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연수강좌

Management of chronic hepatitis B : recent advance in the treatment of antiviral resistance

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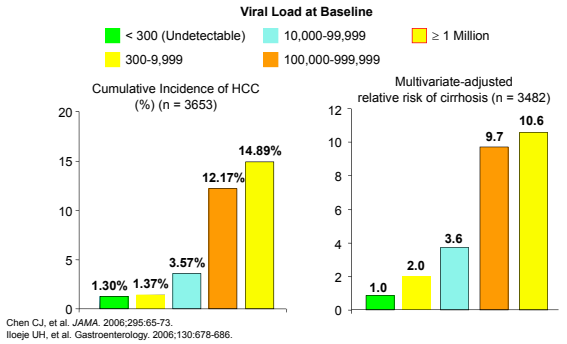
REVEAL Study: HBV DNA Levels and Long-Term Outcomes



Chen CJ, et al. *JAMA*. 2006;295:65-73.
Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

CHB treatment goal: sustained suppression of HBV replication

Primary goal of treatment

Sustained suppression of HBV replication to the lowest possible level[1,2,3]

Outcomes

- Delay in progression to cirrhosis and HCC[4]
- Improved survival[5]
- Reduction in the development of resistance[6]
- Increased rate of seroconversion[7,8]
- Improvement in liver histology[7]
- Normalization of ALT levels[7]

CHB = chronic hepatitis B; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; ALT = alanine aminotransferase; 1. Lok A & McMahon B. *Hepatology* 2007;45:507–549. 2. Liaw YF, *et al. Liver Int* 2005;25:472–489. 3. Keeffe EB, *et al. Clin Gastroenterol Hepatol* 2006;4:936–962. 4. Liaw YF, *et al. N Engl J Med* 2004;351:1521–1535. 5. Niederau C, *et al. N Engl J Med* 1996;334:1422-1427. 6. Yuen MF, *et al. Hepatology* 2001;34:785–791. 7. Marcellin P, *et al. N Engl J Med* 2003;348:808–816. 8. Gauthier J, *et al. J Infect Dis* 1999;180:1757–1762

Phases of Chronic HBV Infection
*Candidates for Therapy**

Immune tolerance

HBeAg (+); HBV DNA high (10^{8-11}); ALT normal

Immune clearance/HBeAg-positive CHB*

HBV DNA (10^{6-10}) and ALT levels high or fluctuating; active inflammation on liver biopsy

Inactive HBsAg carrier

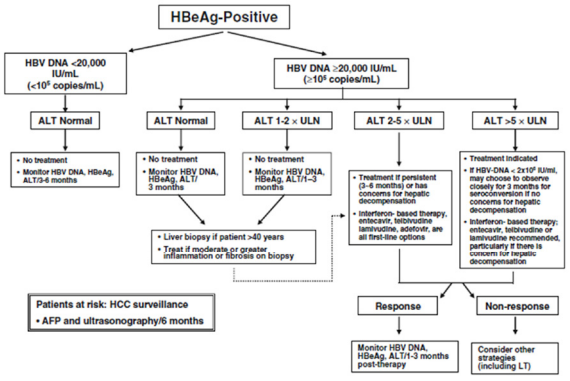
HBeAg (-); HBV DNA low (<10^4); ALT normal

HBsAg may later become undetectable

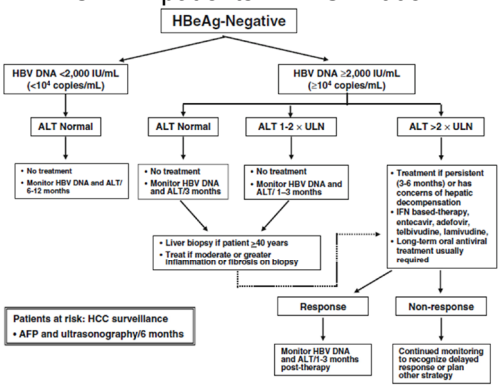
Reactivation/HBeAg-negative CHB*

– HBV DNA (10^{3-8}) and ALT levels high or fluctuating; active inflammation on liver biopsy

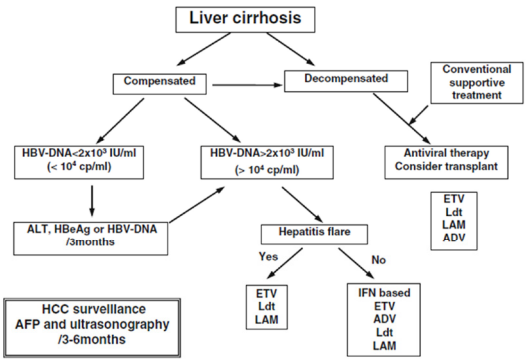
Follow up plan and treatment decision in CVH B patients: APASL 2008



Follow up plan and treatment decision in CVH B patients: APASL 2008



Follow up plan and treatment decision in CVH B patients: APASL 2008



When to Start Therapy:

1) Elevated HBV DNA Level

HBeAg(+) CHB > 20,000 IU/ml (>10^5 copies/mL)

HBeAg(-) CHB >2,000 IU/ml (>10^4 copies/mL)

2) ALT Level above ULN

AASLD, KASL ; > 2X ULN

EASL, Keefe et al ; > 1X ULN

Currently Available Antiviral drugs

Conventional Interferon-α2b

Pegylated Interferon-α2a (Pegasys®)

Lamivudine

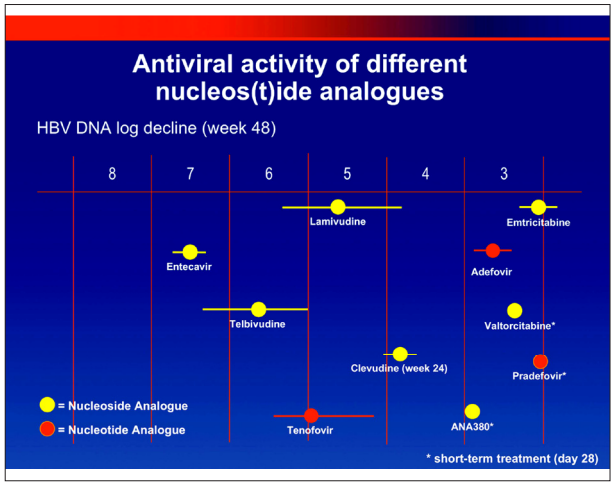
Adefovir

Entecavir

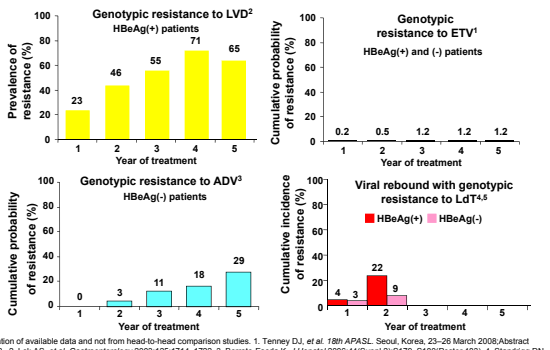
Telbivudine

Clevudine

Tenofovir, Emtricitabine

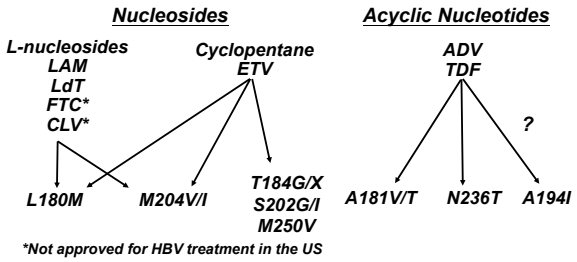


Resistance profiles of 4 antiviral agents in naive patients



Collation of available data and not from head-to-head comparison studies. 1. Tenney DJ, *et al. 18th APASL.* Seoul, Korea, 23–26 March 2008;Abstract O212. 2. Lok AS, *et al. Gastroenterology* 2003;125:1714–1722. 3. Borroto-Esoda K. *J Hepatol* 2006;44(Suppl.2):S179–S180(Poster 483). 4. Standrigg DN, *et al. J Hepatol* 2006;44(Suppl.2):S191(Poster 514). 5. Lai CL, *et al. Hepatology* 2006;44(Suppl.1):222A(Oral 91).

Mutant HBV With Nucleos(t)ides



*Not approved for HBV treatment in the US

Allen MI, et al. Hepatology. 1998;27:1670-1677. Qi X, et al. EASL 2004. Abstract 57. Tenney D, et al. Antimicrob Agents Chemother. 2004;48:3498-3507. Telbivudine [package insert]. Locarnini S. IDRW 2006. Abstract P2. Qi X, et al. Antivir Ther. 2007;12:355-362. van Bommel F, et al. AASLD 2007. Abstract 960.

Viral breakthrough while receiving NA therapy: AASLD 2009

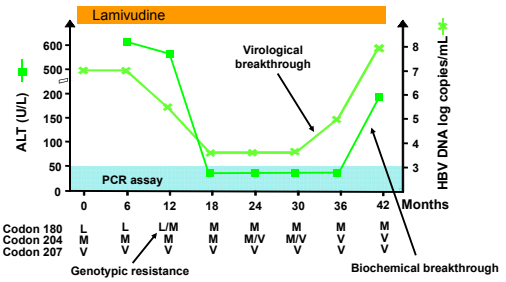
- Compliance should be ascertained
- A confirmatory test for antiviral-resistant mutation should be performed
- All patients with virologic breakthrough(>1log$_{10}$) should be considered for rescue therapy
  - (genotypic resistance? Viral rebound(>10^5)? Biochemical breakthrough(>ULN)?)
- For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, **withdrawal of therapy** may be considered but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares

Management of resistance to oral antiviral therapies

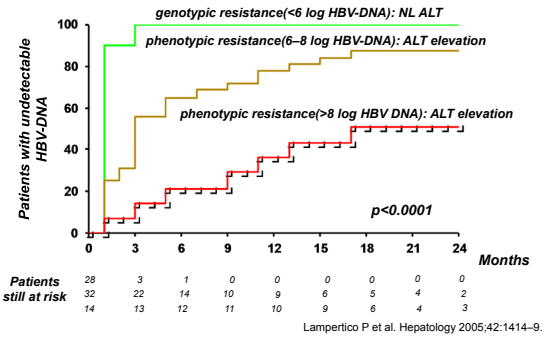
- Possible resistance cases in clinical field
  - LMV-r
  - ADV-r
  - ADV-r after LMV-r
  - ETV 0.5 mg-r, ETV-r after LMV-r
  - ADV+LMV combination-r
  - Clevudine-r, Telbivudine-r
  - ADV+ETV combination-r after LMV-r or ETV-r

Management of LMV-r

- When should rescue therapy be considered?
  - Genotypic resistance? Virological breakthrough(>1log)? Viral rebound(>5log)? Biochemical breakthrough(>ULN)?

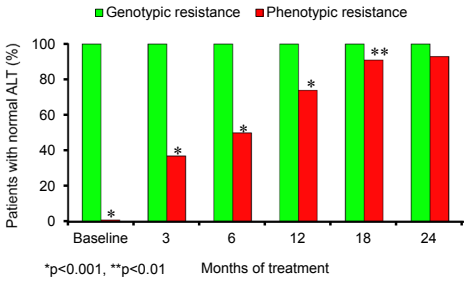


2 year ADV+LAM in 74 HBeAg-neg, LAM-R patients: Virological response



Lampertico P et al. Hepatology 2005;42:1414–9.

2 year ADV+LAM in 74 HBeAg-neg, LAM-R patients: Biochemical response



*p<0.001, **p<0.01

Lampertico P et al. Hepatology 2005;42:1414–9.

Management of LMV-r

❖ When should rescue therapy be considered?

→ Rescue ADV+LMV therapy before biochemical breakthrough could be better than after biochemical breakthrough in terms of virological response

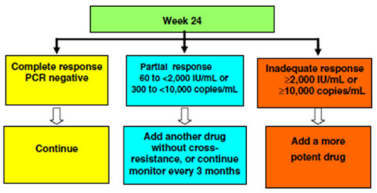
❖ Time lag between genotypic and phenotypic resistance: ranges from 3 to 24 months

→ 3-month interval surveilance would enable timely identification of genotypic resistance

- Unresolved issues
  - Virological breakthrough(>1log)? *vs* some other point?
  - Meaning of biochemical response?

Timing of rescue therapy of LAM-r

- Roadmap concept

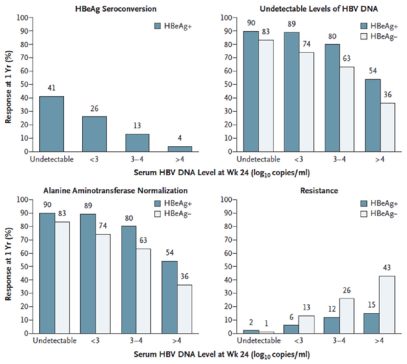


Gane EJ et al. Hepatol Int 2008;2:304–7.

- Applicable to antivirals with low genetic barrier
- Response at 24 week was the most accurate predictor of long term efficacy
  - ALT normalization, HBV DNA non-detectability, HBeAg seroconversion, lack of resistance

GLOBE trial

Telbivudine vs LMV in 1,370 patients



Lai CL, et al. N Engl J Med 2007;357:2576-88.

Timing of rescue therapy of LAM-r

- 5 year LAM in 74 HBeAg-positive

➢ Ideal response definition:
  - HBV DNA <2,000 copies/mL (400 IU/mL), HBeAg seroconversion, normal ALT, YMDD mutations(-)

➢ Treatment failure:
  - HBV DNA >100,000 copies/mL (20,000 IU/mL), HBeAg(+), abnormal ALT

- Cut-off HBV DNA: 2,000 or 800 IU/mL at 4 or 16 week
  - 83.8% or 87.7% chance of 5-year treatment failure

  → addition of or switch to an alternative antiviral should be considered

Yuen MF et al. Hepatology 2007; 46: 1695–703.

Management of LMV-r

- Which agents should be used?

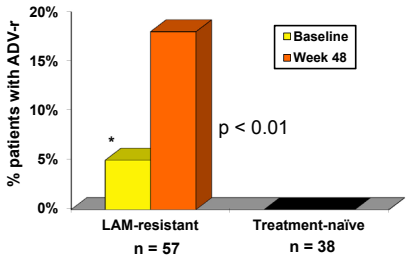
Previous rescue therapy of LMV-r

- LMV resistance

  → Switch to ADV mono or ETV 1mg mono

- Cross resistance: LMV, telbivudine, clevudine
- High genetic barrier in ETV

Development of ADV-r mutants at baseline and 48 weeks with ADV monotherapy

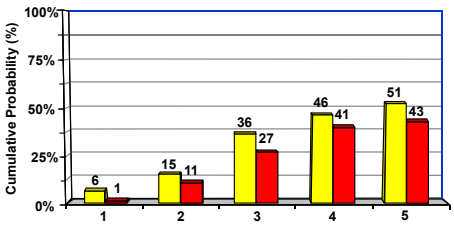


*All were A181T/V ADV-r = A181T/V ± N236T

Lee YS. Hepatology 2006; 43: 1385–91.

Lamivudine-Refractory Cohort (HBeAg+): Cumulative Probability of ETV-r Through 5 Years

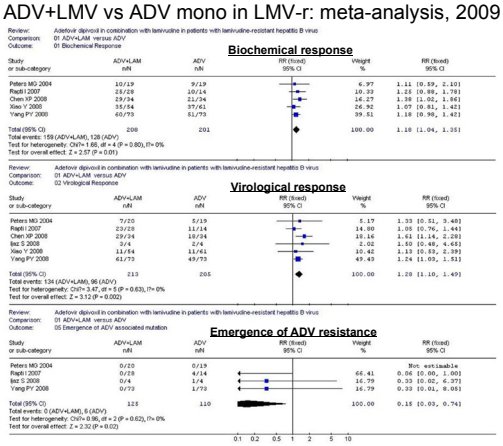
ETVr = LVDr (M204V ± L180M) + T184, S202 and/or M250 substitutions
ETVr + Virologic Breakthrough (≥1 log increase from nadir)



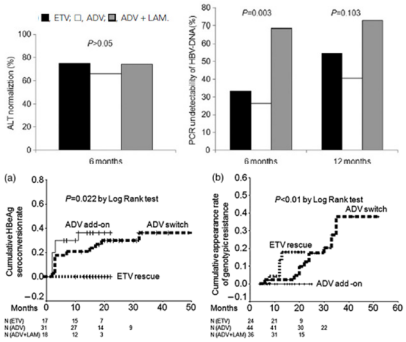
- 72/187 (39%) achieved HBV DNA < 300 c/mL;
- 3/72 (4%) had subsequent genotypic ETV resistance

Tenney DJ, et al. Plenary presentation at APASL 2008
Tenney DJ, et al. Hepatology International 2008;2(1):A88. PL02

ADV+LMV vs ADV mono in LMV-r: meta-analysis, 2009



ETV 1mg vs ADV mono vs ADV+LMV in LMV-r: retrospective cohort study



Kim HJ, et al. J Gastroenterol Hepatol 2010;25(8):1374-80.

Management of LMV-r

❖ ADV+LMV combination is better than ADV mono or ETV mono in terms of subsequent antiviral resistance

❖ Timing of rescue therapy

→ After genotypic and virological breakthrough and Before biochemical breakthrough could be better in terms of virological response

❖ Cut-off HBV DNA

- 60-2,000 IU/mL at 24 week
- 2,000 or 800 IU/mL at 4 or 16 week
  - ─ 83.8% or 87.7% chance of 5-year treatment failure

- Unresolved issues
  - Virological breakthrough(>1log)? *vs* some other point?
  - Meaning of biochemical response?
  - Role of tenofovir? Tenofovir + LMV combination?

Management of ADV-r

- Quality of Evidence Grade II-2 or III
  - Cohort or case-control study, opinions of respected authorities
- Nucleoside analog is effective, but combination therapy is recommended
- Tenofovir mono is effective, but in vitro evidence of cross resistance

➢ In ADV-r with no previous history of NA
  - ADV + LMV or telbivudine or ETV 0.5, Tenofovir + LMV….

➢ In ADV-r with history of nucleoside analog resistance
  - **ADV + ETV 1** (보험 문제가 있는 경우 ADV + LMV or ETV 0.5)
  - Tenofovir + ETV 1 or LMV or ETV 0.5?

Management of ETV-r

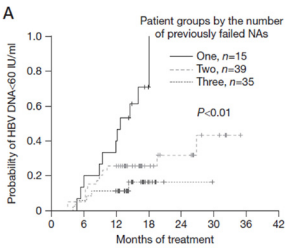
- Quality of Evidence Grade II-3
  - Multiple time series, dramatic uncontrolled experiments

➢ In ETV 0.5-r
  - No sufficient experience
  - ETV 0.5 + ADV or tenofovir, ADV mono? Tenofovir mono?

➢ In ETV 1-r
  - ETV 1 + ADV or tenofovir, ADV mono? Tenofovir mono?

ETV 1 mg + ADV combination

- Could it be the promising combination regimen before the launch of tenofovir?
- 89 patients with previous NA resistance, retrospective



- Number of previous failed NA
- One: LMV only
- Two: LMV + ADV or ETV
- Three: LMV + ADV + ETV

Lim YS, et al. Antivir Ther 2012;17(1):53-60.

Management of Antiviral-Resistant HBV: AASLD 2009 update

➢ Lamivudine-resistant
  → Add adefovir or tenofovir
  → Stop lamivudine, switch to Truvada (tenofovir + emtricitabine)*
  → Stop lamivudine, switch to entecavir → 삭제됨
➢ Adefovir -resistant
  → Add lamivudine
  → Stop adefovir, switch to Truvada*
  → Switch to or add entecavir *†
➢ Entecavir -resistant
  → Switch to or add adefovir or tenofovir → switch to tenofovir or Truvada
➢ Telbivudine-resistant‡
  → Add adefovir or tenofovir
  → Stop telbivudine, switch to entecavir → Stop telbivudine, switch to Truvada

*In HIV co-infected patients; scanty in vivo data in non-HIV infected persons. †Durability of viral suppression unknown, especially in patients with LVD resistance. ‡Clinical data not available.

Lok AS, McMahon BJ. *Hepatology.* 2007;45:507-539.

When to Stop Therapy
Two Distinct Patient Populations

- HBeAg-positive (wild-type)
  - HBeAg loss ± seroconversion
  - Durable suppression of HBV DNA to low or undetectable
  - Therapy discontinued 6-12 months after HBeAg seroconversion and undetectable HBV DNA

- HBeAg-negative (precore and core promoter mutants)
  - HBeAg seroconversion not an endpoint
  - Durable suppression of HBV DNA to low or undetectable
  - Relapse common after stopping oral therapy; therapy usually administered long-term; several years of undetectable HBV DNA may decrease the relapse rate

Summary
Treatment of Hepatitis B

➢ When to start therapy
- Elevated HBV DNA [>20,000 IU/mL for HBeAg(+) and >2,000 IU/mL for HBeAg(-)] plus elevated ALT, and/or significant disease on liver biopsy

➢ When to stop or alter therapy
- HBeAg(+): HBeAg seroconversion and HBV DNA (-)
- HBeAg(-): HBsAg seroconversion, long-term therapy?
- Primary non-response at week 24(<2 $\log_{10}$ reduction)
- Development of antiviral drug resistance
- Inadequate VR (≥2,000 IU/mL) at week 24?

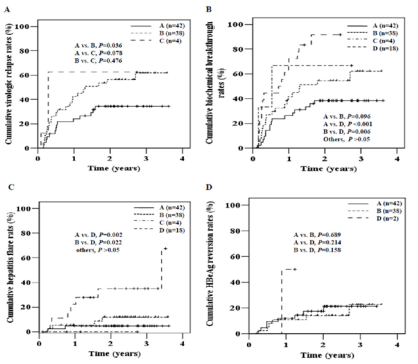
Conclusion
Management of LMV-r

❖ ADV+LMV combination is better than ADV mono or ETV mono in terms of subsequent antiviral resistance
❖ Timing of rescue therapy
→ After genotypic and virological breakthrough and Before biochemical breakthrough could be better in terms of virological response
❖ Cut-off HBV DNA
- 60-2,000 IU/mL at 24 week
- 2,000 or 800 IU/mL at 4 or 16 week
  —83.8% or 87.7% chance of 5-year treatment failure

Future perspectives

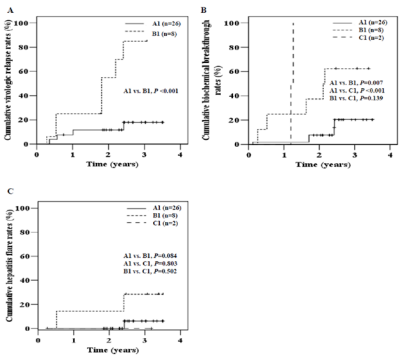
- Tenofovir is now available in Korea
  - Effective in both naïve and LAMr as a monotherapy
  - Low efficacy as a TDF mono in ADVr and high viral load
- Other combination regimen
  - ETV + tenofovir? LAM + tenofovir?
- Reappraisal of Peg-interferon using HBsAg titer
- Intermittent antiviral therapy?

Clinical course after LMV off treatment in 102 HBeAg(+) patients



- Group A
  - HBV DNA <50 copies/mL with HBeAg loss
- Group B
  - HBV DNA 50-10^5 copies/mL with HBeAg loss
- Group C
  - HBV DNA 50-10^5 copies/mL without HBeAg loss
- Group D
  - HBV DNA ≥10^5 copies/mL irrespective HBeAg loss

Clinical course after LMV off treatment in 36 HBeAg(-) patients



- Group A1
  - HBV DNA <50 copies/mL
- Group B1
  - HBV DNA 50-10^5 copies/mL
- Group C1
  - HBV DNA ≥10^5 copies/mL