Comment	Answer
Reviewer	
1) There are some important studies that discuss the significance of pre-S deletion mutation or its combination with other mutations. The author could address this issue in the article. Chen et al (Gastroenterology. 2006 Apr;130(4):1153-68) found that patients with progressive liver diseases have a higher frequency of pre-S deletion and all the deletion regions encompassed T- and B-cell epitopes, and most of them lost 1 or more functional sites. Chen et al. (Gastroenterology. 2007 Nov;133(5):1466-74) found that HBV with a complex mutation pattern (pre-S deletion, T1762/A1764, and T1766 and/or A1768 mutants) rather than a single mutation was associated with the development of liver cirrhosis. Pre-S mutant also plays pathogeneic role in the development of HCC. The pre-S mutant large surface antigens can activate endoplasmic reticulum (ER) stress to induce oxidative DNA damage and genomic instability (Wang et al., 2006). The pre-S mutant also can upregulate cyclooxygenase-2 and cyclin A to induce cell-cycle progression and proliferation of hepatocytes (Wang et al., 2006). A recent study found that vascular endothelial growth factor-A (VEGF-A) is upregulated by pre-S mutants and that pre-S mutant-expressed Huh-7 cells exhibited activation of Akt/mTOR (mammalian target of rapamycin) signaling and increased growth advantage, which could be inhibited by VEGF-A neutralization (Yang et al., 2009).	As suggested, all the mentioned articles were added in their appropriate position.
2) Seroclearance of HBsAg during lamivudine therapy may not indicate viral clearance and mutation in S gene may play a role. A recent study by Hsu et al. (Gastroenterology. 2007 Feb;132(2):543-50) found that a mutation hot spot, P120A in the S gene, was associated with detection failure of HBsAg.	As suggested, all the mentioned articles were added in their appropriate position.
3) There are several studies that investigates the	As suggested, all the mentioned articles were added

significance of HBV basal core promoter mutations (A1762T/G1764A) and the occurrence of HCC and its association with different HBV genotypes. The author could cite more studies in this issue. In several cross-sectional (Baptista et al., 1999; Kao et al., 2003) and longitudinal studies (Chou et al., 2008; Fang et al., 2008; Wu et al., 2008; Yuan et al., 2009), HBV basal core promoter mutations (A1762T/G1764A) are found to be associated with the occurrence of HCC. The REVEAL-HBV study from Taiwan found that the multivariable-adjusted hazard ratio of developing HCC was 1.73 for basal core promoter mutations and that the risk was highest among participants infected with genotype C HBV and who harbored the precore 1896 variant and mutations for the basal core promoter (Yang et al., 2008).	in their appropriate position.