# HIV and HBV

## *what's coming next*

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# Disclosures

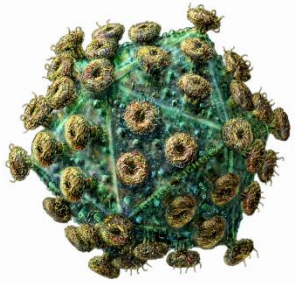
- Joop Arends
  - Advisory boards*
    - ViiV, MSD, Janssen, Abbvie, Gilead, BMS
  - (research) grants*
    - BMS, Abbvie, ViiV, MSD

- Andrew Ustianowski
  - Advisory boards & speaker fees
    - ViiV, MSD, Janssen, Abbvie, Gilead, BMS
  - (research) grants
    - Gilead

***money paid to research account UMC Utrecht***

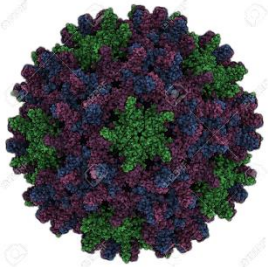
# Interactive presentation

**HIV**



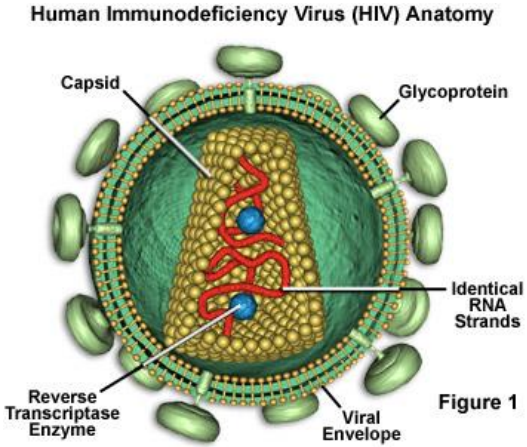
Andrew

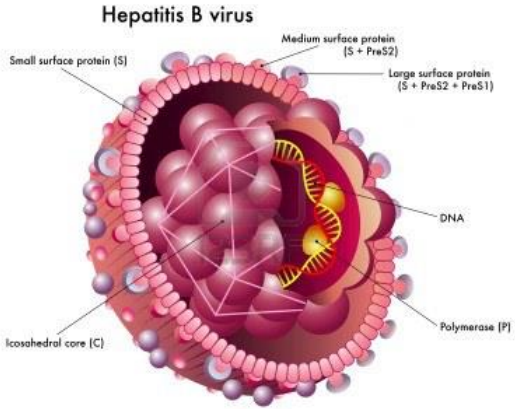
**HBV**

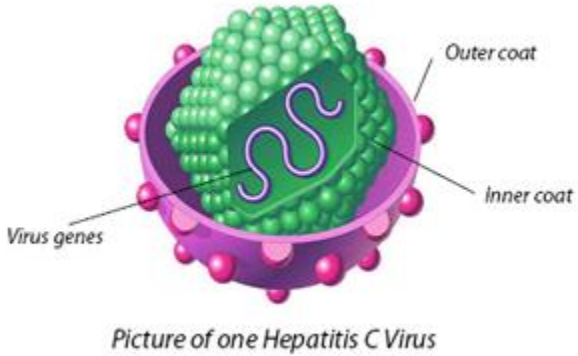


Joop

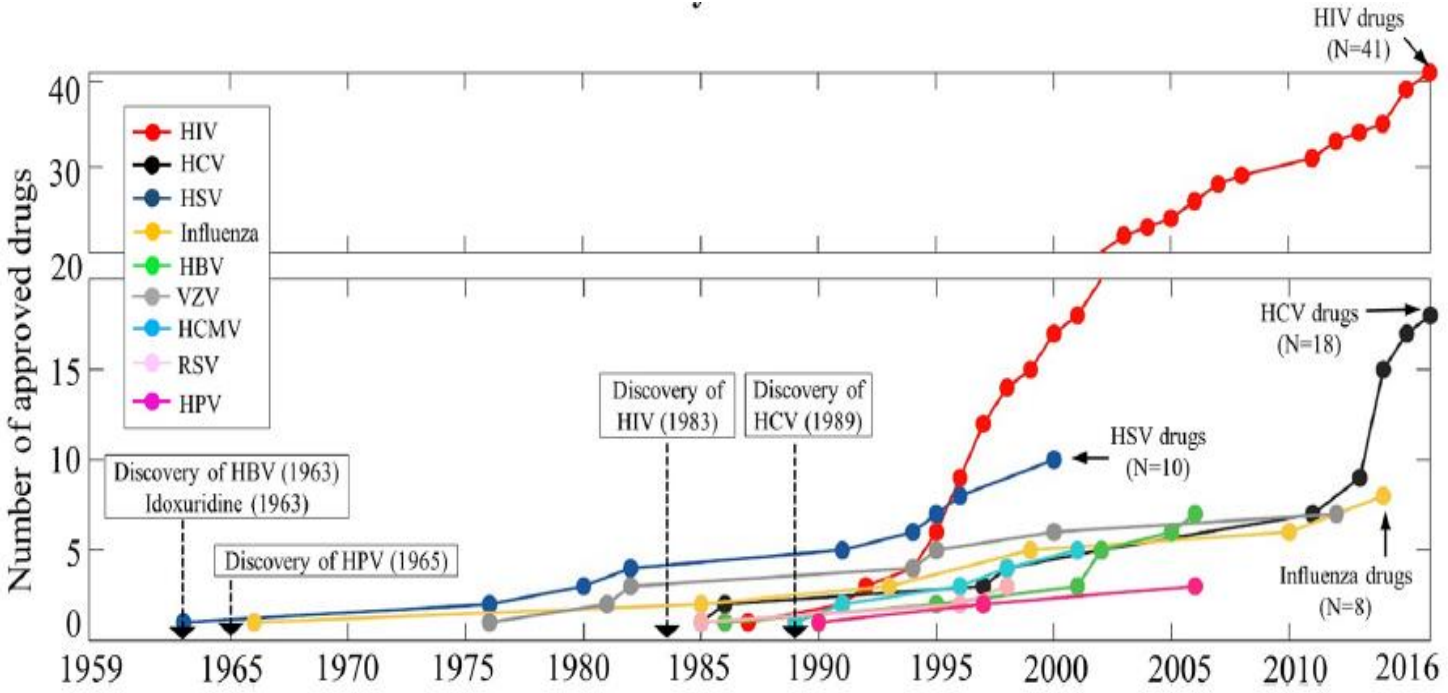
# What do these 3 viruses have in common?



# Advancement in viral drug therapeutics



- Mechanistic insights into viral life cycles and drug therapy targets have also accelerated treatment development in other viral disease like viral hepatitis B and C.

## Discovery of in vitro replicon systems

**HIV**
1984

**HCV**
2003

**HBV**
2013

## Discovery of drug targets

**HIV**
1964 - AZT

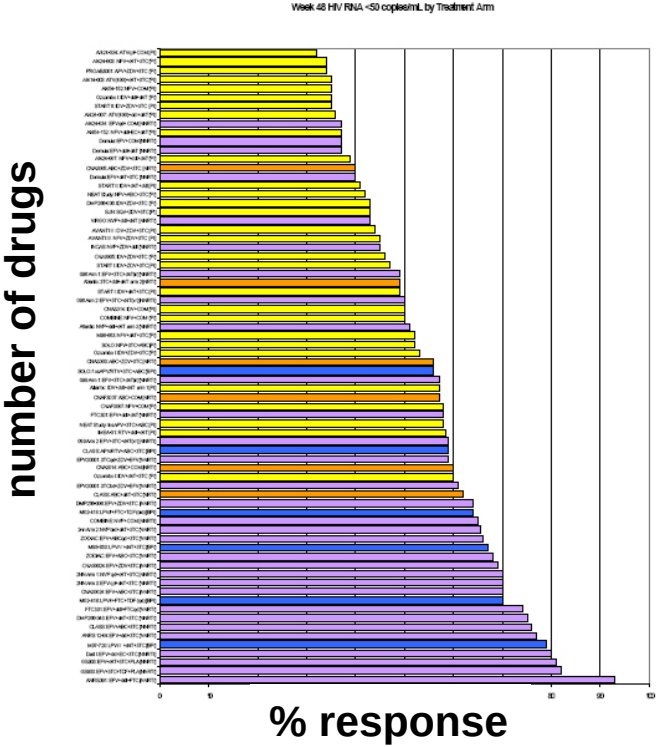
**HCV**
2003 – NS3 protease

**HBV**
2008 - NRTI

# Advancements in antiviral treatment

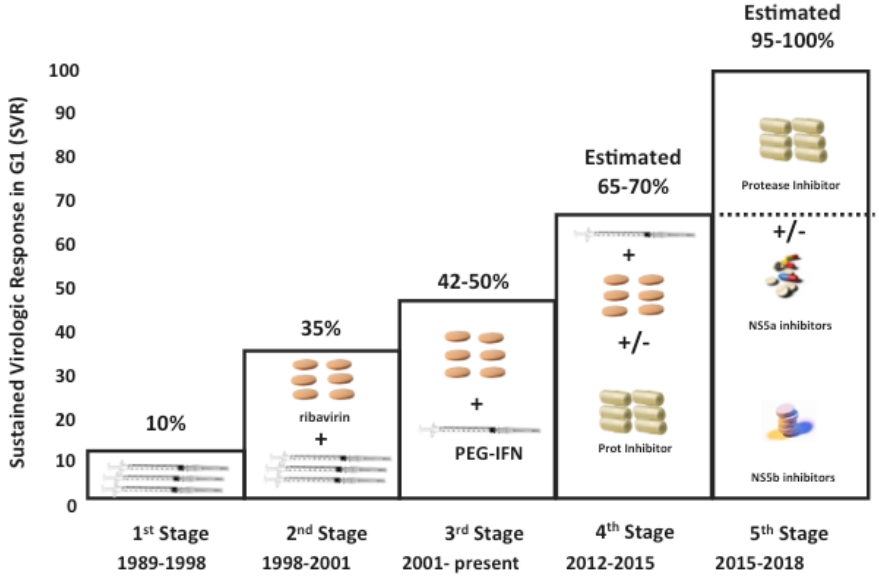


## HIV




## and

## HCV



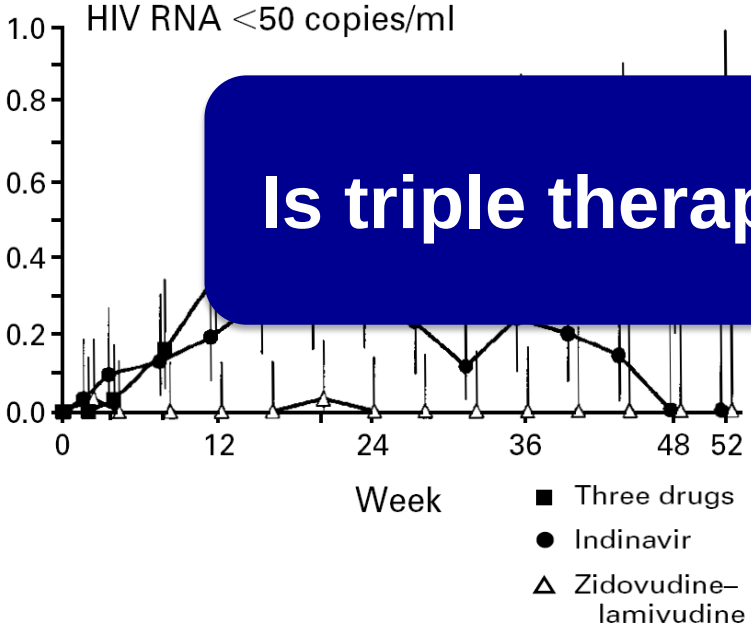
# Similarities in development between 3 viruses

| Topics | HIV in 2000 | HCV in 2014 | HBV in 2020 |
|---|---|---|---|
| Newly identified, effective drugs | ✓ | ✓ | ✓ |
| High cost of drugs and tests | ✓ | ✓ | ✓ |
| Complex drug regimens, side effects | ✓ | ✓ | ✓ |
| Limited data on epidemiologic situation | ✓ | ✓ | ✓ |
| Lack of advocacy for global access | ✓ | ✓ | ✓ |
| Lack of political and financial global commitment | ✓ | ✓ | ✓ |

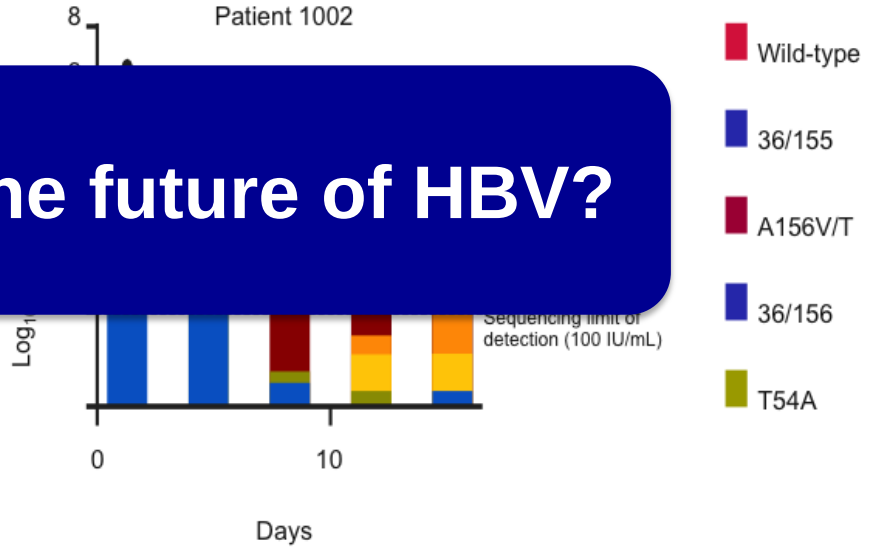
# Major advancements made over time

| | **Progress over time** | | |
|---|---|---|---|
| | **HIV (2000->2010)** | **HCV (2014->2024)** | **HBV (2020->2030)** |
| Cost of drugs | >$10,000 -> <$100 /patient/year | >$10,000 -> <$100 /patient/course | <$1000-> >$10,000 /patient/year |
| Global funding | Low -> Major global initiatives | Medium -> Major global initiatives | Major global initiatives |
| Numbers on treatment in low-income countries | ~50,000 -> 10 million | ? | ? |

# Rapid development of drug resistance with mono-therapy




**Is triple therapy the future of HBV?**

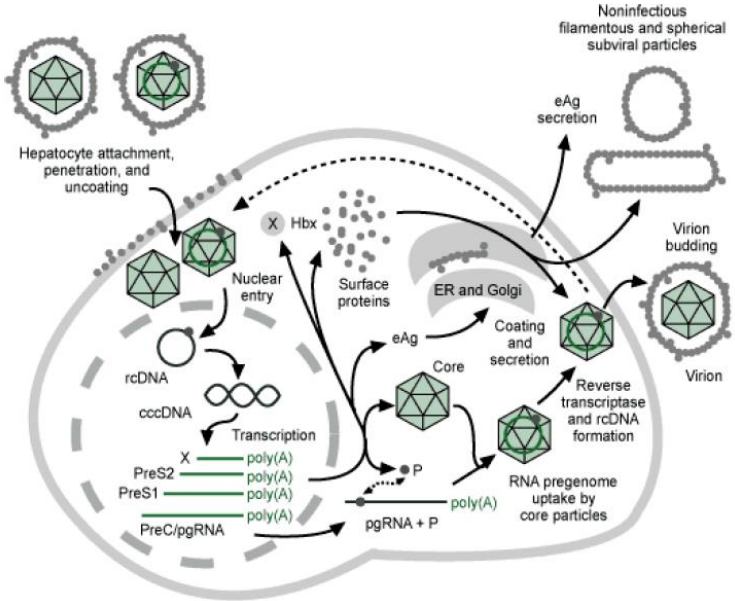



Gulick RM *et al. N Engl J Med*. 1997 Sep 11;337(11):734-9

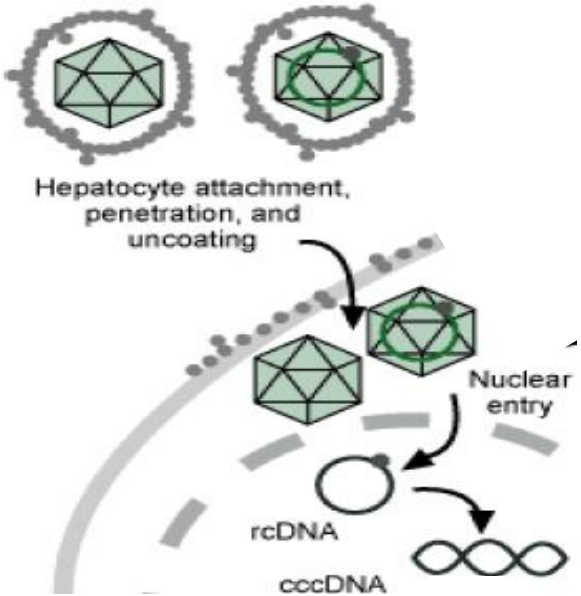
Kieffer TL *et al. Hepatology* 2007;46(3):631–9

# Where are we going with HBV treatments?

- Firstly we need to briefly run over the life-cycle….




# What about viral entry into liver cell and then nucleus?



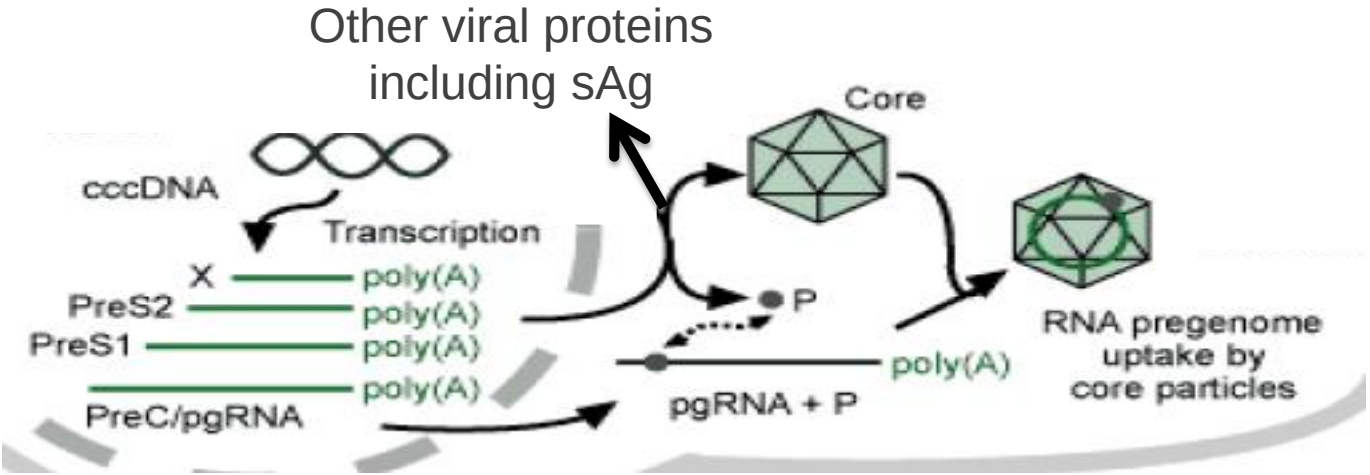

- Viral envelope binds to cell membrane
  - Receptor = sodium taurocholate co-transporting polypeptide
    - (a bile salt transporter)
- Then it is uncoated and viral DNA enters into cell nucleus…

  …and viral genome is converted to cccDNA

  = “covalently closed circular DNA”

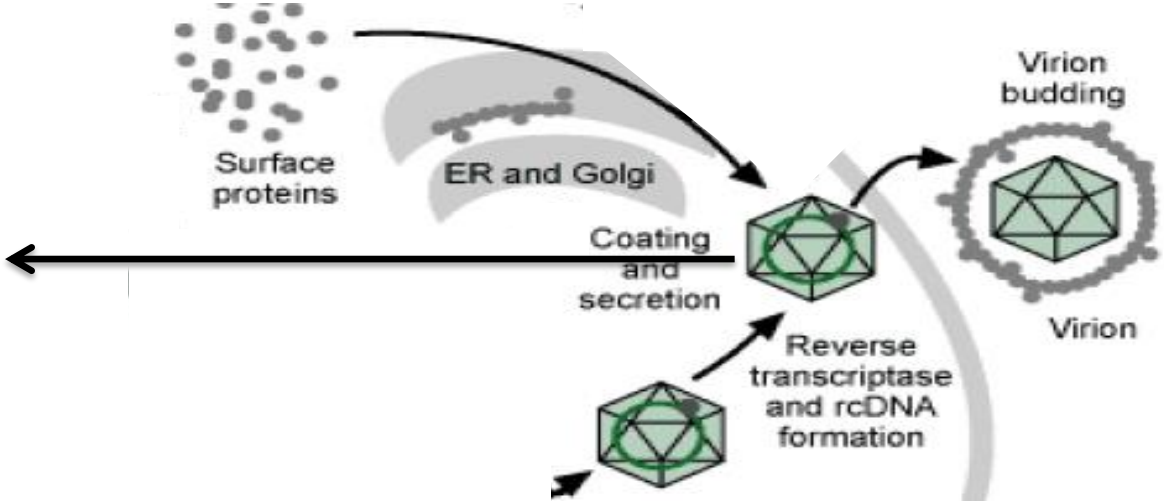
  = HBV ‘mini-chromosome’

# Transcription and translation….



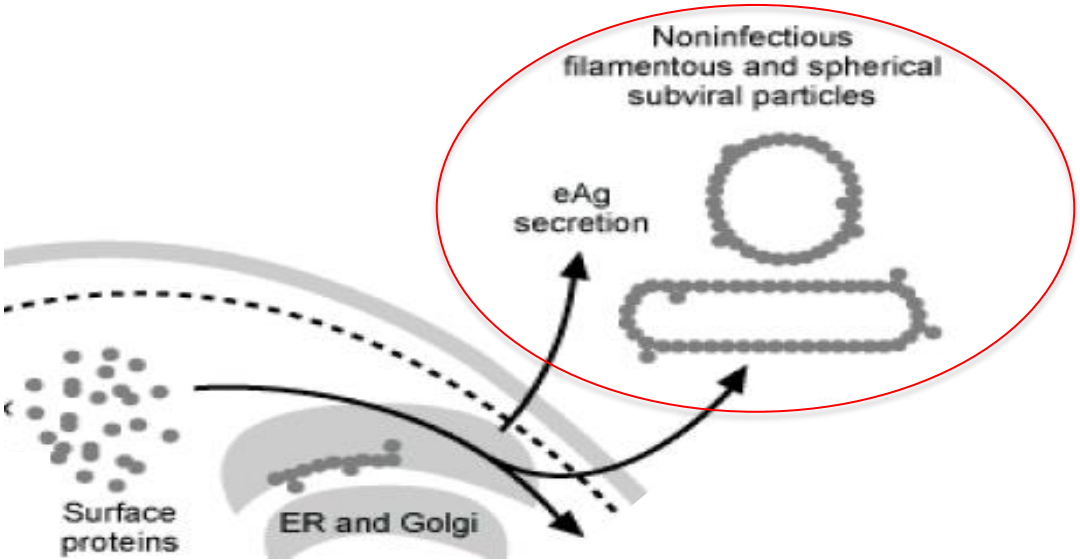

- Products then encapsulated within virus core particle
  - RNA pregenome, nucleocapsid & polymerase proteins

# And then it is released…




- Virus contains a new negative strand DNA which partially synthesises a positive stand
- Coated by envelope proteins ➔ Complete virion ready for release
  - But some is also recycled back into the nucleus and replenishes ccc-DNA

# Not all the proteins end up in the virus particle….

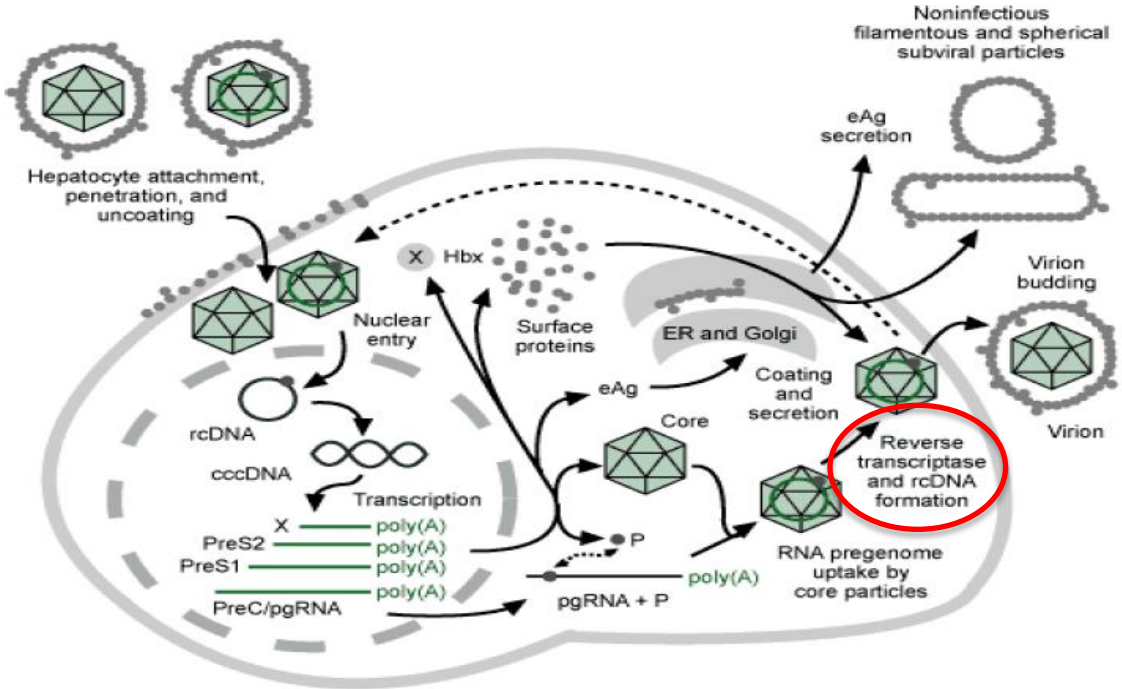



- Why??
  - Immunomodulatory
  - Tolerogenic….
  - Inflammatory….

# OK.. What drugs do we have at present??

- Nucleos(t)ide analogues
  - Tenofovir disoproxil
  - Adefovir
  - Entecavir
  - Lamivudine
  - Emtricitabine
  - Telbivudine

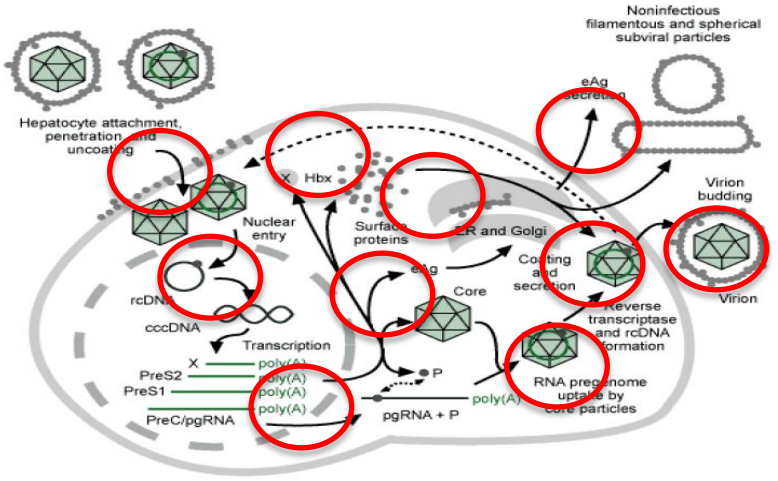
- Newer Nucs
  - Tenofovir alafenamide
  - Besifovir



# Interferon alpha

- Naturally occurring immunomodulator
  - Multiple activities… not entirely clear which are most important

- Specifically
  - Induces an antiviral state in cells
    - Induces degradation
  - Inhibits cellular proli
  - Immunomodulates i

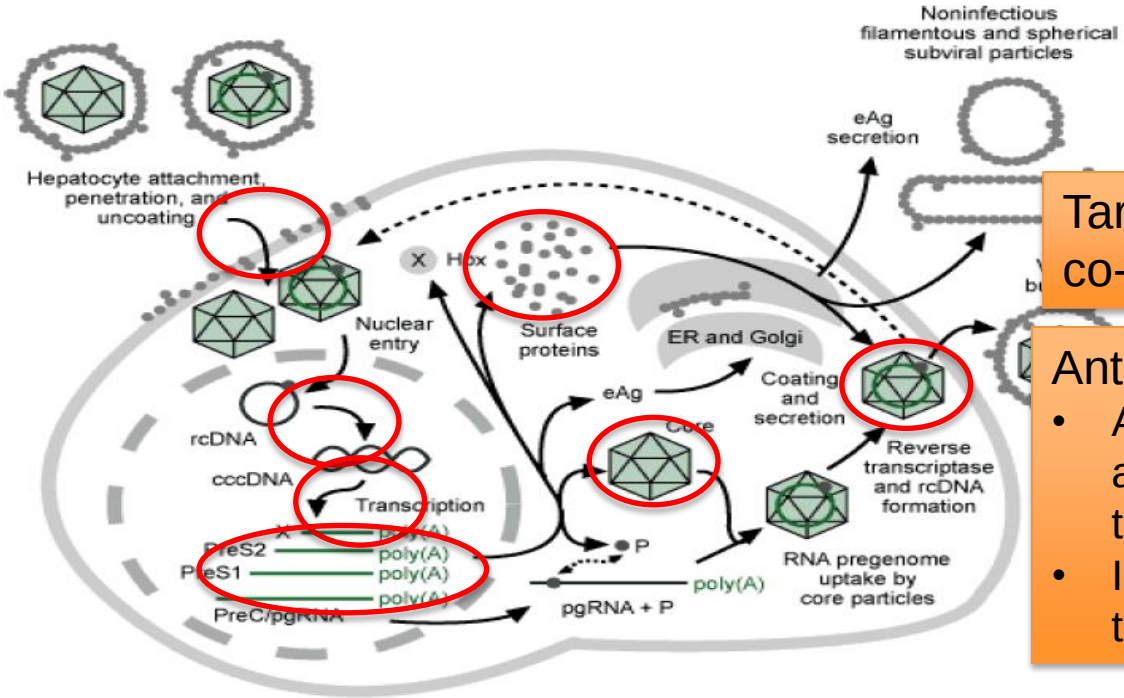


# But we know this usually doesn't result in a proper 'cure'

- There is still active research into combining interferon and nucleos(t)ides…

- But what are the newer possibilities being actively explored?

# Where else could be targeted??



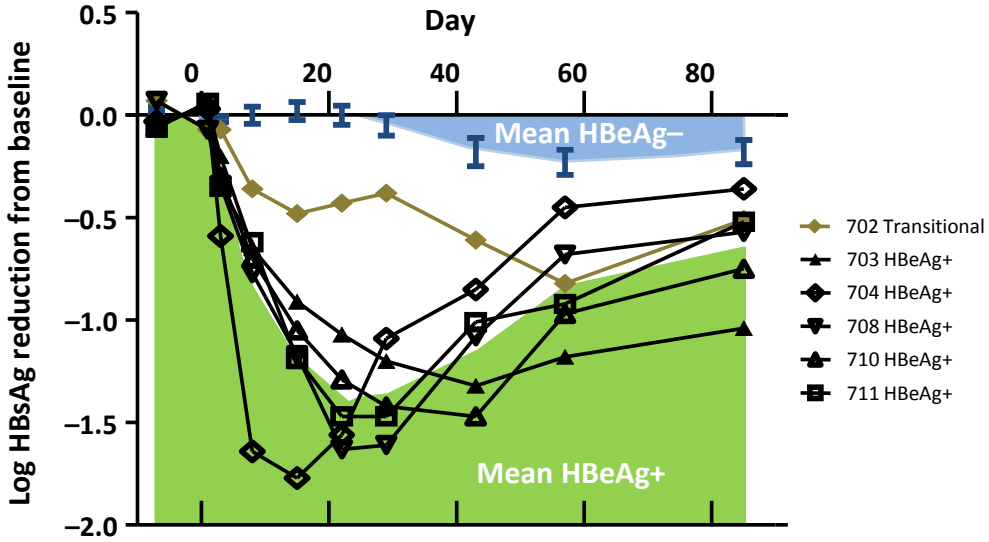

Target the sodium taurocholate co-transporting polypeptide

Antisense & RNAi approaches

- Antisense molecules or ribozymes that are complementary to DNA or RNA templates
- Interfere with transcription and translation

# SiRNA: RNA interference therapy

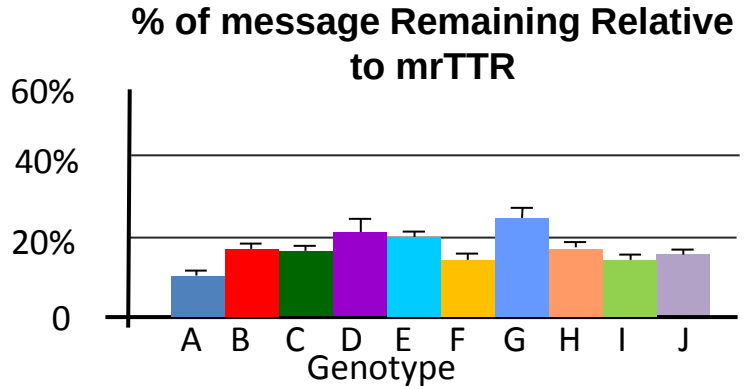
**Reduction of HBsAg in treatment-naïve CHB patients after a single dose of 4 mg/kg ARC-520**




Yuen M-F *et al. EASL* 2016, Barcelona. THU-193

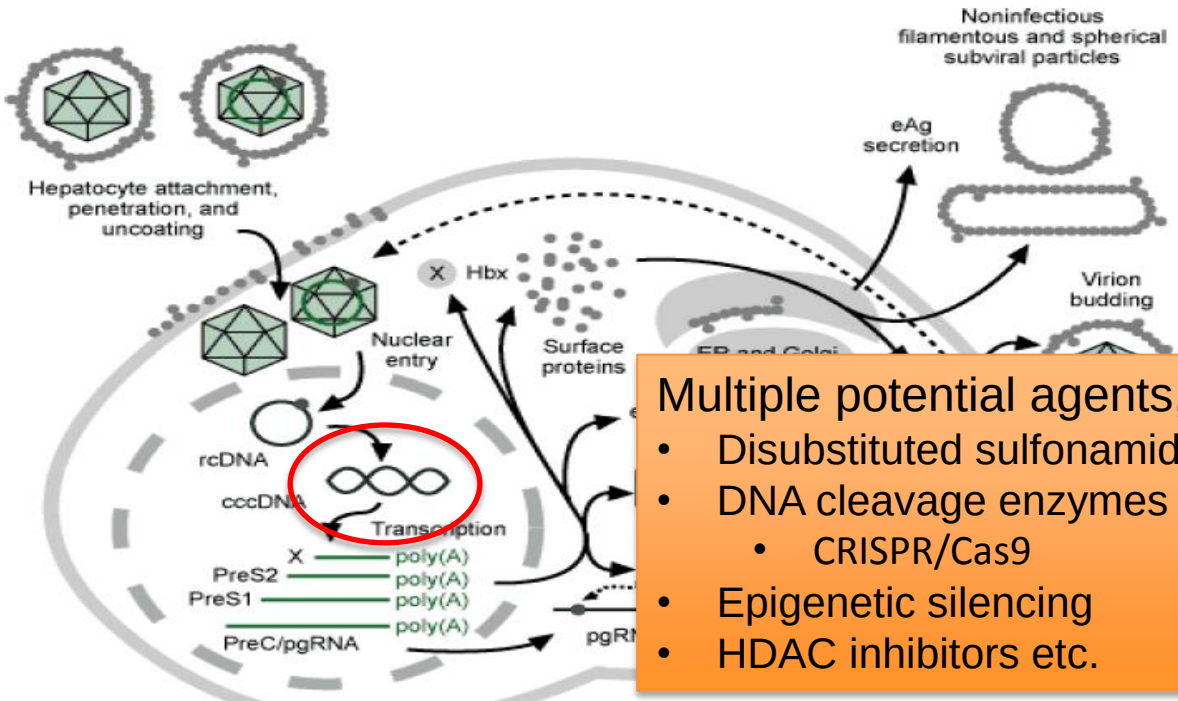
**Hepatocyte Targeting - ALN-HBV**

- N-acetyl galactosamine (GalNAc) ligand binds to asialoglycoprotein receptor (ASGPR)




Wing-Kin Sung *et al. Nature Genetics* 44:765 (2012)

# Direct ccc-DNA inhibitors



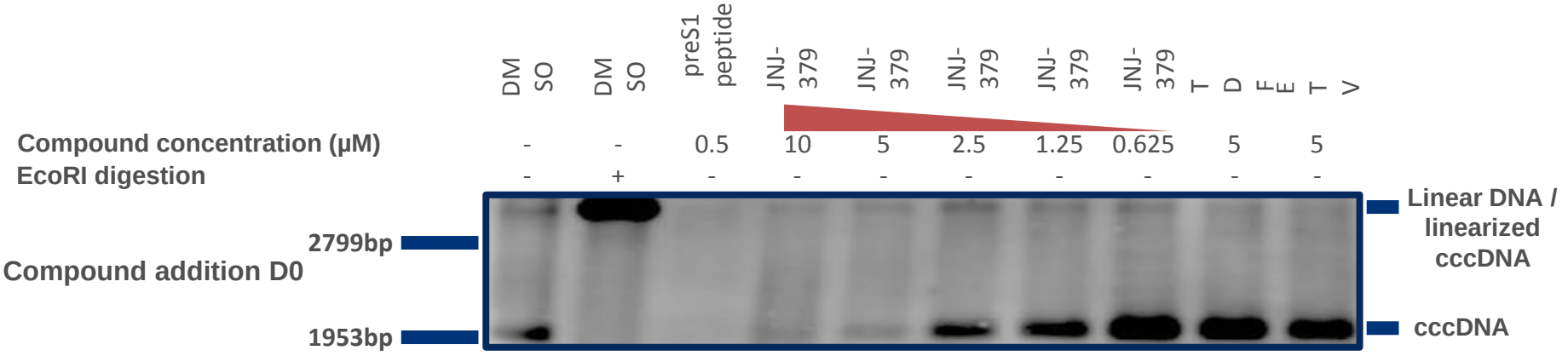

Multiple potential agents, including

- Disubstituted sulfonamide (DSS) compounds
- DNA cleavage enzymes
  - CRISPR/Cas9
- Epigenetic silencing
- HDAC inhibitors etc.

Lucifora J *et al. Science.* 2014 Mar 14;343(6176):1221-8; Ding S and Robek MD. *Hepatology*. 2014 Dec;60(6):2118-21

Pollicino T *et al. Gastroenterology*. 2006 Mar;130(3):823-37

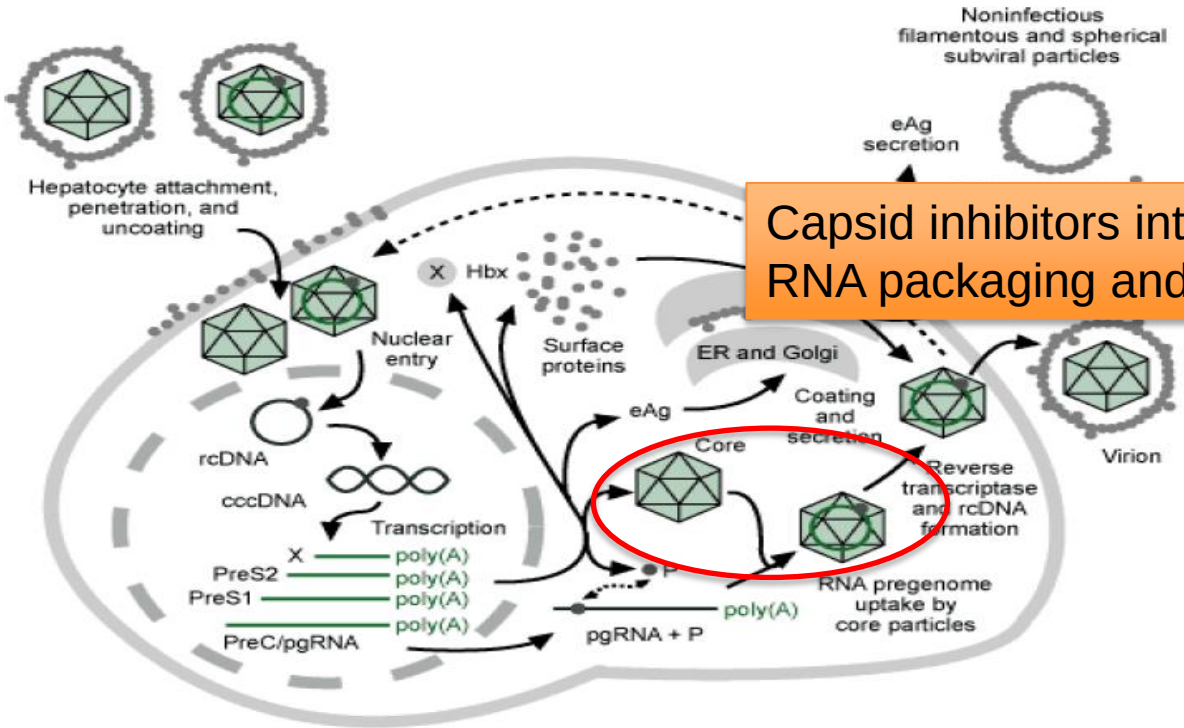
# JNJ-379: Effect on cccDNA in HBV-infected PHHs




Dose-dependent inhibition of cccDNA formation in presence of JNJ-379

Berke *et al. AASLD* 2016

# Capsid Inhibitors



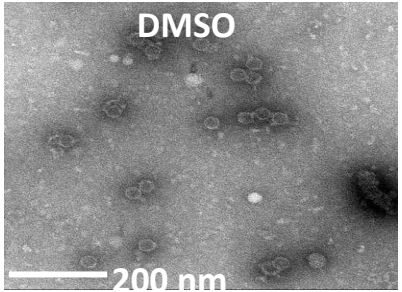

Capsid inhibitors interfere with HBV RNA packaging and capsid assembly

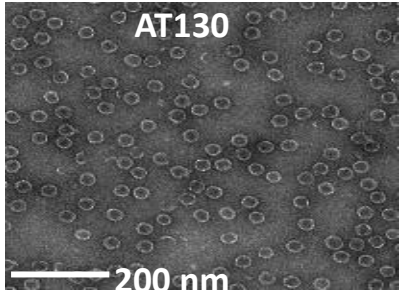
# Capsid assembly modulators

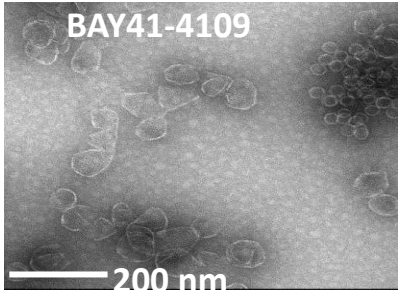
- CAMs induce the formation of two types of capsids *in vitro*
  - Empty capsids with normal geometry and size (class I MOA)
    - Phenylpropenamides (e.g. AT130) and sulfamoylbenzamide derivatives
  - Empty capsids with abnormal geometry and size (class II MOA)
    - Heteroaryldihydropyrimidines (e.g. BAY41-4109)

## Electron microscopy

Recombinant HBV core dimers + 150mM NaCl +/- 30µM CAM (24h)

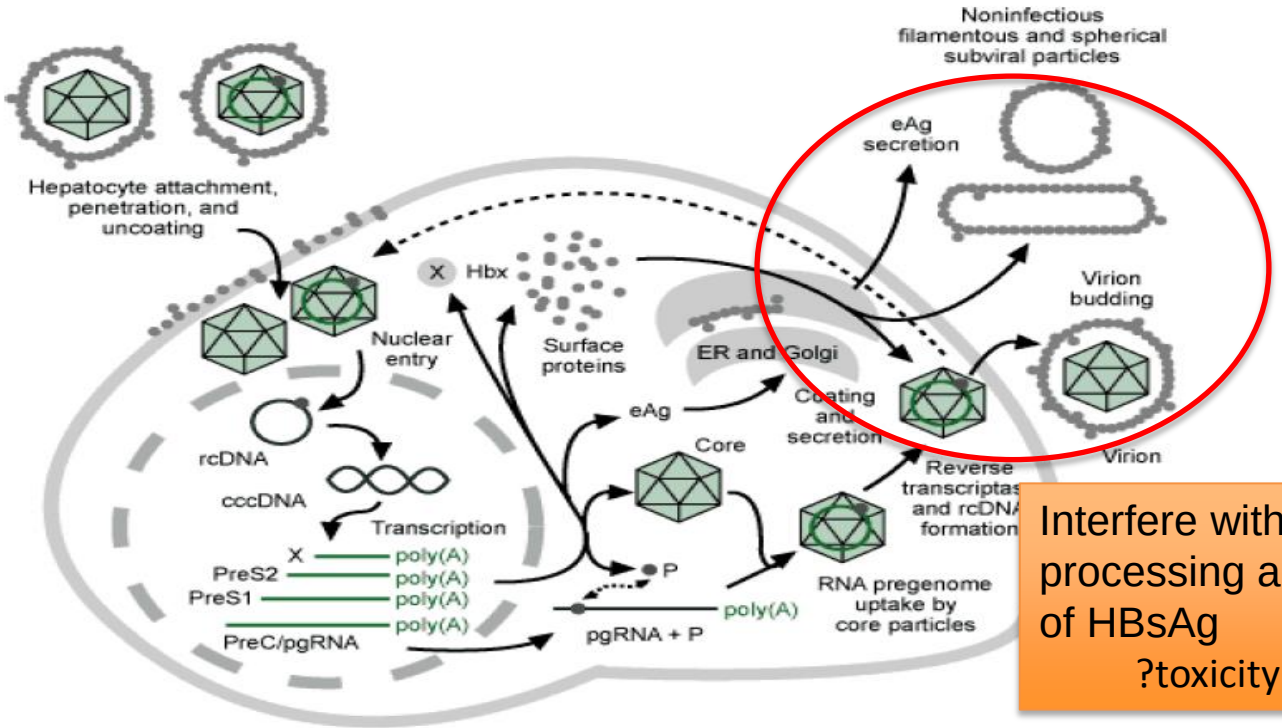



Berke *et al. AASLD* 2016

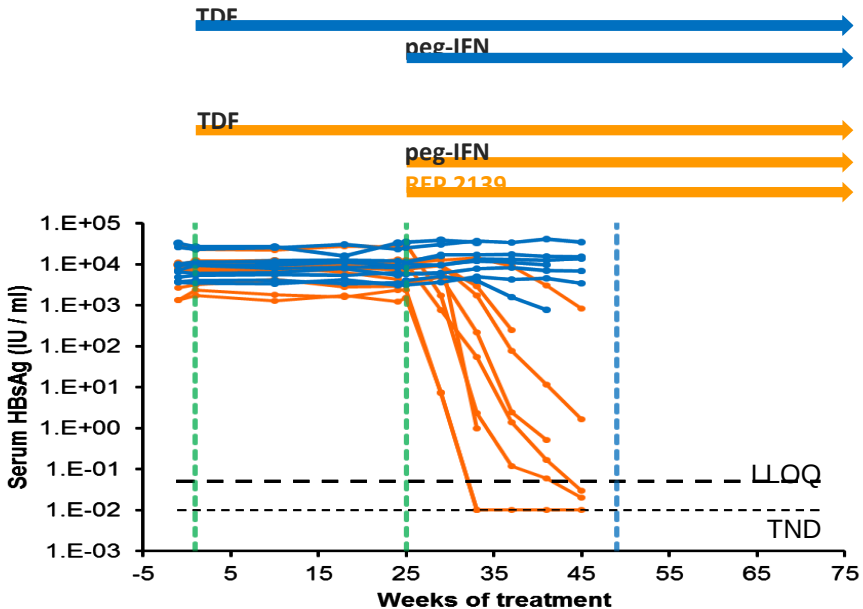
# sAg secretion inhibitors




Interfere with intracellular processing and release of HBsAg

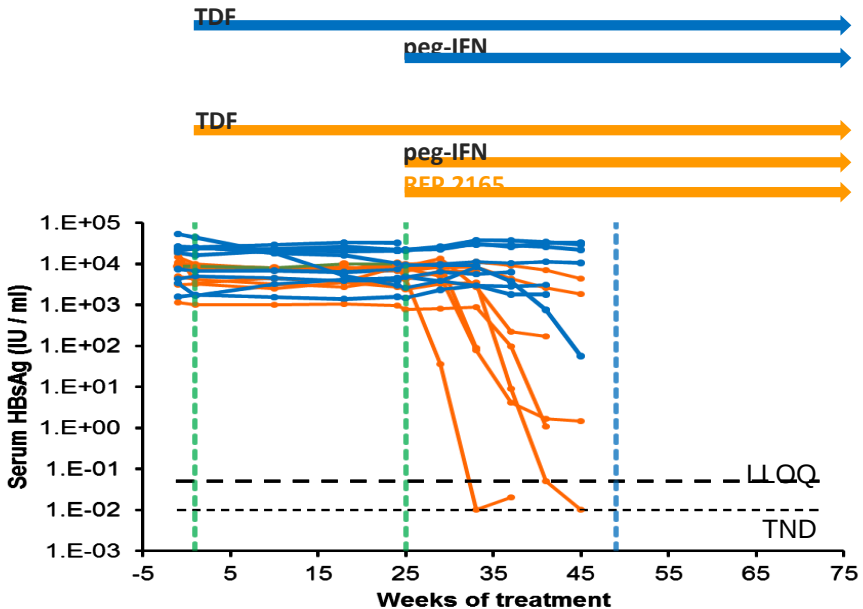
?toxicity potential

## REP 2139




**9/9 HBsAg response > 1 log**

## REP 2165

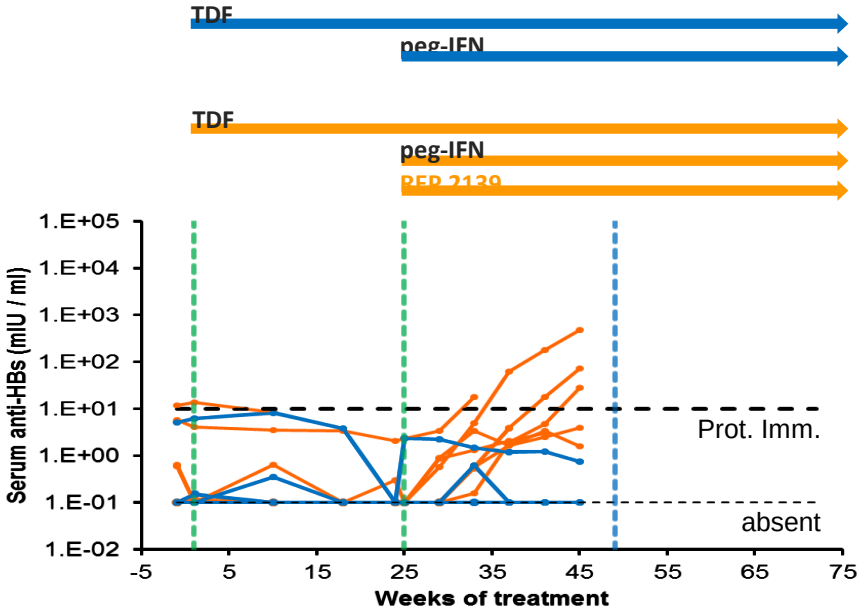



**6/9 HBsAg response > 1 log**

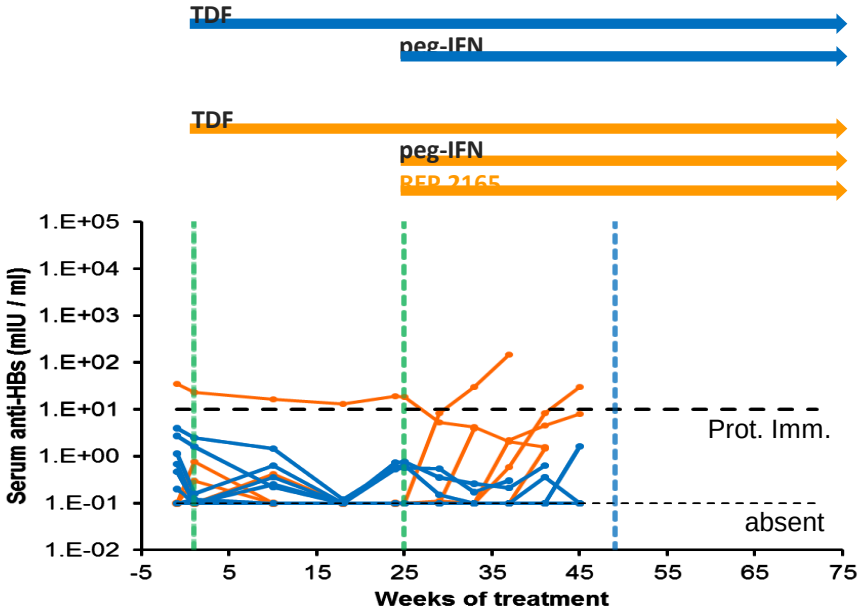
LLOQ = lower limit of quantification (0.05 IU / mL)
TND = HBsAg not detected (0.00 IU / mL)

Bazinet *et al. AASLD* 2016

## REP 2139




## REP 2165

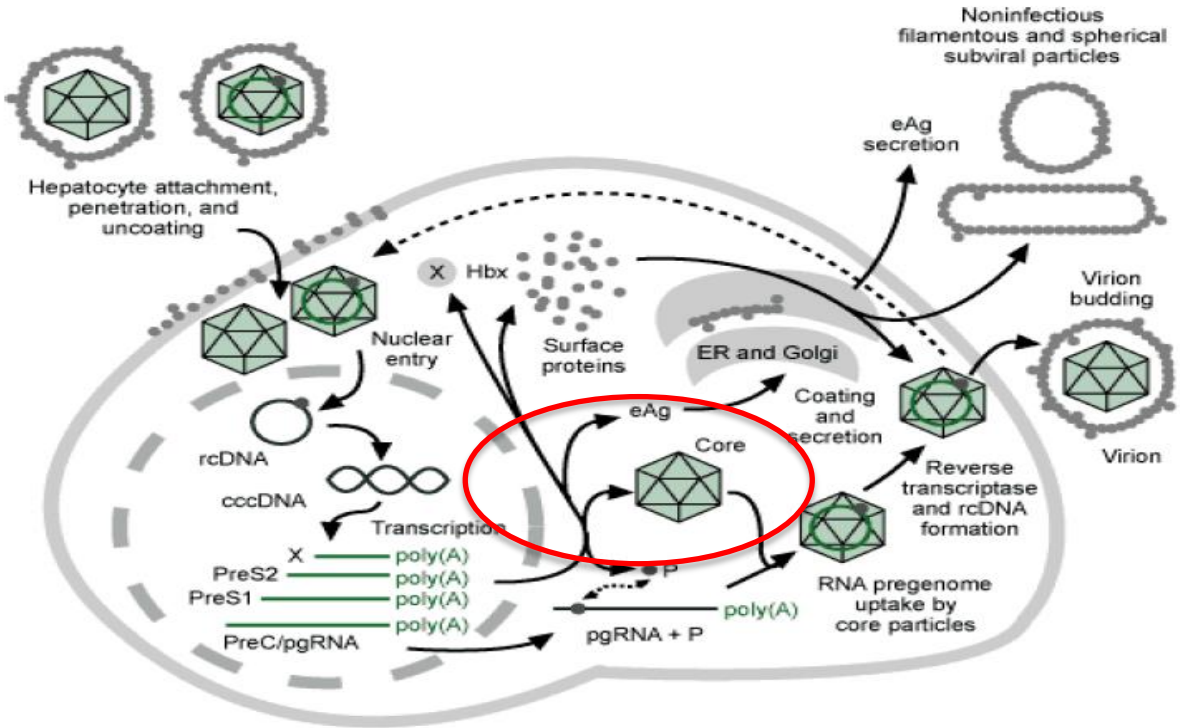



**Elevation in serum anti-HBs correlated with extent of HBsAg reduction**

Prot. Imm. = Architect defined threshold for protective immunity (10 mIU / mL)
absent = no significant anti-HBs present (≤ 0.1 mIU / mL)

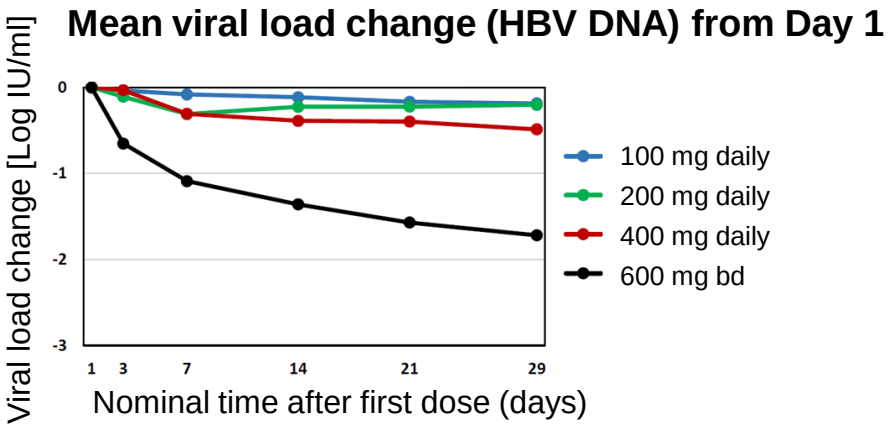
Bazinet *et al. AASLD* 2016

# And there are others…



# NVR 3-778, a **HBV Core Inhibitor**, in HBeAg-Positive Patients

- HBeAg-positive CHB patients
- Serum HBV DNA >20,000 IU/mL
- ALT levels 1-7 times upper limit of normal
- Randomized to NVR 3-778 capsules at 4 doses (*vs* placebo) x 28 days




NVR 3-778 600 mg bd associated with mean 1.72 $\log_{10}$ IU/mL HBV DNA reduction in 28 days

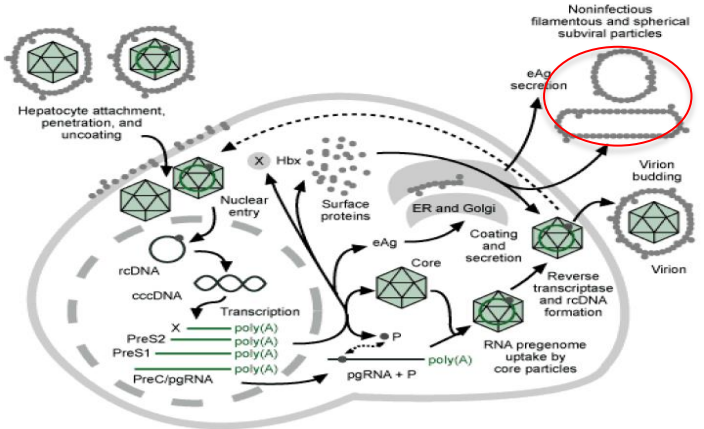
Yuen M-F *et al. AASLD* 2015, San Francisco. #LB-10

# Host-directed agents?

Immune stimulators
- Toll-like receptor agonists
  - TLR 7 (Lanford RE *et al. Gastroenterology.* 2013 Jun;144(7):1508-17, 1517.e1-10; Menne S *et al. J Hepatol.* 2015 Jun;62(6):1237-45)
  - TLR 9 (Goldstein and Goldstein, 2009)
- Lymphotoxin-b receptor agonists (Lucifora J *et al. Med Sci* (Paris). 2014 Aug-Sep;30(8-9):724-6)
- Others…

Checkpoint inhibitors
- PD-, PD-L1, CTL-4 inhibitors etc.

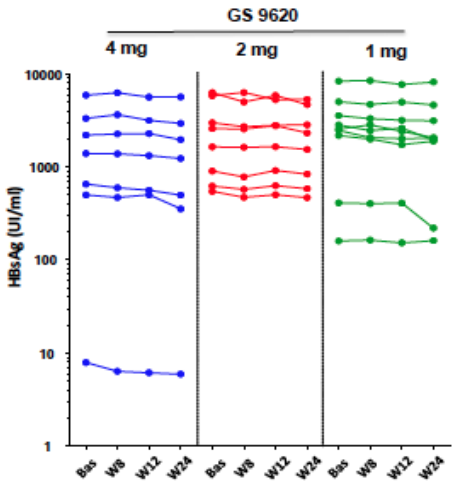
Therapeutic vaccines
- S and Pre-S antigen vaccines
- DNA vaccines (especially of S)
- T cell vaccines



# TLR agonists

**CLINICAL EFFICACY**

**HBsAg changes during GS 9620 therapy**

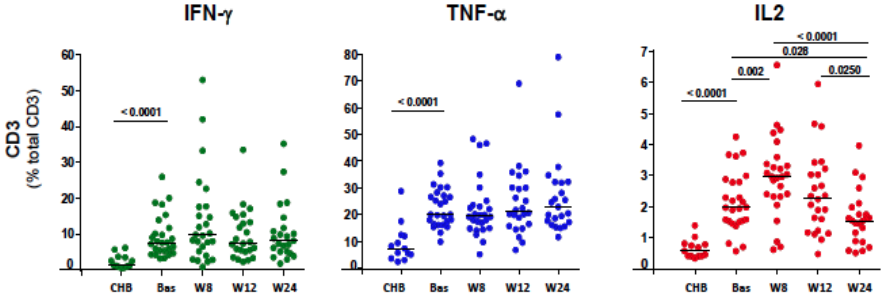



- HBsAg changes were minimal in all cohorts (no patients with >0.5-log10 declines in HBsAg at week 24)
- No patients had HBsAg loss at week 24

Boni et *al. AASLD* 2016

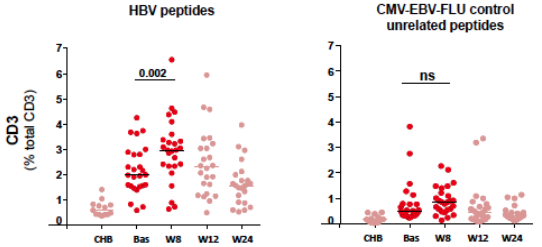
**IN VITRO HBV-SPECIFIC T CELL ANALYSIS**

**GS 9620 can induce a transient improvement of IL2 production by HBV-specific T cells**




**IN VITRO HBV-SPECIFIC T CELL ANALYSIS**

**The GS 9620 effect on IL2 production is detectable with HBV-specific but not with HBV-unrelated control peptides**



# But there are major issues…

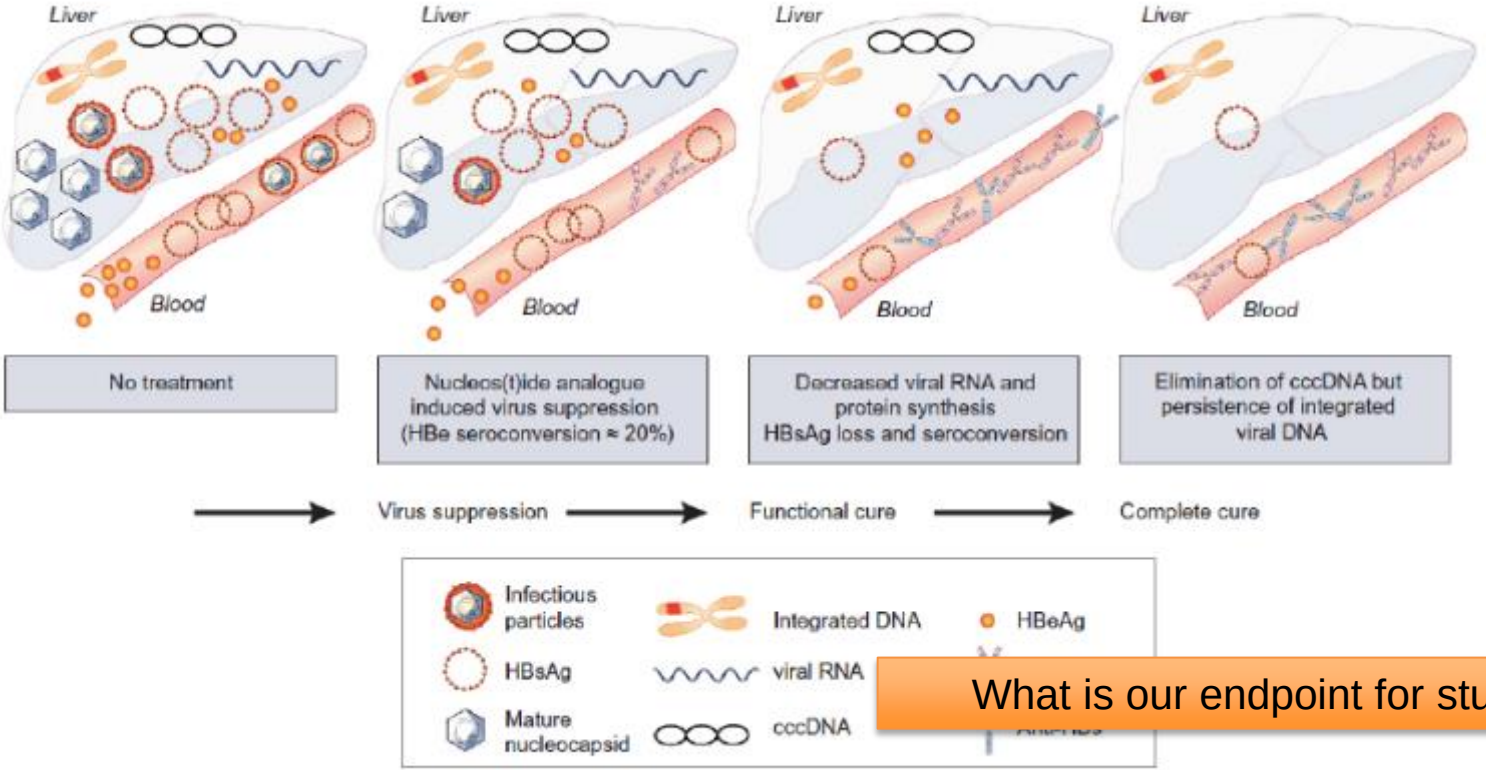
It is quite likely that a single drug or target will not be sufficient

Therefore some kind of combination….

- But how do we decide what to combine with what?

What do we mean by cure?

# What are we aiming for and how do we know we have got there?




What is our endpoint for studies?

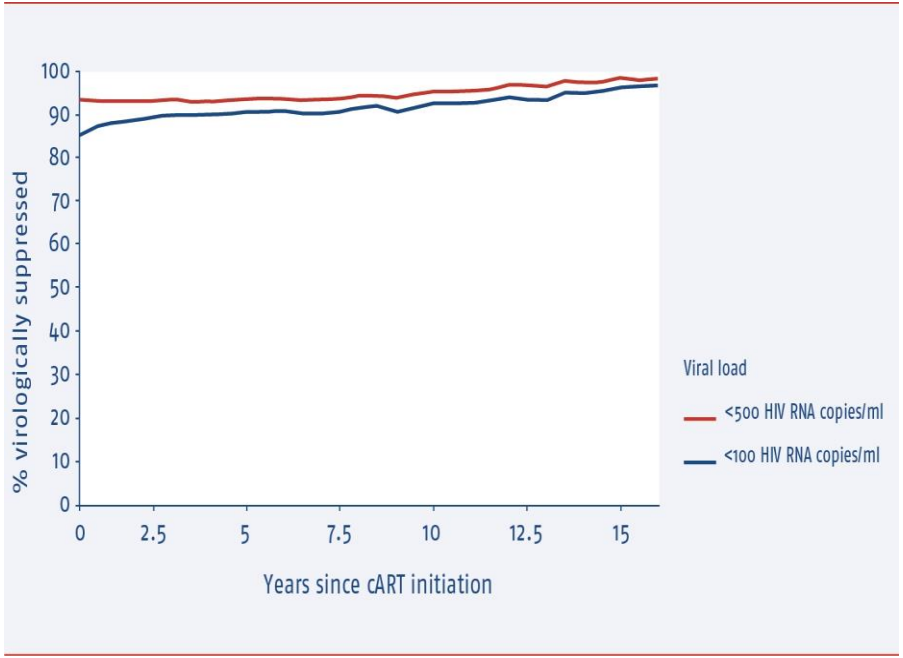
**Table 1. A summary of clinical trials and their strategies for HBV treatment.**

| | Targets | Compounds | Developer | Stage of development | ClinicalTrials.gov identifier |
|---|---|---|---|---|---|
| DAA | HBpol | GS-7340; Tenofovir Alafenamide (prodrug of tenofovir) | Gilead | Phase 3 | NCT01940471 and NCT01940341 |
| | HBpol | AGX-1009 (prodrug) | Agenix | Phase 3 (?) | No identifier found |
| | HBpol | Besifovir | IlDong Pharmaceutical | Phase 3 | NCT01937806 |
| | HBpol | CMX-157 (lipid acyclic nucleoside phosphonate) | Contravir | Phase 1 | NCT02585440 |
| | HBc | GLS-4 (Morphothiadine mesilate) | HEC Pharm/SUnshine | Phase 2 | China-CFDA |
| | HBc | NVR 3-778 | Novira Pharmaceuticals | Phase 1 | NCT02112799 & NCT02401737 |
| | HBs | REP-2139 (nucleic acid polymers) | Replicor | Phase 2 for both HBV and HDV | NCT02565719 and NCT02233075 |
| | Viral RNAs | siRNA: ARC-520/ARC-521 | Arrowhead | Phase 2 | NCT02604212 and NCT02604199 |
| | Viral RNAs | siRNA: ISIS-HBVRx | Ionis pharmaceuticals | Phase 1 or 2 (?) | No identifier found |
| HTA | NTCP | Myrcludex | Hepatera and MYR GmbH | Phase 2 for both HBV and HDV | Development in Russian Federation |
| | Promotion of apoptosis in infected cells | Birinapant | Tetralogic | Phase 1 | NCT02288208 |
| | Prenylation/farnesylation | Lonafarnib | Eiger BioPharmaceuticals | Phase 2 for HDV | NCT02430181, NCT02430194, NCT02511431 |
| | Immune stimulation | Thymosin alpha | Seoul National University Hospital | Phase 4 | NCT00291616 |
| | pDC stimulation | GS-9620 (TLR7 agonist) | Gilead | Phase 2 | NCT02166047 & NCT02579382 |
| | Immune stimulation | INO-1800 | Inovio Pharmaceuticals | Phase 1 | NCT02431312 |
| | Immune stimulation | Cyt-107 (IL-7) | Cythesis | Phase 1/2 (discontinued) | NCT01027065 |
| | Immune stimulation | IFN-lambda | BMS | Phase 2 (discontinued) | NCT01204762 |
| | Adaptive responses | ABX-203 | Abivax | Phase 2/3 | NCT02249988 |
| | Adaptive responses | GS-4774 (therapeutic vaccine) | Gilead | Phase 2 | NCT01943799 & NCT02174276 |
| | Adaptive responses | TG-1050 (therapeutic vaccine) | Transgene | Phase 1 | NCT02428400 |
| | Adaptive responses | DV-601 (therapeutic vaccine) | Dynavax | Phase 1 | NCT01023230 |
| | Adaptive response | HB-110 | Genexine | Phase 1 | NCT01641536 |
| | Adaptive responses | Nivolumab (Anti-PD1 mAb) | Ono Pharmaceuticals/ BMS | Phase 1/2 for HCC | NCT01658878 |

# There is a full pipeline for HBV drugs in development

Durantel D *et al. J Hepatol.* 2016 Apr;64(1 Suppl):S117-31

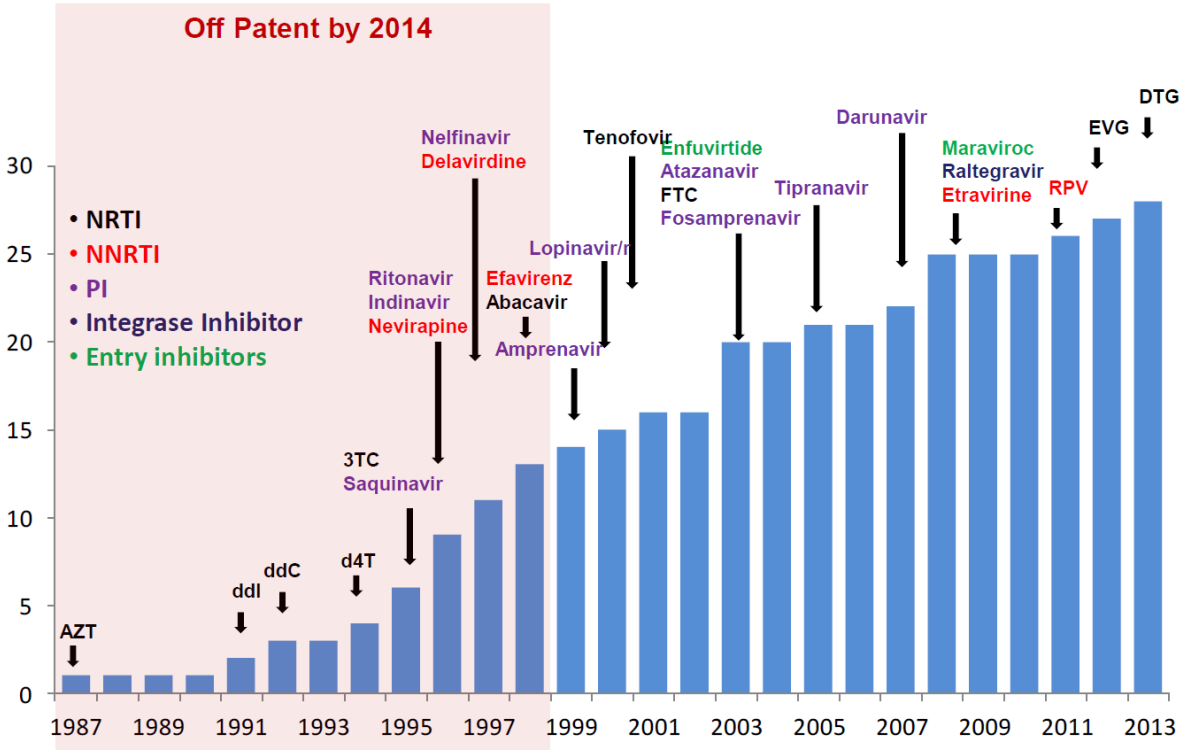
# Do we need more and newer drugs for HIV?




- Viral suppression after start of combination antiretroviral therapy (cART) in previously treatment-naïve individuals
- Other countries lower suppression rates
  - Compliance issues?
  - Resistance issues?

Dutch Monitoring Rapport 2016

# HIV drug development (1987-2013)



# What do we need more in future HIV drugs?

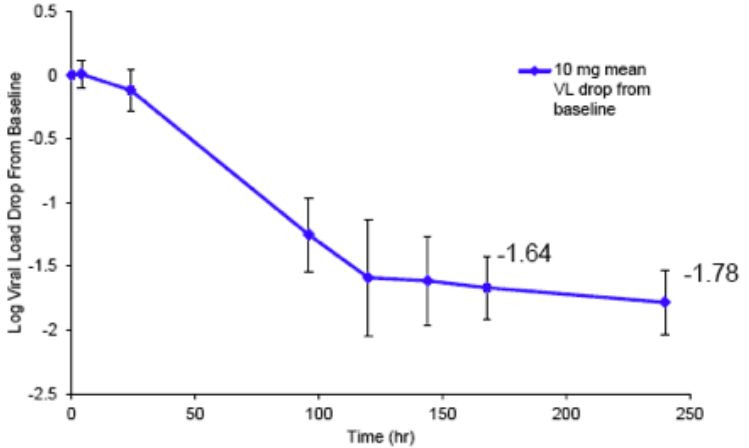
- More convenience
  - NRTI and PI
- Less side-effect / drug-drug interactions
  - NNRTI
- New drug classes
  - Maturation inhibitors, CD4 attachment/ entry inhibitors

# Newer Investigational ART Agents (partial list)

| | NRTI | NNRTI | PI | Entry Inh | II | Maturaton Inhibitor |
|---|---|---|---|---|---|---|
| Phase 3 | | doravirine | | Fostemsavir | cabotegravir | |
| Phase 2 | apricitabine<br>dexelvucitabine<br>festinavir | BILR 355 | | cenicriviroc<br>ibalizumab<br>PF-232798 | GS-9883 | BMS-955176 |
| Phase 1/2 | elvucitabine | | TMC 310911 | HGS004 | | |
| Phase 1 | MK-8591<br>CMX157 | RDEA 806 | CTP-298<br>CTP-518<br>PPL-100<br>SPI-256 | SCH532706<br>VIR-576 | BI 224436<br>INH-1001 | GSK-2838232 |

# MK-8591 (EFdA)

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine (EFdA)
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)




- A single 10 mg oral dose in HIV-infected patients results in 1.6 log decrease in viral load at day 7-10
- Intracellular MK-8591-TP $t_{1/2}$ = 103 hr
- No evidence of resistance out to Day 10

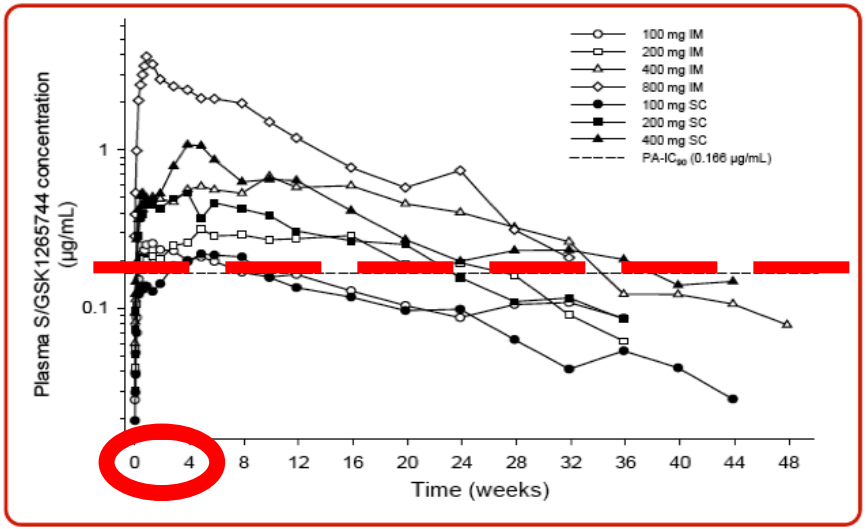
Grobler *CROI* 2016 #98
Friedman *CROI* 2016 #437LB

# Cabotegravir (CAB, GSK 1265744)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral
- Nanotechnology formulation; SC + IM injections
- T ½ 21-50 days!
- Supports monthly or quarterly dosing
  Safety: ISR (all mild) and nodules with SC dosing

**Pharmacokinetics**

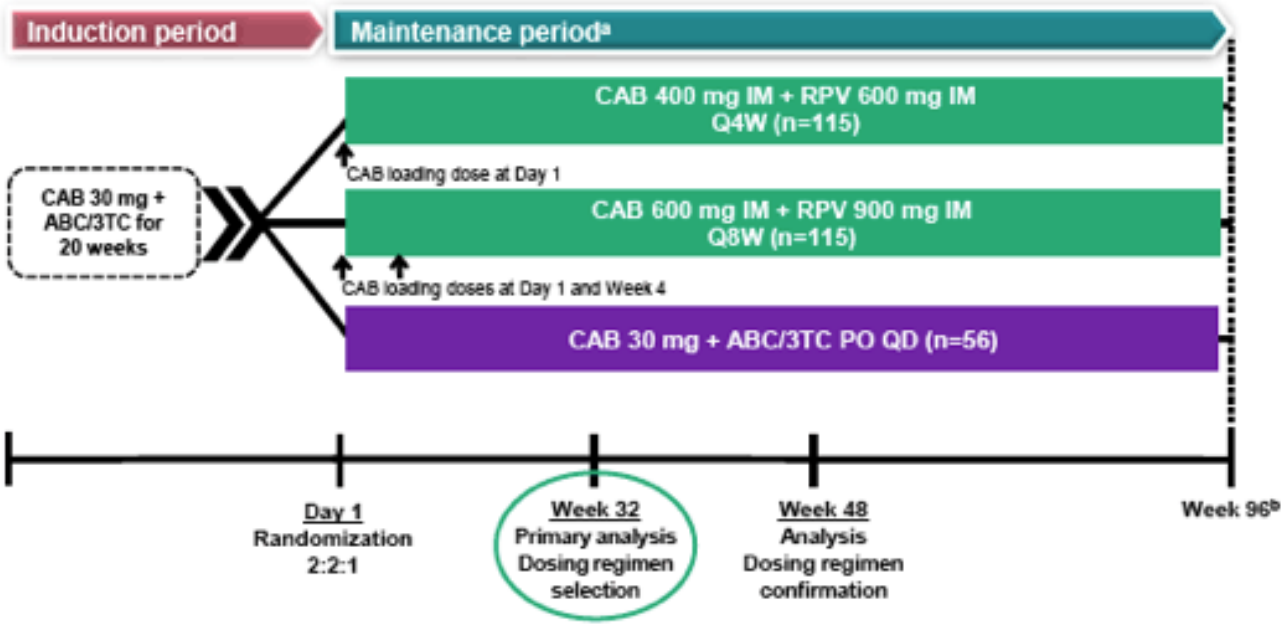
**Figure 4. Mean Plasma S/GSK1265744 Concentration-Time Profiles Following Single Dose LAP Formulation Administration**




Spreen W *et al. J Acquir Immune Defic Syndr.* 2014 Dec 15;67(5):481-6

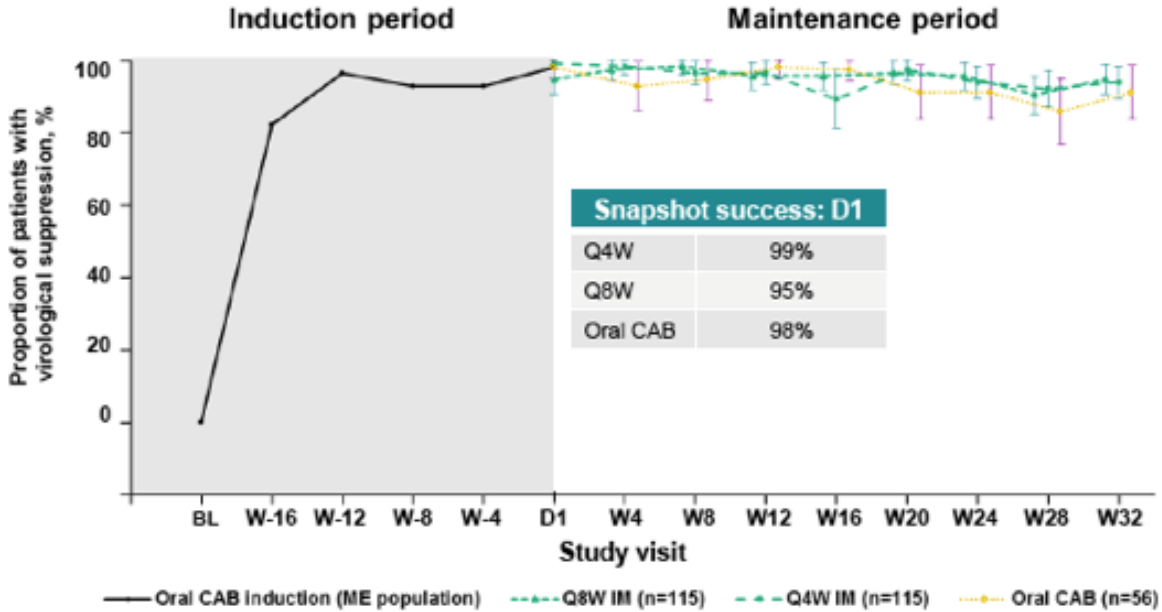
# LATTE-2: CAB + RPV IM Maintenance

Phase 2b multicenter, parallel group, open-label study
Study population: Rx-naïve individuals (N=309)



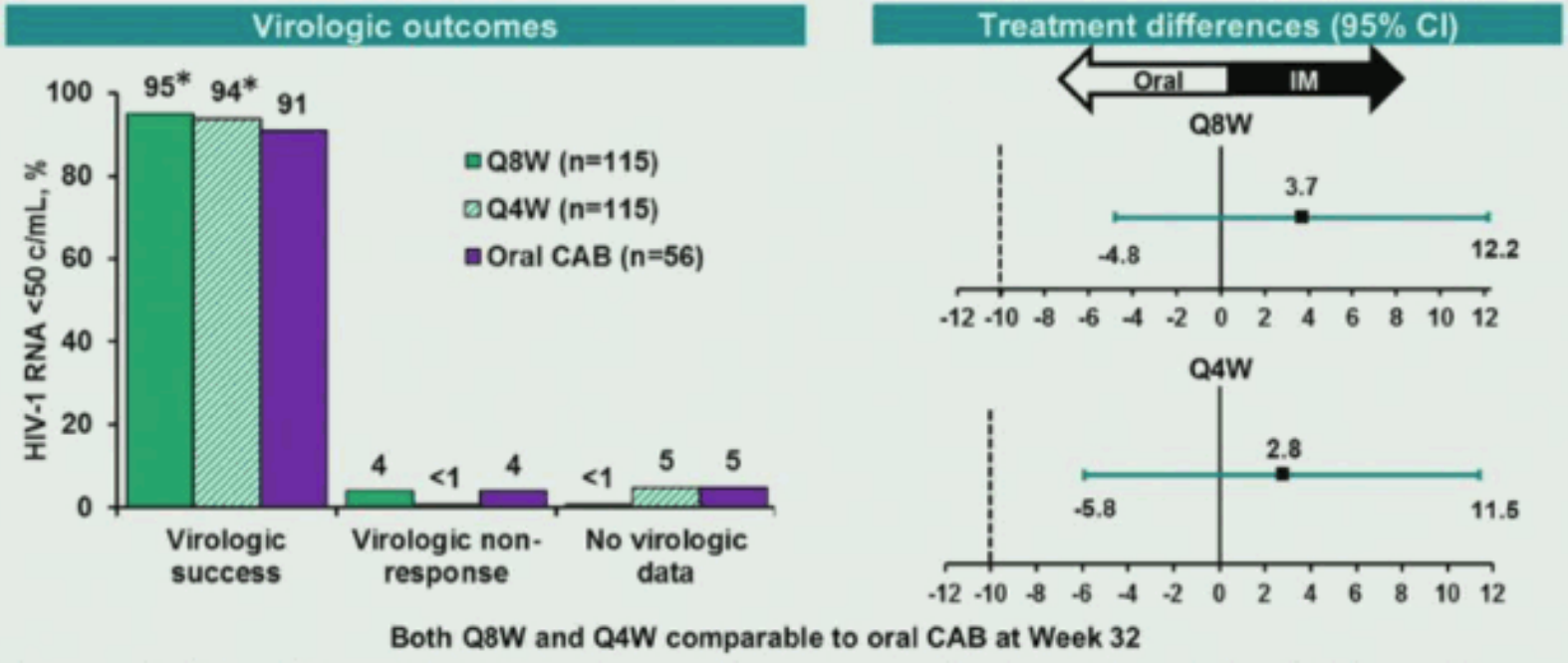

Margolis *CROI* 2016 #31LB

# LATTE-2: Virologic Suppression




Margolis *CROI* 2016 #31LB

# LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)




Margolis *CROI* 2016 #31LB

# LATTE-2: Injection Site Reactions

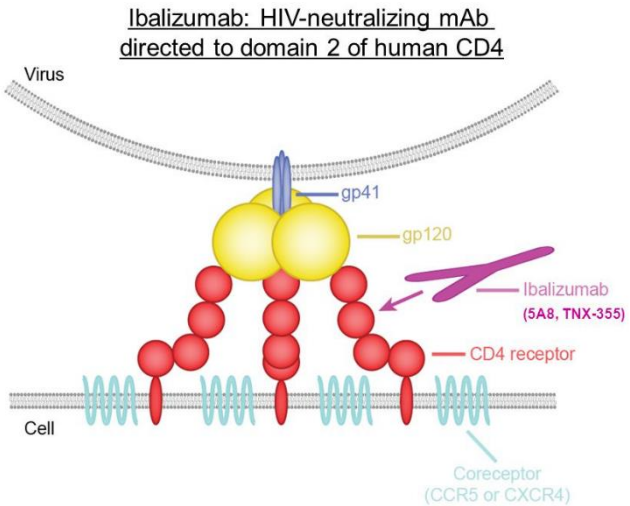
| | Q8W IM (n=115) | Q4W IM (n=115) | IM subtotal (N=230) |
|---|---|---|---|
| Number of injections | 1623 | 2663 | 4286 |
| Number of ISRs (events/injection) | 1054 (0.65) | 1228 (0.46) | 2282 (0.53) |
| **Grades** | | | |
| Grade 1 | 839 (80%) | 1021 (83%) | 1860 (82%) |
| Grade 2 | 202 (19%) | 197 (16%) | 399 (17%) |
| Grade 3 | 12 (1%) | 10 (<1%) | 22 (<1%) |
| Grade 4 | 0 | 0 | 0 |
| **Duration, days** | | | |
| ≤7 | 943 (89%) | 1121 (91%) | 2064 (90%) |
| Median | 3.0 | 3.0 | 3.0 |

- Most common ISR events overall were pain (67%), swelling (7%), and nodules (6%)
- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)[a]
- 2/230 subjects (1%) withdrew as a result of injection reactions (Q8W)

Margolis *CROI* 2016 #31LB

# Ibalizumab – HIV entry inhibitor

- Monoclonal antibody (im or iv) binding to CD4 receptor
- Dosing every 1-4 weeks
  - Phase 1/2-studies in 2004-2009[1]
- FDA orphan drug breakthrough designation




1. Kuritzkes DR *et al. J Infect Dis*. 2004 Jan 15;189(2):286-91; Jacobson JM *et al. Antimicrob Agents Chemother.* 2009 Feb;53(2):450-7; Norris D *et al.16th International AIDS Conference*; August 13-18, 2006; Toronto, Canada

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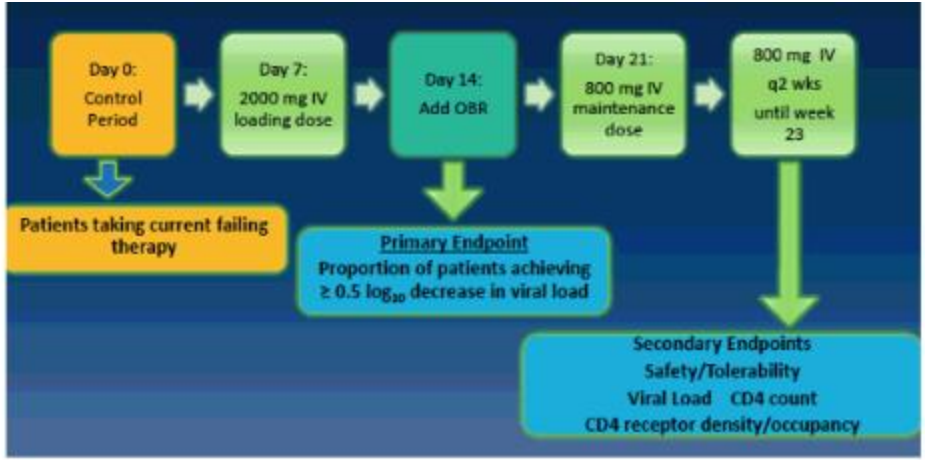
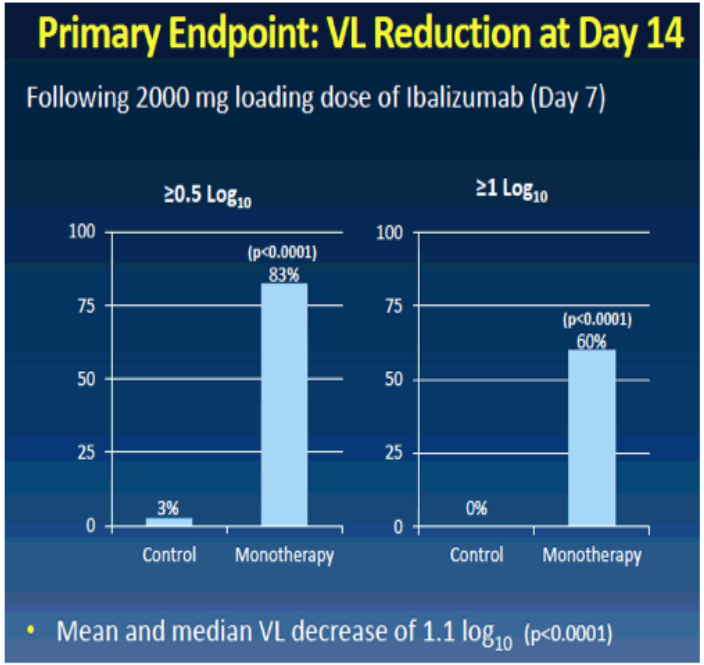
## LB-6. Primary Efficacy Endpoint and Safety Results of Ibalizumab (IBA) in a Phase 3 Study of Heavily Treatment-Experienced Patients with Multi-Drug Resistant (MDR) HIV-1 Infection

**Session:** Oral Abstract Session: Late Breaker Oral Abstracts
*Saturday, October 29, 2016: 11:20 AM*
*Room: 283-285*



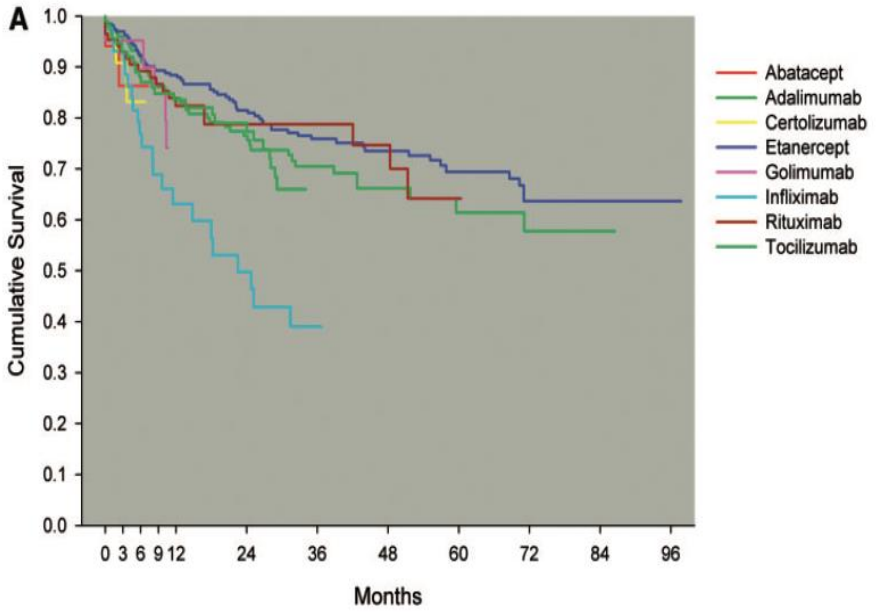




- Documented resistance to at least 1 AVR from 3 classes

# Is compliance a possible drawbacks to these developments?

- Rheumatoid arthritis patients for longer treated at monthly intervals
- 775 RA patients registered in the Danish biologics database (DANBIO)
- Treatment as monotherapy

FIG. 2 Drug adherence, stratified by drug

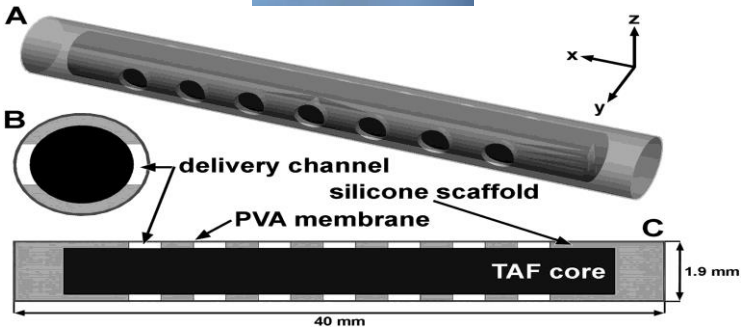


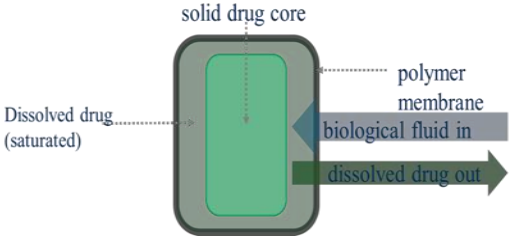
# Are adverse events a possible drawbacks to these developments?

- Newly developed monoclonal antibodies reverse anticoagulant effects of DOACs
- Search for antidote against long-acting anti-HIV drugs in case of adverse events

# It isn’t always new drugs that will lead to longer acting agents…

# Implants

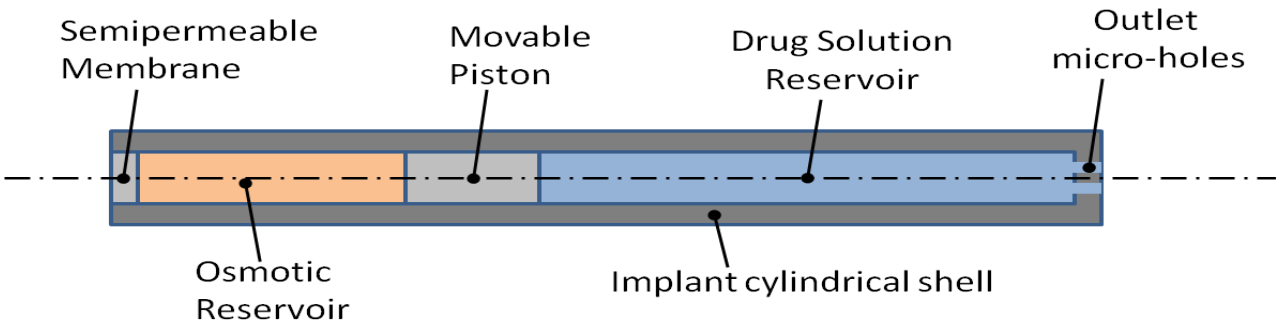



Full-scale TAF-TFPD prototype device
*4 cm long x 2-2.5mm diameter*

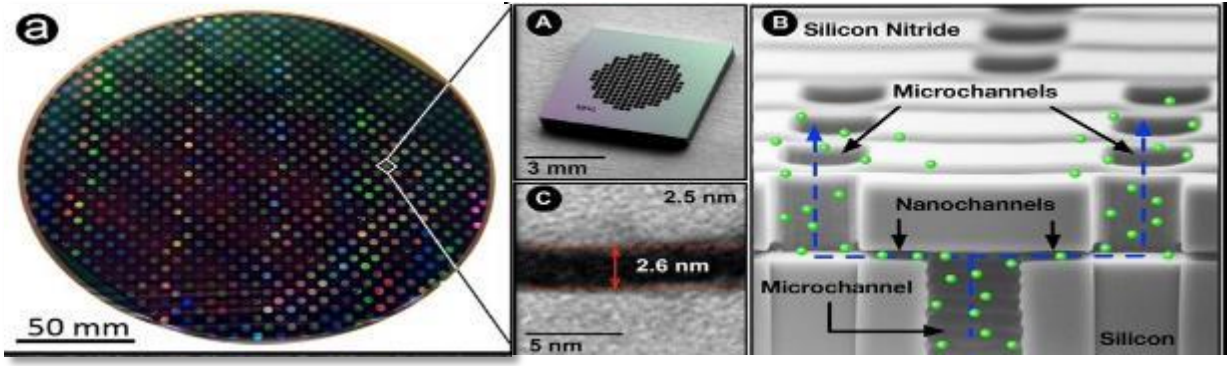
Gunawardana M *et al. Antimicrob. Agents Chemother*. 2015;59:3913-3919; Johnson L *et al. CROI* 2016. #879

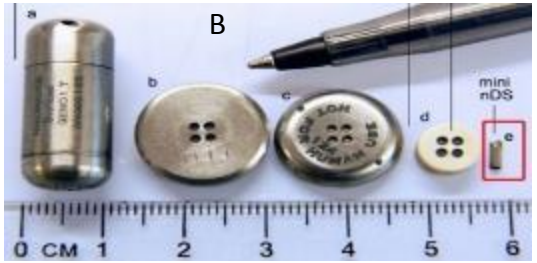
# Osmotic Pump

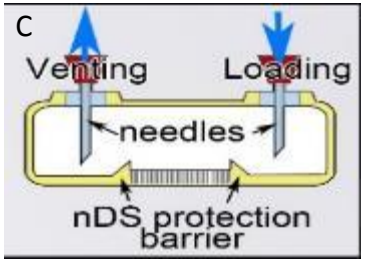


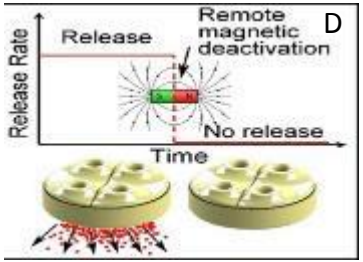

- This osmotic flow is directly proportional to the gradient of concentration of osmolytes in the osmotic chamber
- The inward $H_2O$ flow creates an increased pressure in the osmotic chamber, which exerts a force on the piston

# Nano-channel Implants



# Conclusions

- There are significant overlaps between HIV, HCV & HIV in many ways
  - But also significant differences
- We are just commencing a new era in HBV
  - Better understanding
  - New agents
    - But we have a long way to go…
- There are new agents for HIV
  - Especially those that will allow intermittent dosing
  - And there are technologies that might help too

# Thank you for your attention