HBV Treatment
Past, Present and the Future

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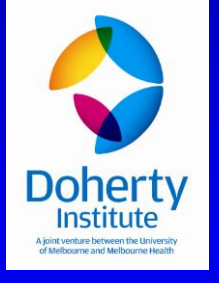


HBV Treatment – Past and Present

Generic Name	Trade Name	Manufacturer	Date Approved for Hepatitis B
Interferon alfa-2b	INTRON® A	Schering Corporation	1991
Peginterferon alfa-2a	PEGASYS®	Hoffman La-Roche	2005
Lamivudine	EPIVIR-HBV®	GlaxoSmithKline	1998
Adefovir dipivoxil	HEPSERA™	Gilead Sciences	2002
Entecavir	BARACLUDE™	Bristol-Myers Squibb	2005
Telbivudine	TYZEKA™	Idenix/Novartis	2006
Tenofovir	VIREAD™	Gilead Sciences	2008

Treatment Endpoints

- Long-term suppression of HBV DNA
  - Ideally by achievement of HBsAg seroconversion
- HBeAg-positive
  - Sustained HBeAg seroconversion
  - If no HBeAg serconversion--> suppression of HBV DNA to low levels
- HBeAg-negative
  - Sustained low level HBV DNA
    - On treatment if nucleosides
    - Off treatment if peg-IFN

AASLD Guidelines
EASL Guidelines
APASL Guidelines

The Past and the Present - Intereron

Immunomodulatory

The Past - Conventional interferon – alpha (IFN-α)

- First compound licenced for treatment of chronic hepatitis B in 1991
- Only effective in a small sub-group of patients

The Present - Pegylated interferon

- More beneficial but still low efficacy
- Renewed interest with introduction of qHBsAg

Role of Quantitative HBsAg

Treatment with PEG IFN +/- LMV

	Week 12 HBsAg on PEG IFN alfa 2a ± LMV	HBV DNA ≤ 10000 copies/ml		HBV DNA ≤ 400 copies/ml		HBsAg loss	
		6 months	4 years	6 months	4 years	6 months	4 years
HBeAg-negative	≤ 1500 IU/mL	59%	39%	39%	31%	**7%**	**23%**
	> 1500 IU/mL	34%	12%	9%	8%	2%	4%

Marcellin, P. et al 2008. AASLD

Role of Quantitative HBsAg

Treatment with PEG IFN +/- LMV

		End of Treatment		
HBeAg-positive	Week 12 HBsAg on PEG IFN alfa 2a ± Lamivudine therapy	HBV DNA ≤ 10,000 copies/ml	HBV DNA ≤ 400 copies/ml	HBsAg loss
	≤ 1500 IU/mL	46.8%	31.2%	**10.1%**
	1501 – 20,000 IU/mL	22.6%	11.1%	1.8%
	> 20,000 IU/mL	8.2%	4.1%	3.3%

Lau, G. et al 2008. AASLD

Update – IFN –HBeAg-positive CHB

- qHBsAg < 300 IU/mL at W24 correlates with SVR
  - *Chan et al 2010 Aliment Pharmacol Ther 32: 1323*
- qHBsAg <1500 IU/mL at W12 corresponds to 57% PPV for HBeAg seroconversion
  - *Lau & Marcellin 2009 J Hepatol 50: 333*
- qHBsAg > 20,000 IU/mL at W12 100% NPV for anti-HBs seroconversion
  - *Liaw et al 2011 Hepatology 54:1591*

Update – IFN –HBeAg-negative CHB

- qHBsAg >0.5 log at W12 leads to ETR in 90%
  - *Moucari et al 2009 Hepatol 49: 1151*
- No or little decline in qHBsAg and <2 log decline of HBV DNA shows a NPV of 100%
  - *Rijckborst et al 2010 Hepatol 52: 454*

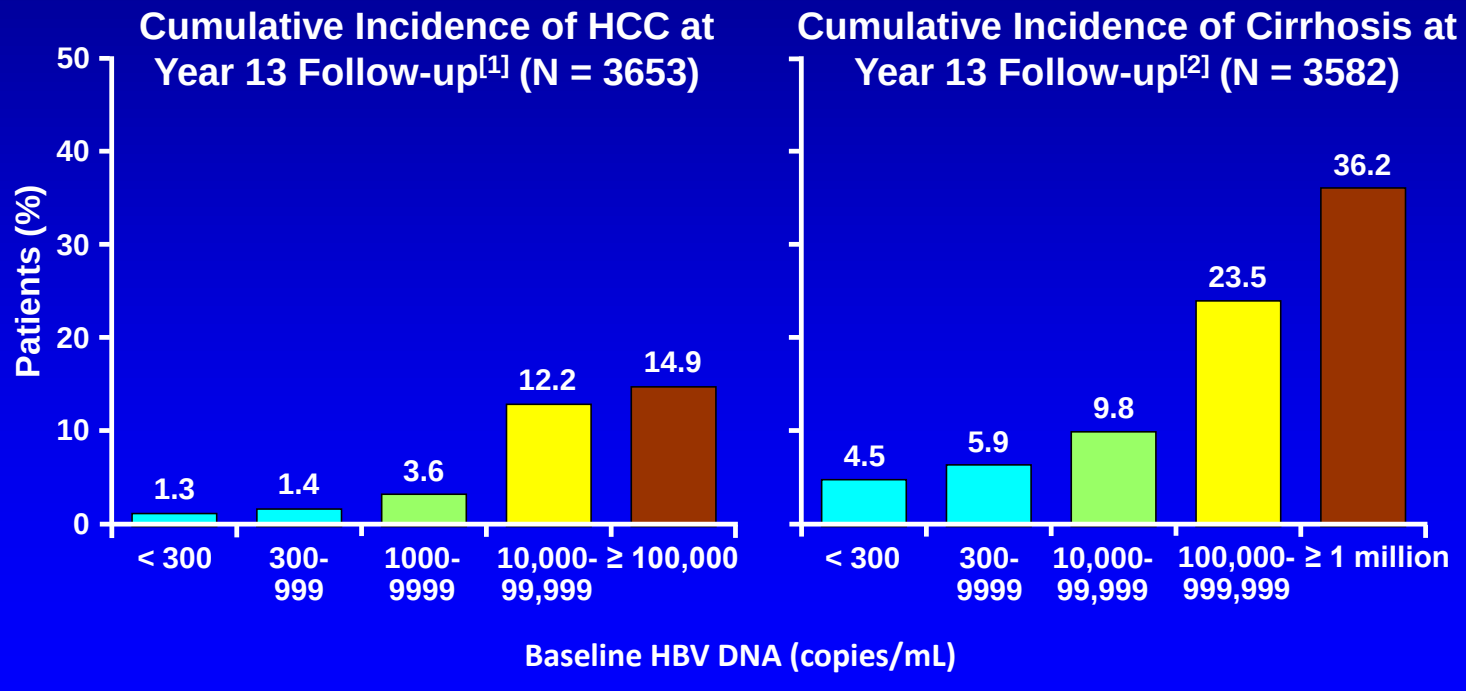
The Past and the Present: Nucleos(t)ide Analogues

– Lamivudine Telbivudine
– Adefovir Tenofovir
– Entecavir

>> Paucity of virus-specific targets – all target HBV RT
>> Long term treatment limited by antiviral resistance

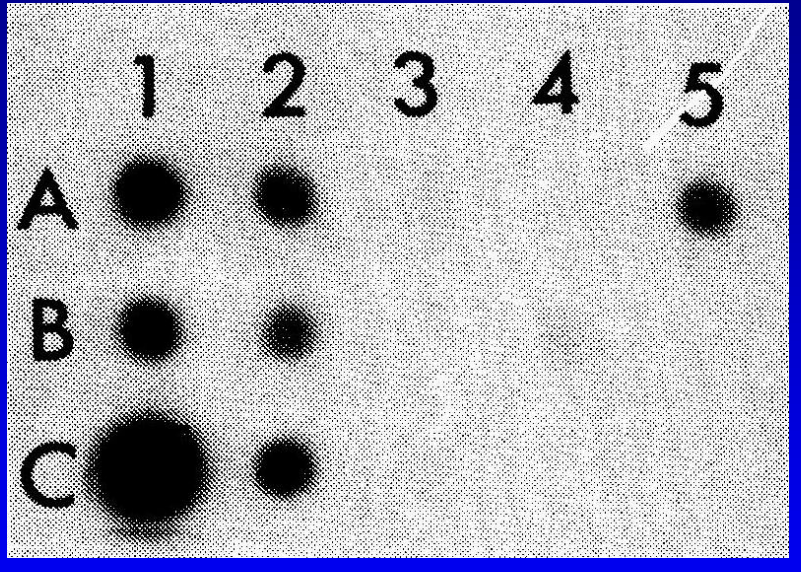
High Baseline HBV DNA Associated With Increased Risk of HCC and Cirrhosis

REVEAL: Long-term follow-up of untreated HBsAg +ve individuals in Taiwan



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

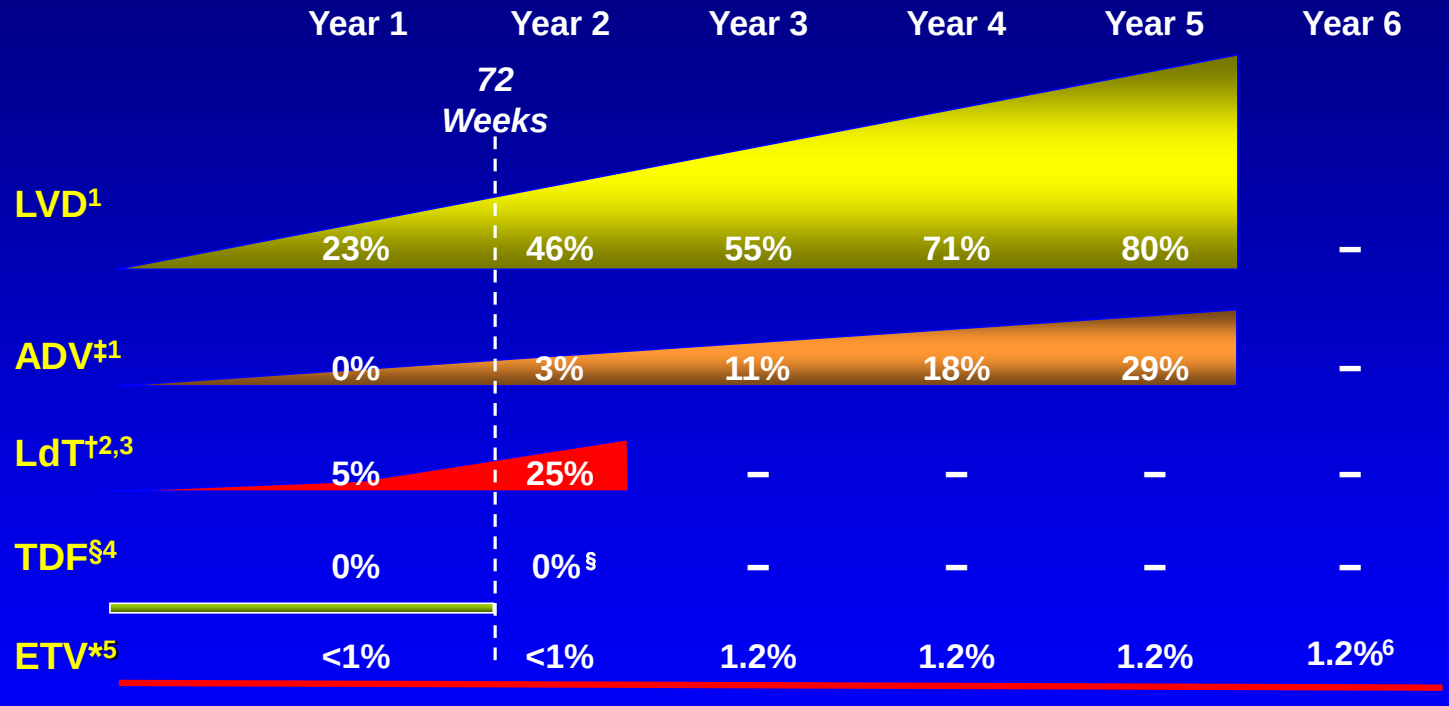
Dot-Blot Hybridisation for HBV DNA in Serum from Patient Co-infected with HIV



Samples Al toA5 are, respectively, from March 12, March 26, May 7, May 15, and May 26,1987. Samples Bl to B5 are from June 26, July 2, and July 6, 1987, and Jan 23 and Dec 28,1988. Samples Cl to C3 are cloned HBV DNA standards of 1000, 100, and 10 pg/ml.

Locarnini, S et al 1989. Lancet;2:1225-1226

Resistance Rates Through 6 Years Among Nucleos(t)ide-Naïve Patients

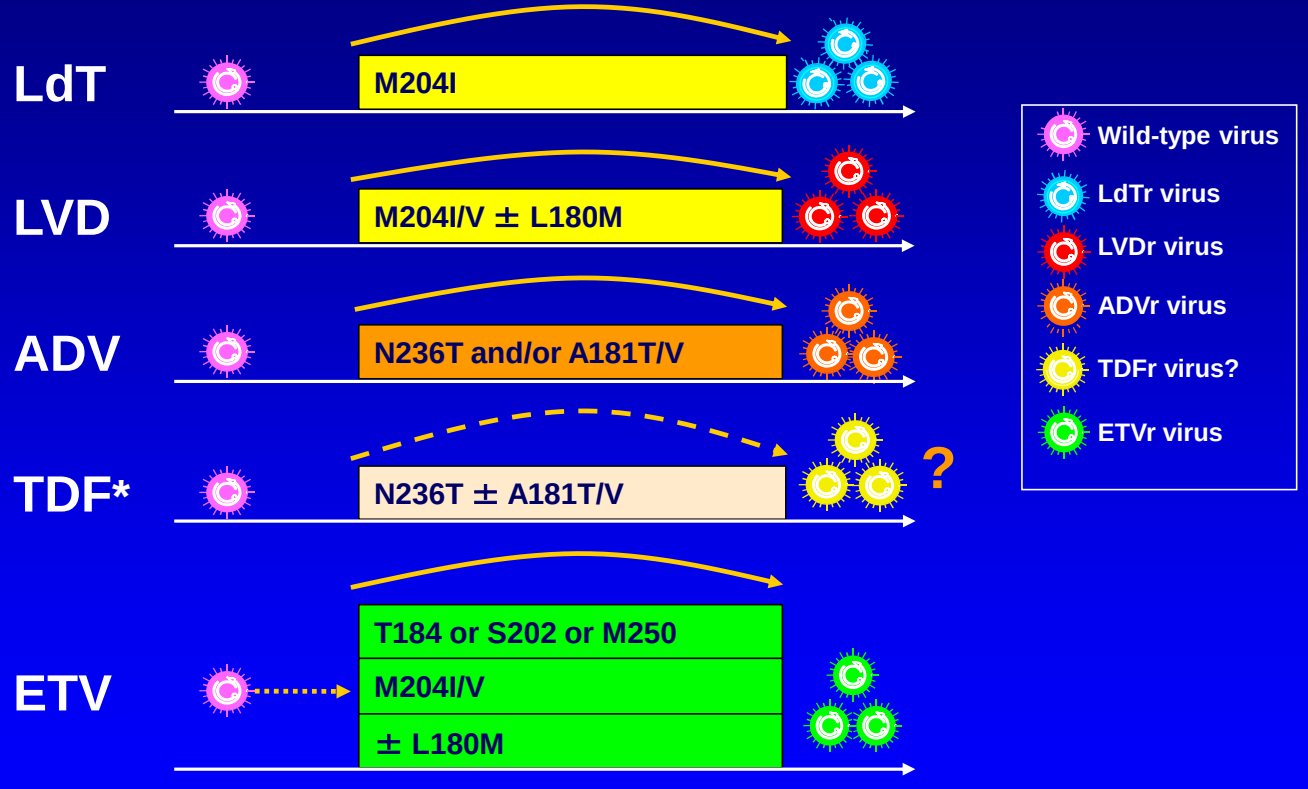


§ Patients with HBV DNA ≥400 copies/mL at Week 72 could add FTC to TDF; 5% were switched by Week 96.[5,6]

* Cumulative probabilities of resistance taken; † Naïve HBeAg (+); ‡ Naïve HBeAg(-); N/A not available.

1. Locarnini S. Hepatol Int 2008;2:147–151. 2. Lai CL, et al. N Engl J Med 2007;357:2576–2578; 3. Liaw YF, et al. Gastroenterology 2009;136:486–495.
4. Snow-Lampart A, et al. AASLD Oct 31–Nov 4, 2008, San Francisco, USA. Poster Presentation 977. Hepatology 2008;48:745A.
5. Baraclude EU SmPC, February 2009. 6. Tenney DJ, et al. EASL April 22–26, 2009, Copenhagen, Denmark, Oral Presentation 1761.

Current Antivirals Have Different Genetic Barriers to Resistance



* Based on blunted responses to TDF in patients with genotypic ADV resistance.

Locarnini S. *Hepatol Int* 2008;2:147–151. van Bömmel F, *et al*. Presented at: *58th Annual Meeting of the American Association for the Study of Liver Diseases,* Boston, USA, 2–6 November 2007; Poster 960. Tenney DJ, *et al*. *Hepatol Int* 2008;2:A88–A89.

Cross Resistance – Treatment Adaptation

- LMV resistance >> Add TDF (ADV if not available)

- ADV resistance >> Add ETV (LMV if not available)
  >> switch to TDF plus 2nd drug
- ETV resistance >> Add TDF (ADV if not available)

- TFV resistance?? >> Add ETV (LMV if not available)

Key: Avoid drugs from the same structural group
Avoid the accumulation of mutations

Treatment Options

Advantages and Disadvantages

Nucleos(t)ide Analogues	Immunomodulatory
Oral administration	Subcutaneous
Potent HBV DNA suppression	Less potent HBV DNA suppression
Antiviral	Antiviral and immunomodulatory
Few side effects	Frequent side effects
Risk of resistance development	No resistance
HBsAg seroconversion rare	HBsAg seroconversion uncommon
Long-term therapy	Finite therapy duration

Stopping Treatment

APASL Recommendation to Stop Antiviral Treatment

In HBeAg-positive patients: when HBeAg seroconversion has developed > 6 months

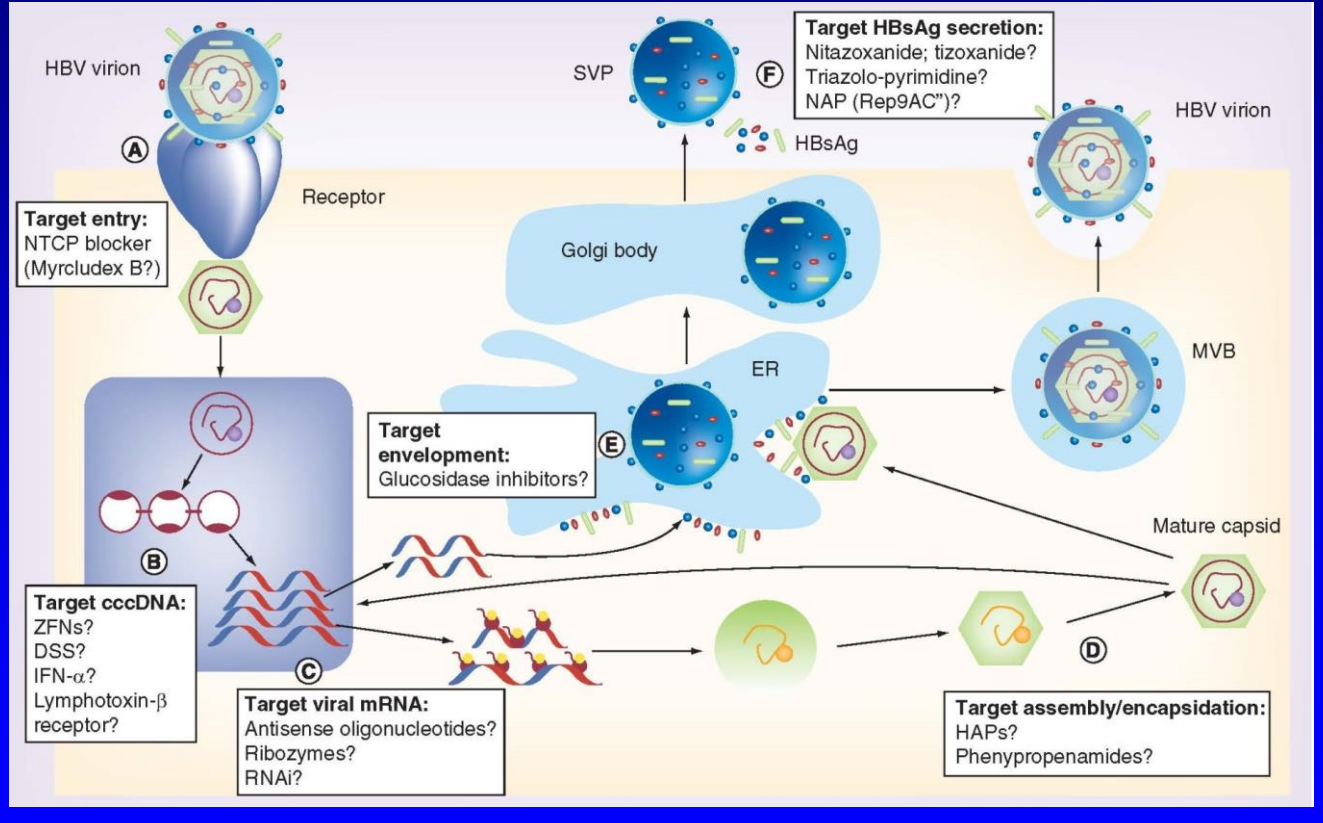
In HBeAg-negative patients: when HBV DNA remaining undetectable for three separate occasions 6 months apart

- Outcomes
  - 25-50% develop viral relapse with hepatitis
  - up to 40% remain virus free (SVR)
  - half of these lose HBsAg
- Factors
  - HBV DNA undetectable at stop
  - HBsAg < 100 IU/ml [low]
  - duration of AV therapy (4-5 years)

Alex Thompson Saturday 10am

Hadziyannis, S et al 2012. Gastro;143:629.
Liang, Y et al 2011. Aliment Pharacol Ther;34:344.
Patwardham, N et al 2014. Aliment Pharmacol Ther;40:804.
He, D et al 2013. BMC Infec Dis;13:458.
Jeng, W-J et al 2013. Hepatol;58:1888.

HBV Lifecycle Showing Novel Approaches for Viral Targets



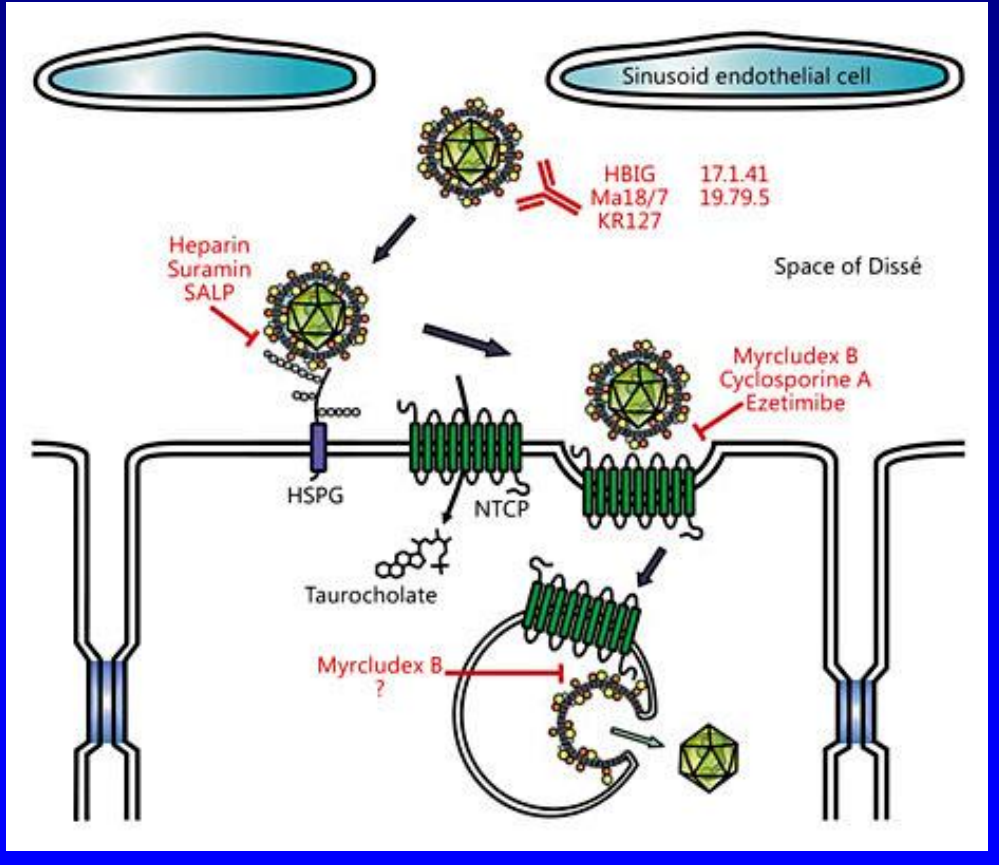
Kapoor R & Kottilil S. 2014. Future Virol;9:565-585

New Agents – The Future

Strategy	Target	Agents		
HBV life cycle	HBV Pol	TAF		
	Viral entry	Myrcludex-B		
	cccDNA	Zinc finger nucleases	cccDNA conversion inhibitors	
	mRNA transcription/ stability	Zinc finger proteins	Epigenetic silencers	RNA silencing - Antisense OGNs - Ribozymes - RNAi
	Viral assembly	HAPs	Phenylpropenamides	
	HBV antigen secretion	REP 9AC'	Small molecule inhibitors of HBsAg secretion e.g. glucovirs e.g. triazolo-pyrimidines	
Immuno-therapeutic	PegIFN-λ1a (IL29)			
	Cytokines	rIL-7	rIL-21	
	TLR agonists	TLR7 (GS-9620)		
	Therapeutic vaccines	Adeno-virus approaches (TG1050)	Tarmogen (GI-13020)	
	Blocking T cell inhibitory receptors	Anti-PD-1 moAB (BMS936558)	Anti-PD-L1 moAb (BMS936559)	
	Intrahepatic blocking of suppressive cytokines / regulatory T cells	TGF-β inhibitors	T reg depletion (e.g. α-CD25, daclizumab)	

Peter Revill Saturday 9:30

Inhibitors of HBV Attachment and Entry



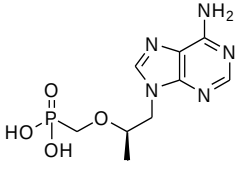
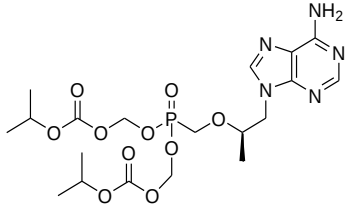
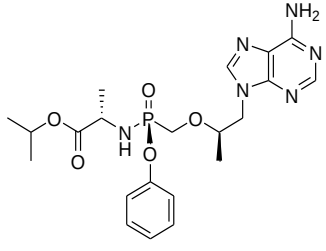
Sodium taurocholate cotransporting polypeptide (NTCP) identified as HBV and HDV receptor in 2012

Myrcludex in phase 2 trials in chronic HBV and chronic HDV decrease in HBV DNA and HDV RNA

Yan H, Elife 2012; 1:e00049
Lempp RA, Urban S. Intervirol 2014'; 57: 151

Reverse Transcription: Improved Potency of NA Tenofovir Alafenamide (TAF)

- TAF = orally bioavailable phoshonoamidate prodrug of tenofovir (TDF
- In comparison with tenofovir, TAF enables enhanced delivery of the parent nucleotide and its active diphosphate metabolite into lymphoid cells and hepatocytes.
- This is attributed to an improved plasma stability and differential intracellular activation mechanism for TAF relative to TDF

EC_{50} HIV-1 (PBMCs)	Tenofovir	Tenofovir Disoproxil	TAF
			
	1.2 µM	0.015 µM	0.003 µM

Action for Hepatitis B

- 2nd National Hepatitis B Strategy 2014 - 2017
- National Hepatitis B Testing Policy 2015
- WHO Global Network for Viral Hepatitis 2012
- ICE – HBV 2015