

Chronic Hepatitis B

Experimental Treatment in the Pipeline

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Treatment for Chronic HBV

- Treatment for chronic HBV has advanced in the last decade.
- Current emphasis is on lowering viral load with the use of oral antivirals.
- Approved nucleoside and nucleotide analogues all inhibit viral replication via the same target: by terminating reverse transcription.
- Drug resistance and cross-resistance has emerged as a major challenge.

Main treatment goals are:

- Sustained HBV suppression (undetectable viral load).
- Remission of liver disease (normal ALT).
- Prevent progression to liver cirrhosis, cancer, or failure.

Treatment for Chronic HBV

There are two types of FDA approved HBV treatment:

1. **Interferon (1992) & Pegylated Interferon/Pegasys (2005)** - \$2,256.68/month
2. **Oral Antivirals**
 - Lamivudine/Epivir-HBV (1998) - \$339.24/month
 - Adefovir/Hepsera (2002) - \$753.68/month
 - Entecavir/Baraclude (2005) - \$779.98/month
 - Telbivudine/Tyzeka (2006) - \$633.22/month
 - Tenofovir/Viread (2008) - \$621.49/month

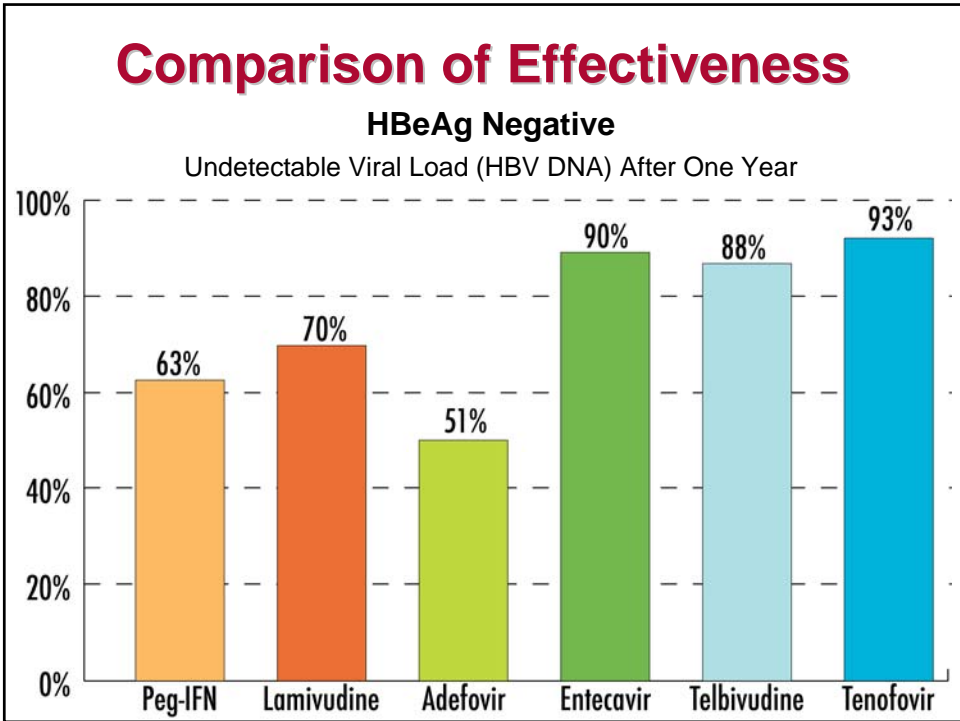
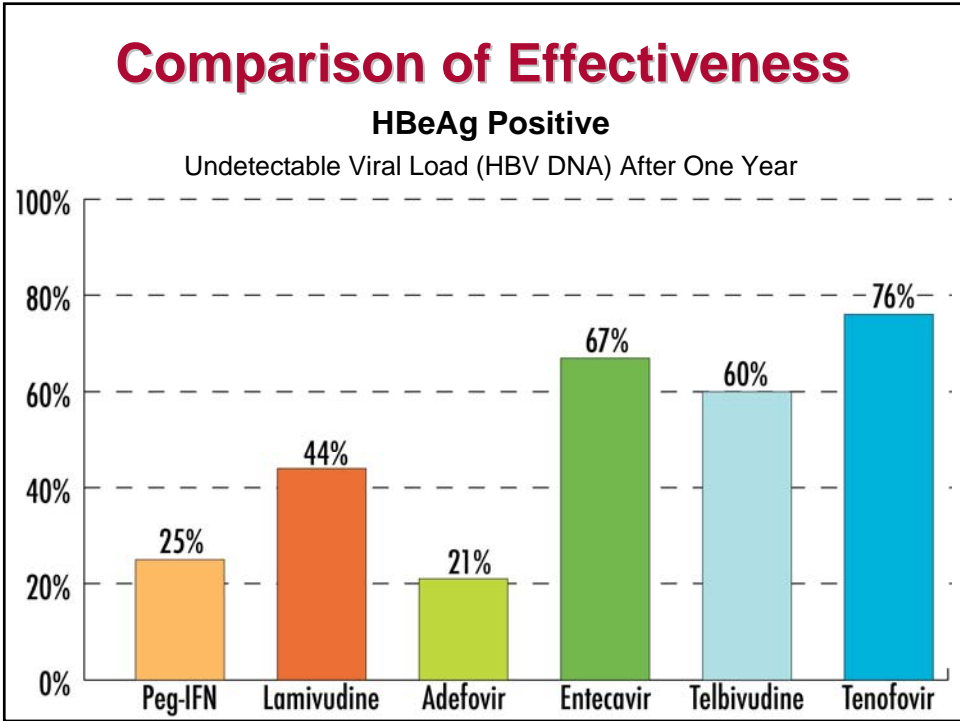
*Prices from DrugStore.com accessed 9/26/08

Pegylated Interferon

- **PROS:** Treatment only for one year. Better durability post treatment.
- **CONS:** Severe side-effects & lack of efficacy in viral suppression.
- Currently recommended as first-line treatment option for both HBeAg positive and negative patients.
- Recent studies from oral antivirals have erased the clinical advantages of Peg-Interferon from earlier data.

Most effective in people with:

- HBeAg positive – Earlier phase of chronic disease
- Genotype A
- Low viral load
- High ALT

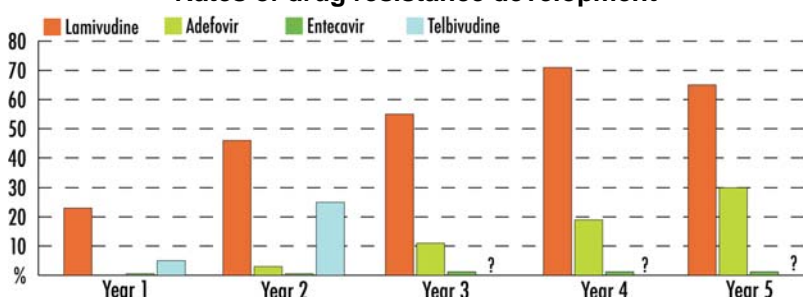


HBV Drug Resistance

One major drawback of oral antivirals is the development of drug resistance, and cross resistance.

- Lamivudine and telbivudine are no longer recommended as first-line therapy due to their weak resistance profiles.
- Adefovir and entecavir loses effectiveness in people with lamivudine and telbivudine resistance.
- Tenofovir resistance has not been well characterized.

Rates of drug resistance development



Current Challenges

- There is a critical need for more potent agents with higher genetic barriers to drug resistance.
- Basic science research on HBV virology lags behind HIV and HCV.
- Lack of new targets on HBV replication hampers development of new drugs.
- Treatment Pipeline is drying up.
- No next-generation treatment approach has yet emerged as a candidate to break the drought.

HBV Experimental Graveyard

Ten companies have suspended development of experimental candidates for HBV in the last two years.

Experimental Candidates	Current Development Status
Amdoxovir, Elvucitabine, Racivir	Being developed for HIV; HBV development suspended after phase II
EHT899, Pradefovir	Development stalled, pending new business partnership
CHB-111 (HepaVaxx), Valtorcitabine	Development suspended after phase I
HepeX-B, UT-231B, HI-8 HBV	Development suspended after phase II

Can Chronic HBV be Cured?

- Current treatment cannot eradicate HBV
- HBV deposits its genetic material, covalently closed circular DNA (cccDNA), into the nucleus of infected liver cells, a relatively stable reservoir
- HBV can reactivate once therapy is stopped
- Majority of chronically infected people likely need lifelong therapy to maintain viral suppression.

Combination Therapy?

- Results from several small trials to date have not improved sustainable efficacy
- May delay development of drug resistance to less potent agents
- Current treatment guidelines recommend combination therapy for:
 - people who have developed resistance with monotherapy, and
 - people at higher risk of developing resistance, such as people with cirrhosis or HIV coinfection

Combination Therapy?

- A few large-scale and long-term combination drug trials are currently underway, with data expected in about four years
- New NIH funded HBV Clinical Trials Network is starting up with 12 sites
- Some providers are arguing for the use of combination therapy in treatment-naive people to
 - forestall drug resistance, given HBV's slow disease progression (measured in decades) and
 - scarcity of new experimental agents.

Combination Therapy?

To demonstrate an advantage over monotherapy and justify the added expense and potential toxicity, combination strategies would need to show

- improved viral suppression,
- higher rates of viral clearance, and
- potential for shorter duration of treatment.

Global HBV Market and Pricing

- Global annual HBV market is currently about \$450 million, primarily from the United States and European Union.
- Projected to reach \$1 billion by 2010 (one tenth the size of the HIV market).
- Pricing has followed the HIV model
- Lack of ADAP like program for HBV
- Private insurance restriction on preexisting conditions
- Limit many people's ability to access new and expensive medications.

HBV Experimental Pipeline

Agent	Class	Sponsor	Status
Emtricitabine (in coformulation with tenofovir)	Nucleoside	Gilead	Phase II
Clevudine	Nucleoside	Pharmasset, Bukwang	Phase III
LB80380	Nucleotide	LG Life Sciences	Suspended
Nitazoxanide	Antiprotozoal	Romark	Phase II
YIC (Yeast-derived immunogenic complex) of HB surface antigen and antibody	Therapeutic vaccine	Beijing Vaccine Institute and Shanghai Medical College, Fudan University	Phase IIb
HBV core antigen vaccine	Therapeutic vaccine	Emergent Biosolutions	Phase II
DNA vaccine pCMVS2.S	Therapeutic vaccine	French National Agency for Research on AIDS and Viral Hepatitis	Phase I/II

Emtricitabine

- Nucleoside analogue close to lamivudine co-formulated with tenofovir as Truvada
- Phase II combination Vs. tenofovir monotherapy
- Patients with detectable viral load on lamivudine or adefovir
- 48-week data showed same response rates: 81% undetectable HBV viral load.
- Trials in HIV/HBV coinfecting people, and people with decompensated liver cirrhosis are currently underway.

Clevudine

- Nucleoside analogue approved in South Korea since 2006
- Phase III Vs. adefovir in treatment-naïve
- Enrollment completion expected end of 2008
- FDA approval around 2010

24-week data from Phase II

In HBeAg-positive:

- 59% undetectable viral loads, and
- 68% normalization of liver function

In HBeAg-negative:

- 92% undetectable viral load, and
- 75% normalized liver function.

Clevudine

- Possible immunomodulatory effect not seen with other oral agents
- 96-week follow-up studies planned to look at
 - Sustained viral suppression six months after stopping 72 weeks of treatment
 - Can potentially shorten treatment duration

LB80380

- Nucleoside analogue
- Phase IIb trial being planned in South Korea
- Looking for development partner in the United States and Europe
- Phase IIa trial showed 4 log drop in viral load in lamivudine-resistant participants
- In vitro study showed active against multiple HBV drug resistant mutations
- Unlikely to reach market before 2013

Nitazoxanide

- Antiprotozoal used to treat intestinal parasites
- Active against hepatitis B and C
- Phase II study Vs. entecavir Vs. combination
- Phase II hepatitis C trial showed improved treatment responses with PEG-IFN + RBV
- Only oral agent in development that is not a nucleoside/nucleotide, potential weapon against HBV drug-resistant mutations.

New Approaches: NUC B1000

- RNA interference-based gene therapy in phase I
- early setback when a patient died in a different gene therapy trial using the same delivery viral vector
- FDA halt development on similar trials
- Allowed to move forward this year following another FDA review and additional patient consent procedures.

New Approaches: Bay 41-4109

- Heteroaryldihydropyrimidine (HAP)
- New target in viral life cycle: inhibits HBV assembly by interrupting viral capsid formation
- Preclinical in vitro and animal studies have demonstrated this compound's ability to inhibit viral replication

Therapeutic Vaccines

- HBV is not directly liver-toxic, liver damage is caused by the immune system killing HBV-infected liver cells
 - There is an effective preventive HBV vaccine
 - Up to 95% of healthy adults can clear HBV without treatment
- Immune-based therapy is a promising research area

YIC (Yeast-derived immunogenic complex) of HB surface antigen and antibody

Results from a phase IIb study from China:

237-person, three-arm, placebo-controlled trial in HBeAg-positive

- Primary endpoint did not reach statistical significance due to high response rate in placebo arm
- Delayed response (44-week) HBeAG seroconversion:
 - 21.8% high dose arm Vs. 7.7% in the placebo arm
- 11 hospitalizations due to serious adverse events, equally distributed across the three study arms, all participants recovered.
- The vaccine is expected to move into phase III with larger cohort and longer treatment period in hopes of getting cleaner results and improved response rates

HBV core antigen vaccine

- Phase II study in Europe
- Drinkable form with an HBV core antigen gene inserted in live attenuated Salmonella bacteria via recombinant technology
- Salmonella bacteria produces the HBV core antigen within gut macrophages, inducing antigen-specific T cells directed to kill HBV infected liver cells
- Plans to launch phase III trials in the United States pending positive outcome

Naked DNA Vaccine

- Phase I/II study in France
- Vaccine induced immune activation to:
 - improve treatment response while on therapy, or
 - delay viral reactivation off treatment
- Phase I data show temporary vaccine induced immune responses in people not responding to therapy
- Began enrollment in 2008, with completion expected in 2010

DNA therapeutic vaccines

- Phase I in Asia
 1. Pfizer and PowderMed's needle-free injection in powder form through the skin
 2. Genexine administered in combination with adefovir

Thymosin alpha 1

- Phase IV in Korea
- An immunomodulator, synthetic version of a substance produced naturally by the thymus
- Approved in over 30 countries to treat HBV
- Combination with pegylated interferon for 3 months, followed by nine months of pegylated interferon alone
- Development plans for the United States are unclear.

Future HBV Research Needs

- An increase in public investment into basic science and natural history research

“An arbitrary value of 20,000 IU/ml was chosen as a diagnostic criterion for chronic HBV at the 2000 NIH Conference.”

- New drug targets and therapeutic approaches are needed to combat drug-resistant HBV
- Long term and large scale studies on optimal starting and stopping points
- New treatment strategies

For more information

Treatment Action Group

www.treatmentactiongroup.org

Hepatitis B Foundation

www.hepb.org

CDC Viral Hepatitis Page

<http://www.cdc.gov/hepatitis/ChooseB.htm>

The logo for the Treatment Action Group (TAG) consists of the letters 'TAG' in a bold, red, sans-serif font. The letter 'A' is stylized with a small dot above it.

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