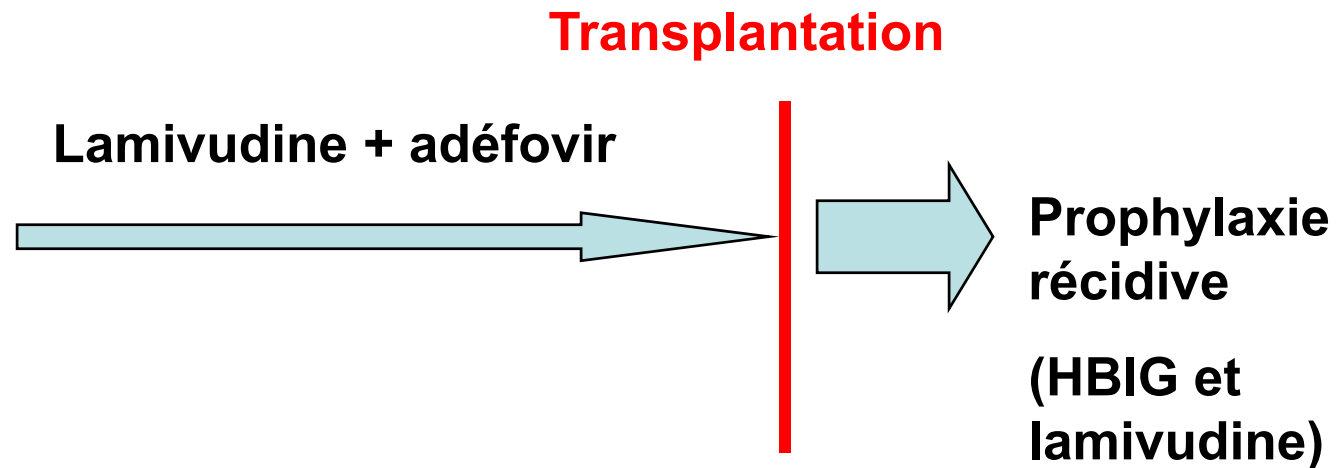


Recommendations for **decompensated cirrhosis**

- *Interferon- α and Peg-Interferon- α should not be used in patients with decompensated cirrhosis.*
- *In decompensated cirrhosis, **independent of the viral load**, antiviral treatment should be promptly initiated with nucleos(t)ide analogues producing rapid viral suppression and low risk of resistance.*
- *Currently, the **combination of lamivudine and adefovir should be recommended** for achieving rapid effect and reducing the emergence of resistance.*
- ***Entecavir** is a promising treatment in this setting but clinical data are currently lacking.*
- *Evaluation for liver **transplantation** should be considered.*

Problèmes en Belgique (5)

Cirrhose décompensée



Belgian Guidelines

Belgian Association for the Study of the Liver
BASL



October 2007



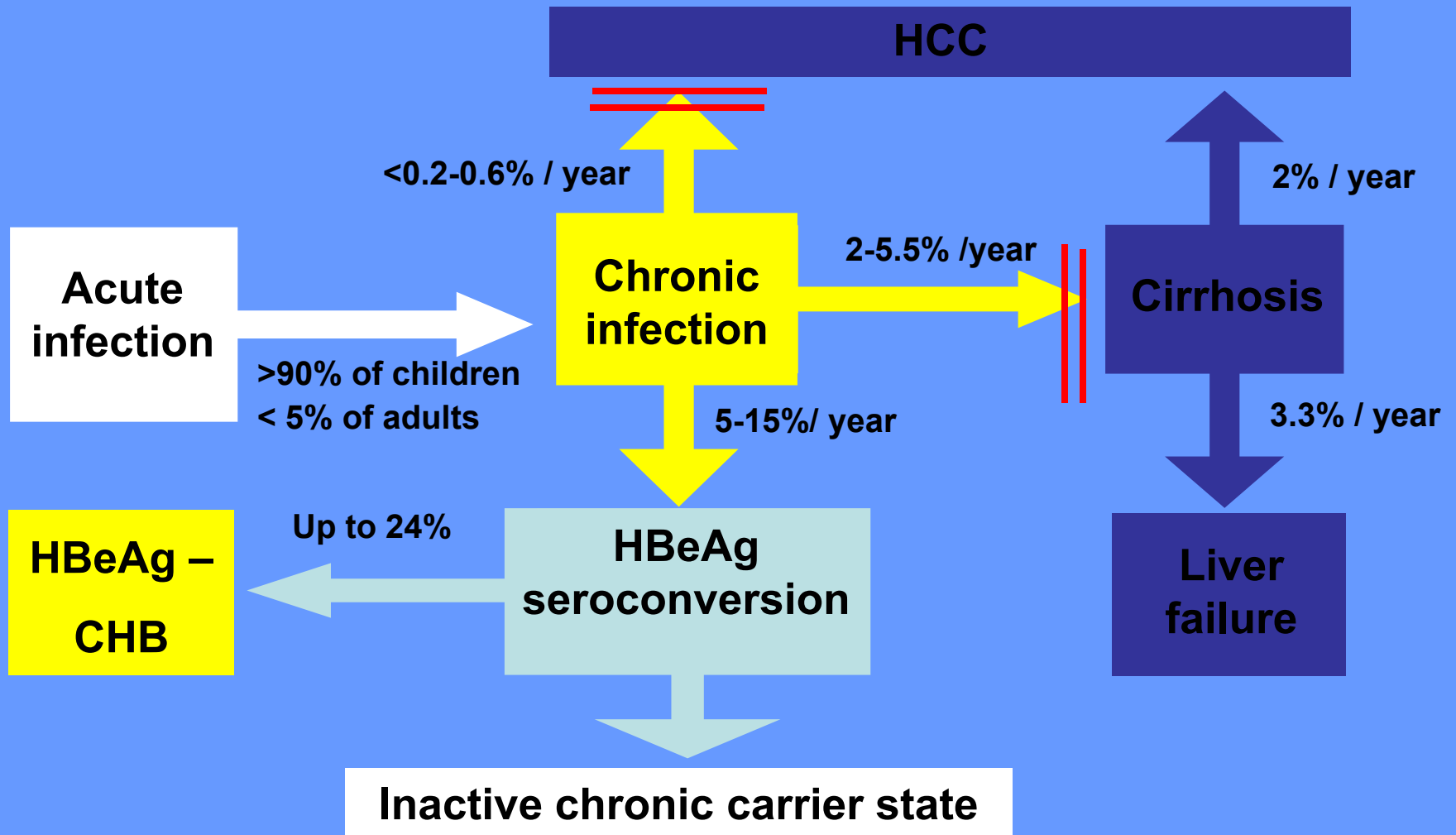
Introduction

- These guidelines are made by all BASL steering committee members
- Provide data-supported approach
- These guidelines may be updated regularly with new information

Prevalence and importance of HBV

- In Western Europe: < 2% HBsAg carriers
- In Belgium: import from high and medium endemic countries
- Natural evolution

Natural History of HBeAg + Chronic HBV



EASL Jury *J Hepatol* 2003;38:533-40
Hsu YS et al. *Hepatology* 2002;35:1522-7

Cost-effectiveness of HBV

- Yearly cost per patient increases with increasing disease progression (Europe and Canada)

Disease state	Cost
Chronic HBV	€ 1,093 - € 3,396
Compensated cirrhosis	€ 1,134 - € 3,997
Decompensated cirrhosis	€ 5,292 - € 8,842
HCC	€ 3,731 - € 9,352
Liver transplantation	€ 25,165 - € 84,568

Definitions:



Primary nonresponse: a $\leq 1 \log_{10}$ IU/mL drop in HBV DNA after 6 m

Virologic breakthrough: increase in serum HBV DNA by $\geq 1 \log_{10}$ (10-fold) above nadir after achieving virologic response, during continued treatment

Biochemical breakthrough: increase in ALT above upper limit of normal after achieving normalization, during continued treatment

Genotypic resistance: detection of mutations that have been shown in *in vitro* studies to confer resistance to the NA that is being administered

Phenotypic resistance: *in vitro* confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered

Indications for treatment: HBeAg-positive pts

- Patients with **high levels of DNA (>20,000 IU/mL)** and **elevated ALT** levels greater than two times the upper limit of normal are the most appropriate candidates to therapy.
- Patients with **low levels of HBV DNA (<20,000 IU/mL)** and **normal ALT** (immune tolerant phase) are not recommended routinely for treatment. Due to the low levels of HBV DNA, the majority of these individuals are at low risk of disease. They should be monitored to ensure stability of HBV DNA and ALT levels.
- Patients with **high levels of HBV DNA (>20,000 IU/mL)** with **persistent borderline normal or slightly elevated ALT**, have a low probability to obtain HBeAg seroconversion with treatment. **Liver biopsy should be considered, particularly in individuals older than 35-40 years of age**, and treatment should be considered if moderate/severe inflammation or significant fibrosis are found.
- Liver biopsy is usually not necessary in young patients (below 30y) who are **HBeAg-positive and have persistently normal ALT**. In the absence of biopsy, patients should be monitored to observe for increase in ALT level

Indications for treatment: HBeAg-negative pts

- The recommendations are the same as for HBeAg-positive pts.
- The **threshold of HBV DNA** levels for considering a treatment is lower: ≥ 2000 IU/mL.

Indications for treatment: decompensated pts

- Treatment is considered regardless of the HBeAg status but with detectable HBV DNA levels

Drugs available

Drug	Cost per year	in B	TT duration
Peg-interferon α2a	11.468 €	1°line	48w
Lamivudine	749 €	1° line	?
Adefovir	6.159 €	2° line	?
Tenofovir	5.811 USD*	No	?
Entecavir	6.159 € °°	2°line	?
Telbivudine	4.536 € °	No	?
Emtricitabine	\$ 3,872*	No	?

*At the time there are no prices available for these drugs in Belgium, we used the prices from the paper of Hoofnagle et al {Hoofnagle, 2007}.

°: the prices given for telbivudine are these of our surrounding European countries, the price in Belgium is not published yet

°°: the price for entecavir 1mg and not for the 0.5 mg dose

First line drugs

- **Pegylated interferon** (no resistance, 27% seroconversion rate HBeAg)
- **Nucleos(t)ide analogues** but:
 - chance to cure depends on rapidity of viral decline: efficacy, potency
 - chance to develop resistance depends on genetic barrier of the drug and rapidity of viral decline => **thus choose the drug with most potent antiviral activity and the lowest resistance rate** (entecavir, adefovir, tenofovir, telbivudine)
 - Occurrence of cross resistance and transmission of resistant strains

Efficacy for HBeAg +



	Peg IFN	Lami	Adef	Entec	Telbi
DNA decrease EOT (\log_{10})	- 4.5	-5.8	- 3.5	-6.9	- 6.5
HBeAg seroconversion EOT (1y TT)	27%	20%	12%	21%	22%
Histologic improvement EOT	38%	49-56%	53%	72%	65%
ALT normalisation EOT	39%	40-75%	48%	68%	77%
Cost per year	€ 11,468	€ 749	€ 6,159	€ 6,159	€ 4,536

Efficacy for HBeAg -



	Peg IFN	Lami	Adef	Entec	Telbi
DNA decrease EOT (\log_{10})	- 4.1	- 4.2	- 3.9	- 5	- 5
Histologic improvement EOT 1y	48%	40%	64%		
ALT normalisation EOT	38%	73%	72%		74%
Cost per year	€ 11,468	€ 749	€ 6,159	€ 6,159	€ 4,536

Follow up of the patients

- **FU during therapy:**

- **Peg IFN:** monthly lab tests + HBV DNA every 3m

- **Nucleos(t)ide analogues:**

- HBV DNA every 3 m to detect viral breakthrough (resistance) and primary non-response ($< 1\log_{10}$ decrease at 6m).

- Check for genotypic resistance?

- Depending on the response at 6m, therapy should be adapted. 3 monthly FU of DNA is required.

- **FU after stop therapy:**

HBV serology and HBV DNA at 6m



Current situation in Belgium

a. Pegasys (48 w)

- Pegasys voor CHB die :
- nooit werden behandeld = naive ptn
- voordien werden behandeld met lami (zou ook moeten kunnen voor andere nucleos(t)ide analogen)
 - stopgezet > 6m na vervaldatum vd laatste machtiging voor terugbetaling v deze molecule en een hervat HBV DNA gerealiseerd op intervallen $\geq 3m$: wie kan dat begrijpen? = wetstraatlees

Bilan omvat:

- HBsAg + $\geq 6m$ (toch niet altijd mogelijk om 6 m te wachten)
- HBeAg +/-
- HBV DNA > 10^5 copies/ml ≈ 20.000 IU/mL (voor HBeAg neg: vanaf 10^4 copies/ml ≈ 2.000 IU/mL)
- ALT > 2N
- Leverbiopsie: matig tot ernstige necrose
- Geen biopsie indien hemofilie of antico
- Ik bevestig de afwezigheid van precirrose en cirrose, LTx en co-infectie met HIV (goed gecompenseerde cirrose mogelijks geen probleem; pre-cirrose = geen erkende wetenschappelijke term; waarom niet met LTx en HIV?)

Current situation in Belgium

b.1. Lamivudine (Zeffix) tabletten 100 mg

Eerste aanvraag voor 12m

- 3 voorwaarden moeten voldaan zijn:
 - HIV negatief
 - HBV DNA +
 - Verhoogde ALT (stel cirrose met hoge HBV DNA en normale transen: ook indicatie voor behandeling)
- HBeAg +/-
- + één vd volgende:
 - leverbiopsie toont fibrose of inflammatie
 - hemofilie pt
 - antico pt
- Ptn die moeten lami krijgen als profylaxe voor chemoTT? Vaak N ALT waarden en geen verhoogd HBV DNA
- Lami post Ltx indien geen medicatie vooraf
- Lami niet meer eerste lijnsbehandeling voor CHB

Hernieuwing (voor maximaal 5 jaar)

- omstandig verslag
- biologische controles max 3m oud
- aantonen dat het vervolg vd behandeling medisch verantwoord



Current situation in Belgium

b.2. Lamivudine (Zeffix) oplossing 5 mg/ml

Eerste aanvraag voor 12m

- 3 voorwaarden moeten voldaan zijn:
 - HIV negatief
 - HBV DNA
 - Verhoogde ALT

HBeAg +/-

- + één vd volgende:
 - leverbiopsie toont fibrose of inflammatie
 - hemofilie pt
 - antico pt

Pt voldoet gelijktijdig aan volgende 2 voorwaarden:

- Creatinine klaring < 50 ml/min
- Heeft orgaantransplantatie ondergaan of staat op wachtlijst
- **Waarom niet buiten setting van transplantatie?**

Hernieuwing (voor maximaal 5 jaar)

- omstandig verslag
- biologische controles max 3m oud
- aantonen dat het vervolg vd behandeling medisch verantwoord is



Current situation in Belgium



c. Adefovir (Hepsera)

Eerste aanvraag voor 12m

A. chron HBV met :

- stijging ALT
- aanwezigheid v HBV DNA
- leverbiopsie toont fibrose én inflammatie **(waarom hier EN en in de andere OF)**
- CHB met hemofilie:
 - stijging ALT met 2x HBsAg + met 6m interval
- OF
- gedecompenseerde cirrose Child klasse B of C
- Voor beide situaties
 - heeft de pt een behandeling ondergaan met lami die haar doeltreffendheid verloren heeft, bewezen door :
 - Voor HBeAg + vóór start lami: terugkeer van ALT en van HBV DNA boven de niveaus gemeten voor aanvang van lami of door verslechtering histologisch beeld
 - Voor HBeAg negatief vóór start lami: terugkeer van HBV DNA waarde > 100.000 IU/ml of door verslechtering histologisch beeld
 - **Waarop is de waarde 100.000 IU gebaseerd bij HBeAg negatieven? De definitie van resistentie zoals nu internationaal gedefinieerd moet aanvaard worden als criterium: stijging van > 1log₁₀ tov nadir**

B. Maximale dosis = 10 mg/d

Current situation in Belgium



Adefovir (Hepsera)

C. De behandeling wordt gestopt wanneer:

- verlies van doeltreffendheid wanneer ALT en HBV DNA terugkeren boven de waarde vóór aanvang van adefovir behandeling
- in geval van seroconversie indien HBeAg + vóór behandeling: ontstaan van HBeAb, verdwijnen van HBeAg en HBV DNA aangetoond door 2 bloedonderzoeken met minstens 6 weken tussentijd (moet 6 maand zijn)
- in geval van seroconversie indien HBeAg neg (precore mutant) voor behandeling: ontstaan van HBs seroconversie, verdwijnen van HBsAg en HBV DNA aangetoond door 2 bloedonderzoeken met minstens 6 weken tussentijd (moet 6 maand zijn, men moet 6m behandeling verder zetten wanneer seroconversie opgetreden is: zowel voor HBeAg +/- =consolidatie behandeling)
hier adefovir noodzakelijk als eerste lijn ipv tweede lijn

D. Hernieuwing (voor maximaal 4jaar = 5 jaar in totaal)

- Omstandig verslag + aantonen dat geen verlies v doeltreffendheid aanwezig is of seroconversie aanwezig is zoals beschreven in punt C: **cave mogelijkheid om nog 6m consolidatiebehandeling te geven**
- **indien ptn goed zijn, (laag HBV DNA, geen resistentie: onbeperkte goedkeuring en niet max 3 of 5j). Geldt ook voor andere NA**

E. Terugbetaling samen met andere middelen:

- Adefovir + Intron A of Roferon is nooit toegestaan
- Adefovir + lami: enkel terugbetaald in HBeAg negatieve (precore) patiënten, resistent tov lami (waarom enkel in HBeAg - en niet HBeAg + => kans op resistentie veel minder)

Current situation in Belgium



d. Entecavir (Baraclude) 1mg

- **Eerste aanvraag voor 12m**
- **A. chron HBV met :**
 - stijging ALT
 - aanwezigheid v HBV DNA
 - leverbiopsie toont fibrose of inflammatie
- **CHB met hemofilie of onder antico:**
 - stijging ALT met 2x HBsAg + met 6m interval**OF**
- **Gedecompenseerde cirrose Child klasse B of C zijn uitgesloten (hier is er evenwel nood!)**
- **De pt een behandeling ondergaan met lami die haar doeltreffendheid verloren heeft, bewezen door terugkeer van ALT en van HBV DNA boven de niveaus gemeten vóór aanvang van lami of door verslechtering histologisch beeld (de internationale definitie van resistentie moet als criterium worden erkend)**
- **B. Maximale dosis = 1mg/d**
- **C. De behandeling wordt gestopt wanneer:**
 - verlies v doeltreffendheid wanneer ALT en HBV DNA terugkeren boven de waarde vóór aanvang van entecavir behandeling of door verslechtering van histologisch beeld
 - in geval van seroconversie indien HBeAg + voor behandeling: ontstaan van HBeAb, verdwijnen van HBeAg en HBV DNA aangetoond door 2 labos met minstens 6 weken tussentijd **(moet 6 maand zijn: om consolidatie behandeling te garanderen)**

Current situation in Belgium

Entecavir (Baraclude) 1mg

- **Eerste aanvraag voor 12m**
- - in geval van seroconversie indien HBeAg neg (precore mutant) voor behandeling: ontstaan van HBs seroconversie, verdwijnen van HBsAg en HBV DNA aangetoond door 2 labos met minstens 6 weken tussentijd (**moet 6 maand zijn om consolidatie behandeling te garanderen**)
- **Noodzaak entecavir als eerstelijnsbehandeling te kunnen gebruiken in een dosis 0,5 mg/d**
- **Indien lami resistentie => switch naar entecavir maar cross resistance aanwezig: dus is veel minder efficiënt! Met de huidige strategie legt men hypotheek op latere behandelingen met morbiditeit en ziektekost als gevolg!**
- **D. Hernieuwing** (voor maximaal 2 jaar = 3 jaar in totaal)
- Omstandig verslag + aantonen dat geen verlies v doeltreffendheid aanwezig is of seroconversie aanwezig is zoals beschreven in punt C
- **Indiende behandeling efficiënt blijft (laag HBV DNA, geen resistentie: onbeperkte goedkeuring en niet max 3 of 5j): MAAR: Momenteel geen gegevens**
- **Geldt ook voor andere NA (idem)**
- **E. Terugbetaling samen met andere middelen:**
 - Zeffix, Hepsera, Intron A of Roferon, Pegasys is nooit toegestaan

Needs in Belgium



- **HBV DNA** measurements 4x/year reimbursed (now 2 times)
- **First line therapies:**
 - entecavir
 - adefovir
 - telbivudine
 - Peg-IFN (is already available)
 - lamivudine is available in first line but should only be used in special situations (prevention of reactivation without necessity of biopsy or abnormal liver tests, fulminant hep B without necessity of biopsy, preTx if waiting time short)

Needs in Belgium: when to stop TT

Peg-IFN: treat 48 weeks and stop

Nucleos(t)ide analogues:

-HBeAg+ patients: if HBe seroconversion occurs (development of anti HBeAb) treatment should be continued for at least 6 m after seroconversion. The seroconversion should be confirmed on 2 lab tests: then TT can be stopped.

- HBeAg- patients: if HBs seroconversion occurs (development of anti HBsAb) treatment should be continued for at least 6 m after seroconversion. The seroconversion should be confirmed on 2 lab tests: then TT can be stopped.

Treatment in which chronic HBV patients

- **HBeAg +:**

- if HBV DNA > 20,000 IU/mL
- Liver biopsy: inflammation **or** fibrosis
- Liver tests ALT may be normal
- Switch or add on therapy should be possible if virological breakthrough is observed (> 1log₁₀ increase HBV DNA compared to nadir)
- Reimbursement until HBe seroconversion (except peg IFN = 48w tt), with 6m consolidation tt
- If cirrhosis: treat if HBV DNA+

Treatment in which chronic HBV patients

- **HBeAg -:**

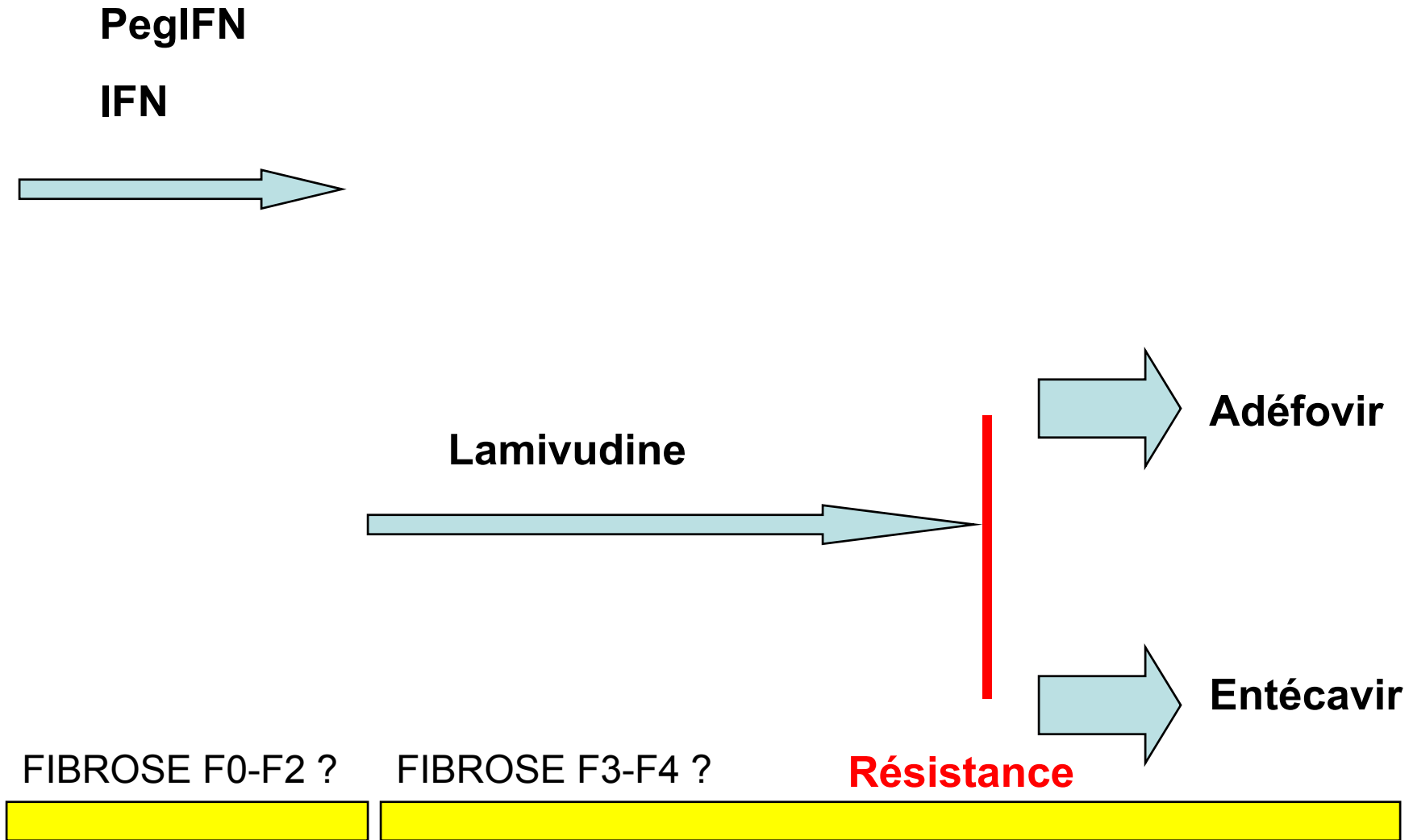
- if HBV DNA > 2.000 IU/mL
- Liver biopsy: inflammation or fibrosis
- Liver tests ALT may be normal
- Switch or add on therapy should be possible if virological breakthrough is observed (> 1log₁₀ increase HBV DNA)
- Reimbursement until HBs seroconversion (except peg IFN = 48w tt), with 6m consolidation tt
- If cirrhosis: treat if HBV DNA+

Treatment in **Special groups**

- **HBV-HDV** coinfection: peg-IFN 1y for HDV
- **HBV-HIV**: peg-IFN should be possible
- **Fulminant hep B**: lamivudine
- **Cirrhosis**: if HBV detectable: treat with NA (including entecavir)
- **HBV reactivation prevention**: lamivudine (start 1w before IS until 3m after exposure; if DNA pre chemo > 2.000 IU/mL: treat until < 2000 IU/mL)
- **HBV and LTx**: HBIG + NA continuation independently of HBV DNA (lifelong)

Situation actuelle

Conseil de bonne pratique



Pr Trépo (*SRBGE Bruxelles 2006*)

- C
- B

Pr Trépo (*SRBGE Bruxelles 2006*)

- Curable
- Bad

Hépatite B

- Potentiellement mortelle
- Evolution difficilement prévisible
- Nombreux traitements
- Non curable

Hépatite B

Quels sont les meilleurs schémas thérapeutiques?

Hépatite B

Quels sont les meilleurs schémas thérapeutiques?

- Personne ne sait !

Prise en charge du patient porteur du virus B: recommandations de la BASL 2007

Dr Jean Delwaide
CHU Sart Tilman

Recommendations for the specific current Belgian situation (2):

- *Reimbursement of non L-nucleosides adefovir , entecavir currently - and tenofovir in near future - for use in 1st and 2nd line is needed for optimal long term HBV disease management.*
- *Avoid continued lamivudine 1st line treatment to prevent further cumulative resistance problems. Its use should be restricted to add on therapy in case of resistance to 1st line adefovir therapy and indications with limited duration of therapy such as prevention of reactivation of inactive carriers undergoing chemotherapy.*
- *For current lamivudine resistant patients, adefovir add on therapy should be reimbursed.*