Viral Hepatitis Prevention Board

20 YEARS VHPB: ACHIEVEMENTS, IMPACT AND REMAINING CHALLENGES IN PREVENTION AND CONTROL OF VIRAL HEPATITIS
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Lessons learnt from previous TMs and what needs further follow-up of VHPB

- HBV escape mutants
- Booster policy
- Safety issues

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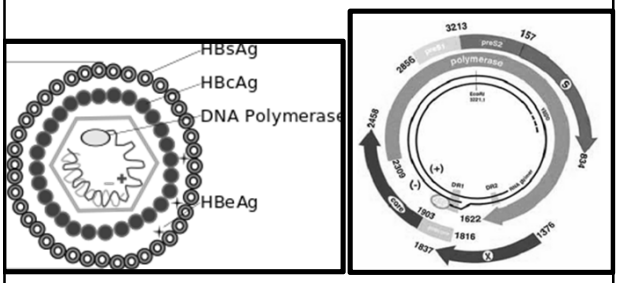
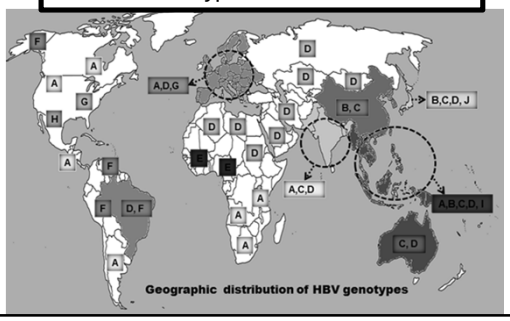
Are viral escape mutants (VEMs) a matter of concern?



Hepatitis B genotypes and serotypes

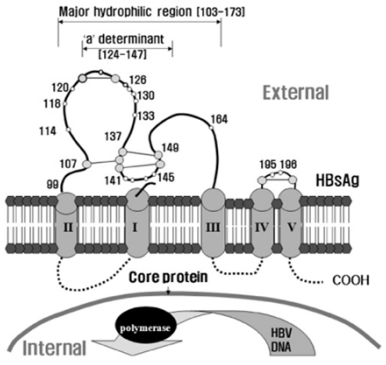
- 8 genotypes (A-H)
- 4 major serotypes (adw, adr, ayw, ayr)
- 9 minor serotypes



Emergence of HBV mutants

- Following this strategy of replication involving a RT lacking proof-reading capacity, HBV shows greater mutability than other DNA viruses.
- Error-prone replication leads to $2x10^4$ base substitutions per site per year.
- Mutations can occur in all 4 genes through:
  - spontaneous errors of viral Pol
  - as a consequence of pressure by the host immune system
  - by exogenous factors including immunization or treatment with antiviral drugs.

Major hydrophilic region and **a** determinant of surface gene on surface protein



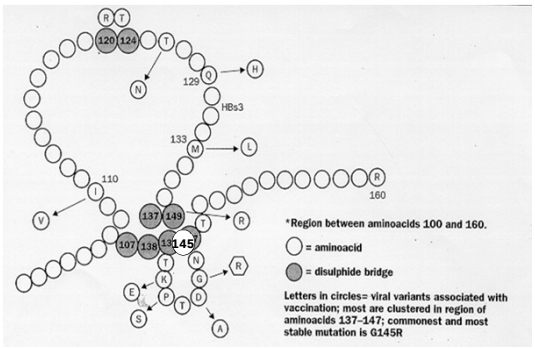
S-gene mutants

- Neutralizing (i.e. protective) Abs induced by vaccination are targeted towards the conformational epitope of the **a** determinant . This provides protection against all HBV genotypes and subtypes conferring broad immunity.
- Alterations of residues within this region can lead to conformational changes that can allow replication of the mutated HBV in vaccinated people.

G145R features

- Point mutation from guanosine to adenosine at nt position 587resulting in aa substitution from G to R at position 145 of the **a** determinant.
- Since the G145R substitution alters the projecting second loop the **a** determinant, neutralizing Abs induced by vaccination are no longer able to recognize the mutated epitope.
- G145R was shown to be viable, infectious and pathogenic in chimpanzees.

HBsAg mutants



Zuckerman AJ, Lancet 2001; 355:1382-4

Vaccine-escape HBV mutants

- S gene mutants may take advantage on the wild-type in escaping the immunity of vaccinated people.
- Mutants occur in presence of anti-HBs in:
  - infants born to HBV+ carrier mothers treated with HBIG plus vaccine
  - liver transplanted patients who received HBIG for prophylaxis
- HBIG can be the major driving force for the selection VEMs.

Is VEMs prevalence increasing?

- Worldwide spread and whether their frequency is increasing with the increasing coverage rate and extension of vaccination, is still a matter of study.
- No increase of prevalence in Taiwan among children and adolescents covered by universal vaccination over a period of 20 years (*Hsu HY, JID 2010*).
- HBV mutants capaple of infecting people are emerging in China 13 years after implementation of universal vaccination (*Biant, J Virol 2013; Biant, Microbe 2013*).

Is VEMs prevalence increasing?

- Both HBsAg carrier rate and prevalence of variants are decreasing even though the variant prevalence is decreasing at lower rate (71% vs 33%) (*Jilg W et al, J Virol 2014; Shouval D, J Virol 2014*)

POL-gene mutants

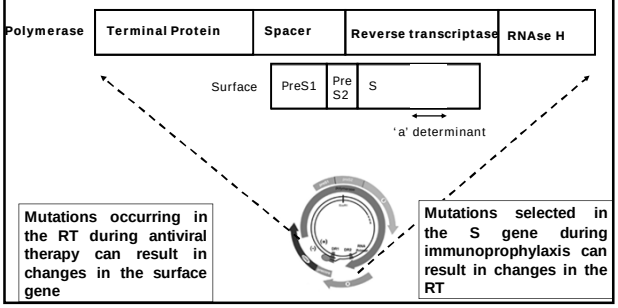
- NAs have provided effective treatments to CHB patients, significantly reducing morbidity and mortality.
- Selection and emergence of drug-resistant mutants can lead to treatment failure and progression to LD.
- Resistance due to mutations in the Pol gene is followed by a virological and then biochemical (↑ ALT) breakthrough and worsening of LD.

Antiviral resistant mutations

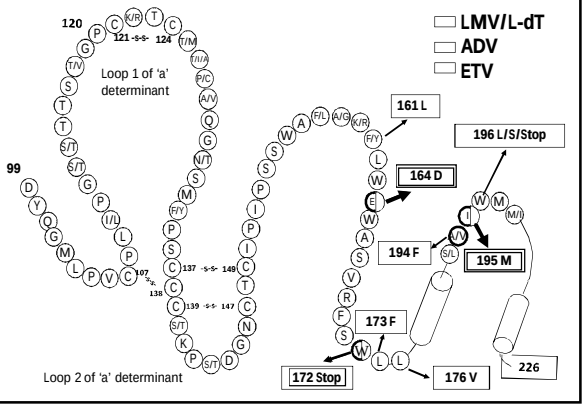
- Pol gene mutations located within the catalytic domain of RT region a particulary common following LMV treatment *(up to 80% after 5 years of treatment)*.
- The rate of emergence of resistant viruses after treatment with other NA is lower than that of LMV but still substantial in most cases.

Polymerase-HBsAg Overlap

Genes encoding surface antigen and the polymerase overlap



HBsAg Mutation Selected by LMV/ADV/ETV



What is the public health impact of NA resistant mutants?

Antiviral drug-associated escape mutants may infect both naïve and immunized people, potentially affecting the efficacy of both the antiviral treatment and the vaccination programmes.

What is the meaning of this finding?

Is it only a matter
of academic research interest
or
is a crucial problem with far-reaching implications in terms of public health?

Conclusions – 1

- Vaccination has clearly proved to be very successful
- Cases of HB in fully vaccinated people are rare.
- Breakthrough infections caused by S-gene mutants are occasionally reported but at present they do not pose a serious threat to the established vaccination programs.
- The emergence of drug resistant mutants with alterations in the ***a*** determinant of the S protein is of concern since the pool of patients with CHB potentially in need of treatment with NA is huge.
- Global surveillance networks should be set up to monitor the epidemiological dynamics and pubic health impact of vaccine-escape/treatment-escape mutants.

Conclusions – 2

- Chronic HB guidelines recommended that *Entecavir* (ETV) or *Tenofovir* (TDF) drugs with high potency and the lowest rate of resistance, should be chosen as a first-line treatment.
- The development of novel NAs with a high barrier to resistance is warranted.
- Global surveillance networks should be set up to monitor the epidemiological dynamics and public health impact of vaccine escape and treatment resistant mutants.