Simplified protocol for the treatment of Chronic Hepatitis B

(last updated according to EASL 2017 & AASLD 2018)

When to treat HBV?!!

- According to recent
  - EASL guidelines (2017)
  - EASL (European association for the study of the liver)

- The patient with HBV is only indicated for treatment in the following conditions:

1) HBe- antigen positive or negative with HBV DNA PCR is ≥2000 in addition to either
   - ALT > ULN [Upper limit of normal]
   - And/ or biopsy of at least moderate necroinflammatory activity or ≥F2 by fibroscan.
2) Any patient with cirrhosis (compensated or not) with any positive PCR.
3) patients with HBe- antigen (positive) and PCR> 2000, with normal ALT, but age > 30 years
4) Patients with HBe antigen positive or negative and PCR > 2000 with normal ALT, But only when there are family history of cirrhosis, HCC or extrahepatic manifestations of HBV.
5) Patient with PCR > 20,000, and ALT > 2 ULN(american protocol, AASLD).

Workup before treatment :-

- Baseline Basic investigations including: CBC, Complete liver function tests, renal functions, Coagulation profile.
- Serology including HBs-Ag & HBe-Ag.
- HBV DNA by PCR {viral load}.
- Fibroscan or biopsy.
- U/S abdomen.

Drug therapy and the treatment Strategy

- There 2 options of treatment:-
  - A. Oral Nucleotide Analogue therapy
  - B. Injectable Pegylated interferon PEG-IFN
- If the patient's status is HBe- Antigen positive, the oral Nucleotide Analogues [NA] therapy is the first line and is the preferred.

- **NA (Nucleotide Analogues): -**

* Choose one of the following

- Tenofovir 300 mg tab (the best)
  Trade Name [Tenaviron 300 mg) Once daily
- Entecavir 0.5 mg tab
  Trade Name Baraclude 0.5 mg
  Egyptian: Tecavir 0.5 mg tab once daily

✓ N.B:

- in cirrhotic patients , the dose of Entecavir is 1 mg tab once daily
- bothTenofovir and Entecavir have high barrier to HBV resistance , So they have long term Anti-viral efficacy leading to undetectable HBV DNA in the vast majority of compliant patients ,moreever,they have favourable safety profile.
- Lamivudine [Nucleoside analogue]
  is not recommended by the guidelines for the treatment recently as it shows resistance . It has low barrier to HBV resistance
- Adefovir is not as effective as Tenofovir and entecavir in the treatment of Chronic HBV hepatitis , it also has low barrier to HBV resistence so, it is not recommended for the treatment of HBV by EASL guidelines .

✓ in cases of renal impairment , entecavir is used instead of Tenofovir

✓ Side affects of NA are minimal.

▸ If the patient's status is HBe Antigen negative , the treatment with Injectable Pegylated interferon [PEG-IFN] is preferred over NA therapy , but NA can be used with less satisfiable results.

PEG- IFN

❖ *Trade name*: Pegasys 180 ug s.c once weekly for 48 weeks

- This therapy is called fenite therapy as it has certain limited duration (48 weeks)
- It has long term immunological control .
- Patient selection according to disease activity, HBV genotype, stage of the disease, as well as levels of HBV DNA , HBs Ag and HBe Ag status can be helpful indicators to detect the individual response probability.

❖ *Side effects:* Very bad (difficult to tolerate)

- Flu like (high fever, marked myalgia)
- Bone marrow suppression & neutropenia
- Thyroid dysfunction
- Depression

✓ N.B: PEG-IFN is contraindicated in decompensated cirrhosis.

Target of therapy (both NA or PEG-IFN)

Endpoint of the treatment

Achievement of the following

❖ **Virological response**

a) In patients treated with NA therapy:
Is defined as undetectable HBV DNA (PCR) < 10 IU/ml

b) In patients treated with PEG-IFN:
Is defined as serum HBV DNA (PCR) < 2000 IU/ml usually at 6 months and at the end of therapy

❖ **Biochemical response :**

Persistent normalisation of ALT with treatment

❖ **Histological response :**

Improvement of fibrosis degree by ≥ 2 degrees

- **Serological response :**

- If the patient's status is HBe antigen positive , so the first target is HBe -antigen loss , then the appearance of anti-HBe antibody , then HBs -antigen loss with or without the appearance of anti-HBs Antibody .

✓ N.B: HBe Ag positive patients have more favourable serological response than HBe Ag negative patients

- If the patient's status is HBe Antigen negative , so the only target is loss of HBs Ag with or without the appearance of Anti-HBs Antibody [difficult , the patient is often failing to achieve that , and he might continue on treatment indefinitively , if he is on NA therapy

Important definitions:

- **Partial Virological response:**
  Is defined as decrease in HBV DNA of more than 1 log10 but detectable HBV DNA after 12 months of treatment with NA therapy.
- **Primary Non-response:**
  Is defined as less than 1 log10 a decrease of serum HBV DNA (PCR) after 3 months of therapy. It warrants stoppage of treatment and replacement with another treatment.
- **Virological breakthrough**:
  Is defined as confirmed increase HBV DNA level more than 1 log10 compared to the nadir (lowest value) HBV DNA level on therapy .

Monitoring of patients who are on treatment :

- During treatment , Liver function tests should be performed every 3 months during the first year and every 6 months thereafter.
- Serum HBV DNA(PCR) should be performed every 3 months during the first year and every 6 - 12 months thereafter .

- HBs Antigen should be checked at 12 months interval if HBV DNA remains undetectable, while patients who clear HBs Ag should be tested for Anti-HBs Ab.
- Renal function tests should be performed every 3 months during the first year , and every 6 months thereafter.
- Patients under effective long term NA therapy should remain under surveillance for HCC every 6 months by U/S scan.

Monitoring of patients who are currently not treated

[with periodic ALT, HBV DNA , and fibroscan]

- Patients with HBe Ag positive chronic HBV infection who are younger than 30 years old and don't fulfill the indication's criteria for treatment should be followed at least every 3 - 6 months .
- patients with HBe Ag negative chronic HBV infection with serum HBV DNA < 2000 IU/ml who don't fulfil the indication's criteria for treatment , should be followed up every 6 - 12 months
- Patients with HBe Ag negative chronic HBV infection and serum HBV DNA ≥ 2000 that don't fulfil the indication's criteria for treatment, should be followed up every 3 months in the first year, and every 6 months thereafter.

When to stop the treatment ?!

[Discontinuation of NA therapy]

- NAs should be discontinued after confirmed HBs Ag loss with or without appearance of Anti-HBs Ab (seroconversion)
- NAs can be discontinued in non- cirrhotic HBe Ag positive CHB patients who achieve stable HBe seroconversion and undetectable HBV DNA (PCR) and who complete at least 12 months of therapy .
- NAs can discontinued in selected non-cirrhotic HBe Ag negative patients who have achieved long term (≥ 3 years) virological suppression.