NAPs for treatment of chronic hepatitis D: a tale from real life?

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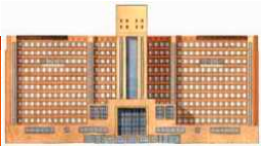
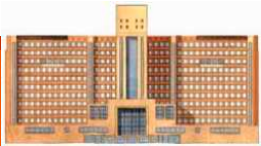
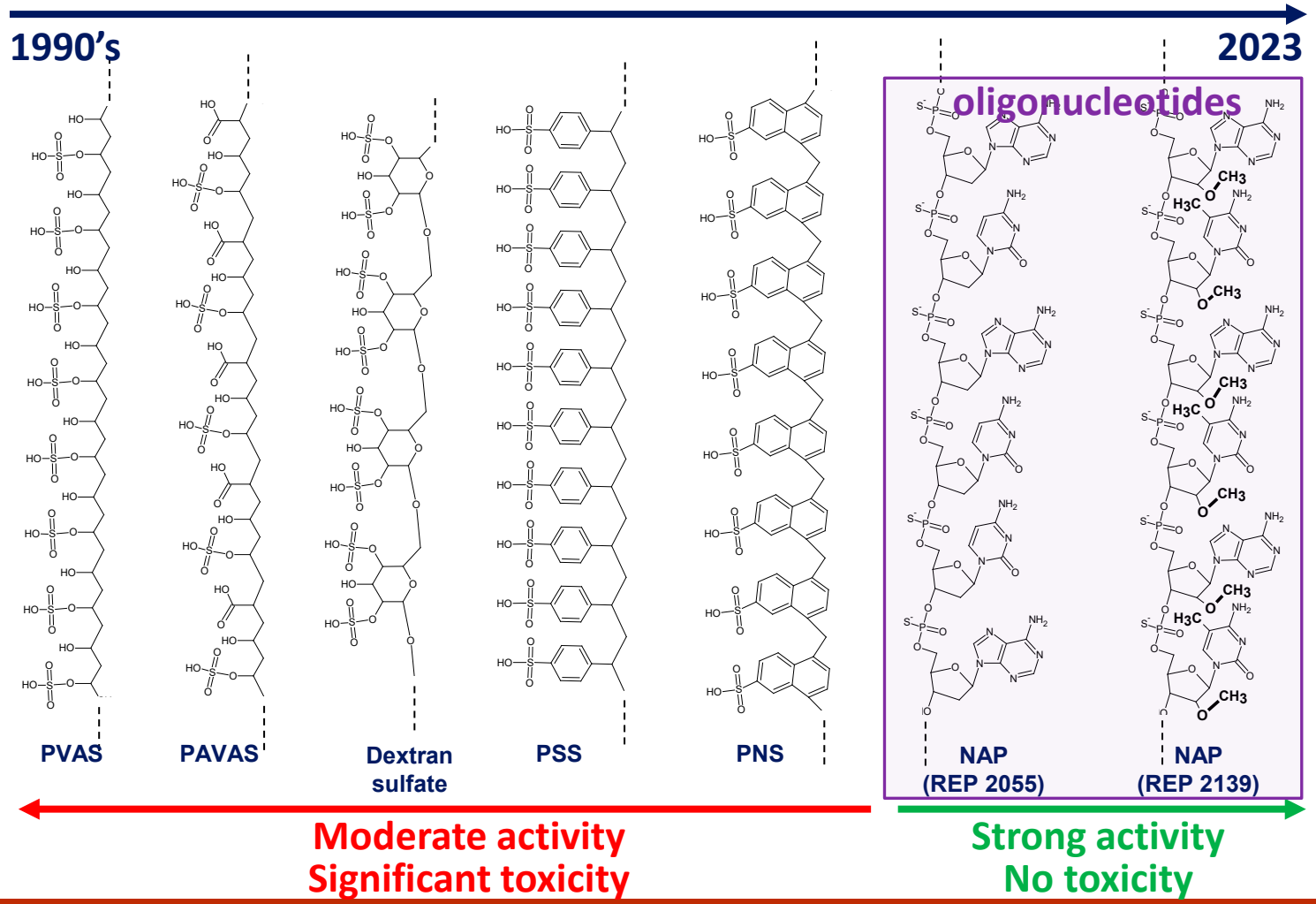


NAPs for treatment of CHD: a tale from real life?

1. Evolution of Nucleic Acid Polymers (NAPs)… until REP 2139-Mg
2. Mechanism of action: what we know so far
3. Phase II clinical trial in chronic hepatitis D (CHD): results from REP 301
4. Real-life experience in France: results from compassionate use

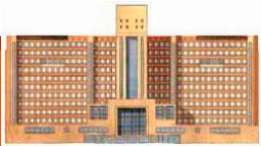


Evolution of NAPs: a long way until REP 2139-Mg

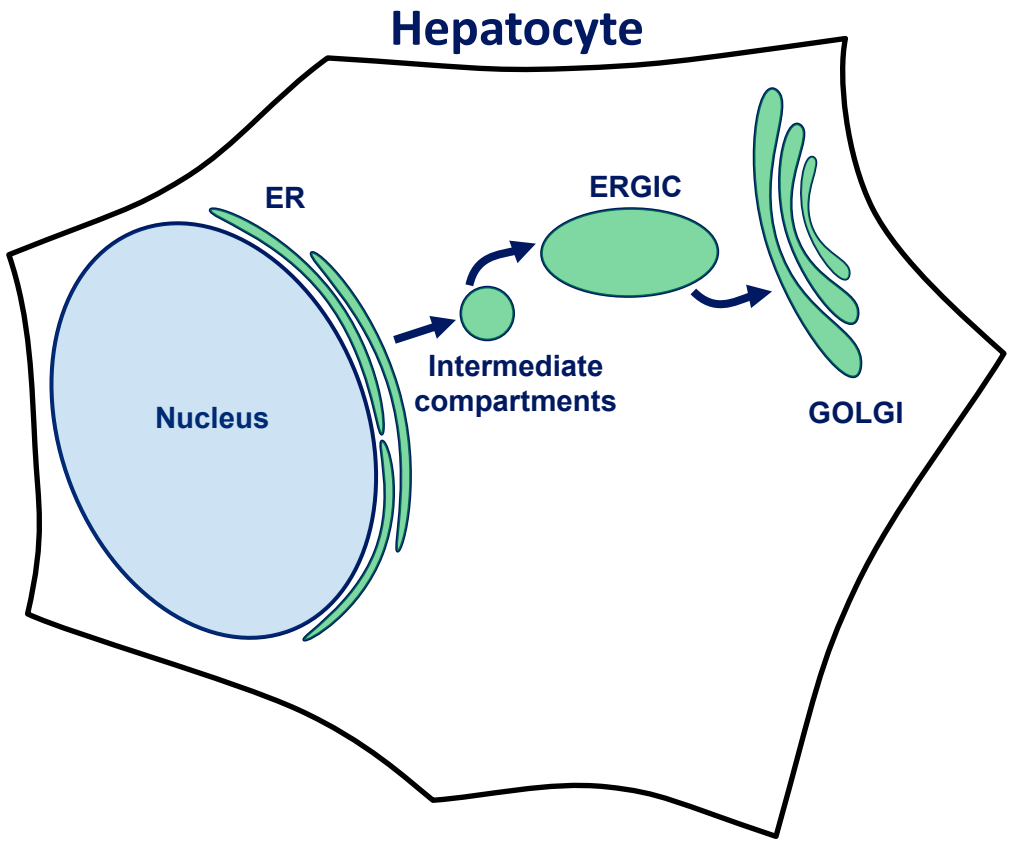


REP 2139-Mg is a oligonucleotide polymer of alternating adenosine and cytidine.

Vaillant A, Antiviral Res 2016.



REP 2139-Mg: mechanism of action



Passage through secretory pathway (transient)

- Target the host HSP40 chaperone DNAJB12
- Blocks inhibition of HBV SVP assembly
- Blocks envelopment of HDV RNP

Accumulation in nucleus (progressive with continued dosing)

- Targets S-HDAg and L-HDAg
- Inhibits replication / morphogenesis of HDV upstream of RNA envelopment (mechanism under exploration)

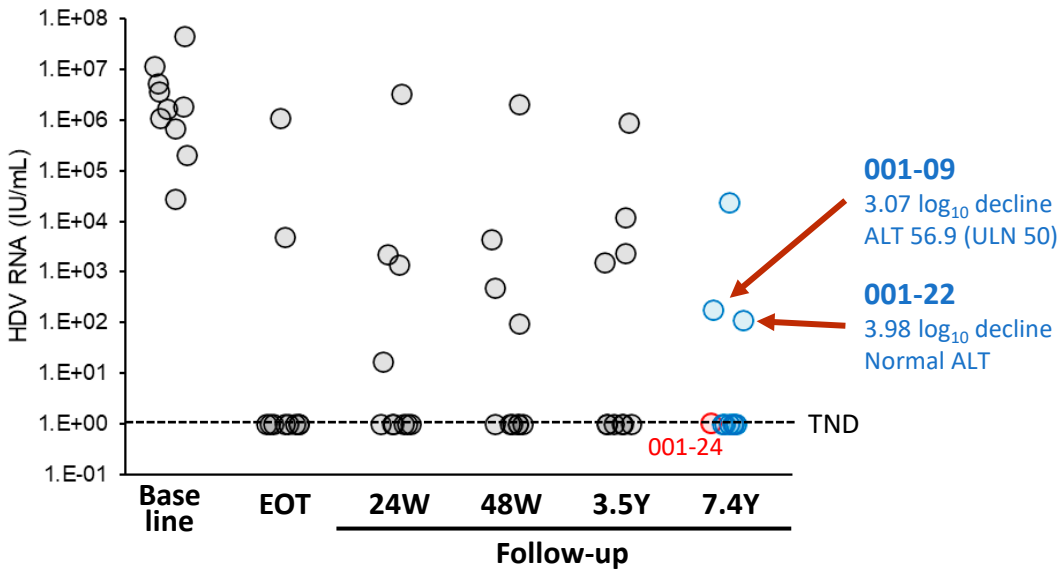
REP 2139-Mg: phase II clinical trial in patients with CHD

Study REP 301

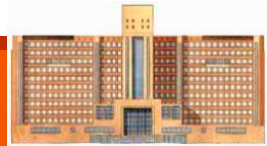
N=12

15 weeks	15 weeks	33 weeks
REP 2139 500 mg IV QW	REP 2139 250 mg IV QW + PEG-IFN 180 ug SC QW	PEG-IFN 180 ug SC QW

	REP 2139 monotherapy	End of combination therapy	End of treatment	24 week follow-up	1 year follow-up
HBsAg reduction (log from baseline)	3·31 (1·99)	4·15 (2·24)	3·45 (2·70)	2·99 (2·88)	3·06 (2·96)
HBsAg negative*	2 (17%)	4 (33%)	5 (42%)	5 (42%)	5 (42%)
Anti-HBs positive†	5 (42%)	6 (50%)	6 (50%)	5 (42%)	5 (42%)
HDV RNA reduction (log from baseline)	4·21 (1·99)	5·68 (1·14)	5·34 (2·34)	4·87 (2·55)	4·51 (3·47)
HDV RNA negative‡	4 (33%)	10 (83%)	9 (75%)	7 (58%)	7 (58%)



Bazinet M, *et al*. Lancet Gastroenterol Hepatol 2017.

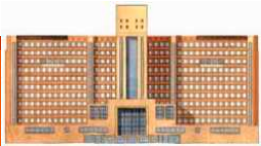


REP 2139-Mg in real life: compassionate access

- **Compassionate access to REP 2139-Mg in eligible patient populations worldwide**
  - HDV with previous failure to pegIFN, bulevirtide and lonafarnib
  - HDV decompensated cirrhosis
  - HBV with compensated or decompensated cirrhosis

➢ **Scheduled treatment duration of 48 weeks with REP 2139-Mg 250 mg SC QW + TDF 245 mg PO QD + with PEG-IFN 90µg SC QW (only with compensated cirrhosis and if no contra-indication)**

- **33 enrollment patients**: France (18 patients, 8 centers), Israel (1 patient, 1 center), Austria (3 patients, 1 center), Turkey (4 patients, 1 center), Italy (4 patients, 1 center), Germany (1 patient, 1 center), Australia (1 patient, 1 center), Canada (1 patient, 1 center)



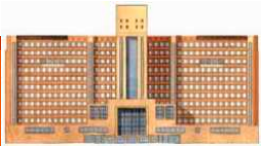
REP 2139-Mg: the French experience

”Eiffel Tower”, 1985
Jean-Michel BASQUIAT & Andy WARHOL

REP 2139-Mg in HDV compensated cirrhosis and BLV failure

Virologic response during therapy								
Virologic response	**Duration of therapy**							
	1-4 weeks (n=13)	**5-8 weeks (n=13)**	**9-12 weeks (n=12)**	**13-24 weeks (n=10)**	**24-48 weeks (n=6)**	**> 48 weeks (n=2)***	**Removal of NAP + pegIFN (n=2)**	**Removal of TDF (n=1)**
HDV RNA decline < 2 $\log_{10}$ from baseline	3	3	4	2	1			
HDV RNA ≥ 2 $\log_{10}$ decline from baseline		3		2	2			
HDV RNA < LLOQ			2			1		
HDV RNA target not detected **	1	1	2	4	3	1	2	1
HBsAg decline < 1 $\log_{10}$ from baseline	2	2	2	2	1			
HBsAg > 1 $\log_{10}$ decline from baseline			1		1			
HBsAg > 2 $\log_{10}$ decline from baseline		1	3	1		1		
HBsAg < 10 IU/mL					1	1		
HBsAg < 0.05 IU/mL				2	2		2	1
Anti-HBs seroconversion			1	2	2	1	2	1
ALT normal	1			3	2		2	1

Bourliere M, *et al*. Poster SAT-169, EASL 2023.



REP 2139-Mg in HDV decompensated cirrhosis

Patient baseline characteristics			
Patient	**1** (RCAP 5)	**2** (RCAP 8)	**3** (RCAP 11)
Age (years)	56	56	47
Sex	Female	Female	Male
Ethnicity	Caucasian	African	African
ALT (U/L)#	168	64	89
Total bilirubin (μmol/L)	15	44	24
Albumin (g/L)	28	24	24
Platelets (10^9/L)	56	90	35
INR	1.26	1.92	1.67
Child-Pugh / MELD	B8 / 9	C12 / 17	C10 / 13
HDV genotype*	1	5	5
HDV RNA (IU/mL)	$1.09x10^7$	4285	34138
HBsAg (IU/mL)	1177	4270	1273
HBeAg status	Negative	Negative	Positive
HBV DNA (IU/mL)	Target not detected	Target not detected	< 10 IU/mL (LLOQ)

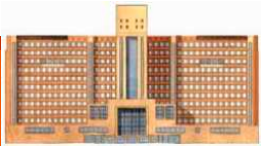
Patient 1 with complete virological response and HBs seroconversion

Patient 2 had liver transplantation at W10 with negative HDV-RNA

Patient 3 had HDV-RNA 2.7 log decline at W11 of therapy

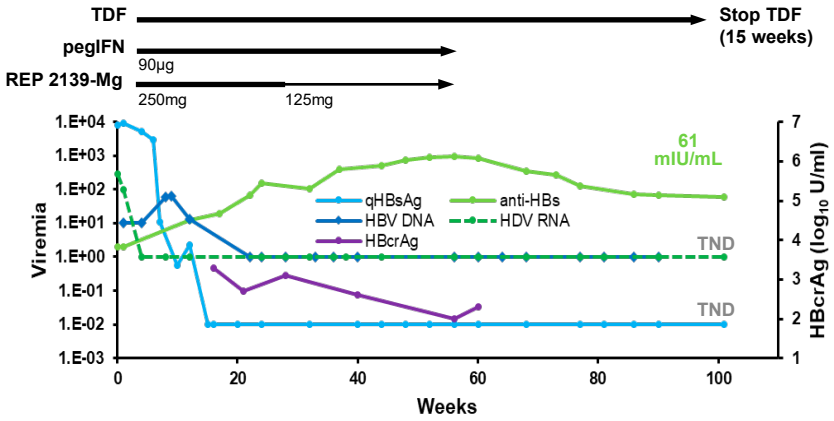
Improvement of liver function in patients 1 and 2 since W4

No systemic side effects

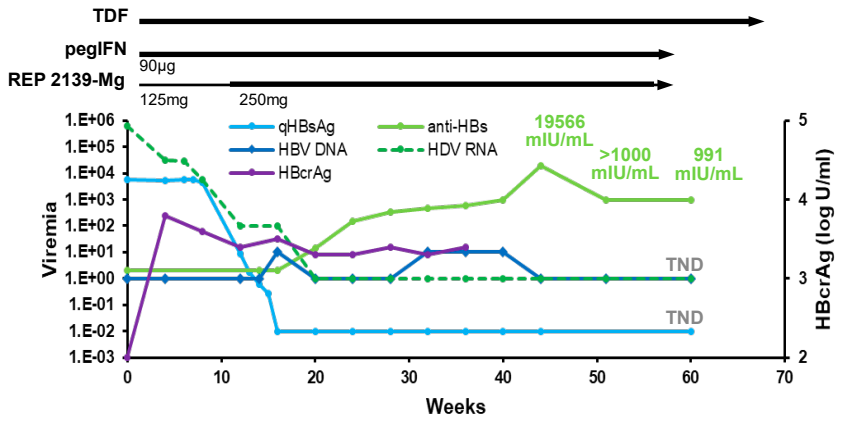


HDV virological control after the end of treatment

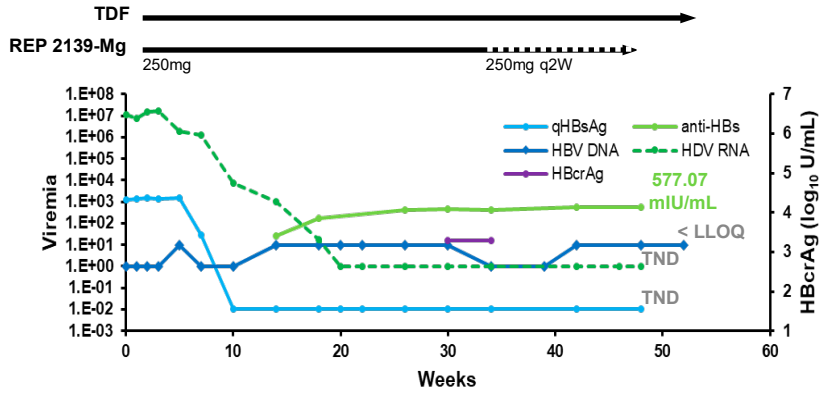
Patient 1
Senegalese male, 51 years
HDV GT-5, cirrhosis Child A
Previous failure on pegIFN + BLV



Patient 2
Caucasian male, 47 years
HDV GT-1, cirrhosis, stage 1 varices
Previous failure on pegIFN + BLV



Patient 3
Caucasian female, 56 years
HDV GT-1, decompensated cirrhosis
Naïve, Child B8 with ascites



Bourliere M, *et al*. Poster SAT-169, EASL 2023.
Stern C, *et al*. Poster SAT-183, EASL 2023.

REP 2139-Mg: a happy ending for HDV patients in real life

Patient #2: HDV decompensated cirrhosis with HCC and severe ascites

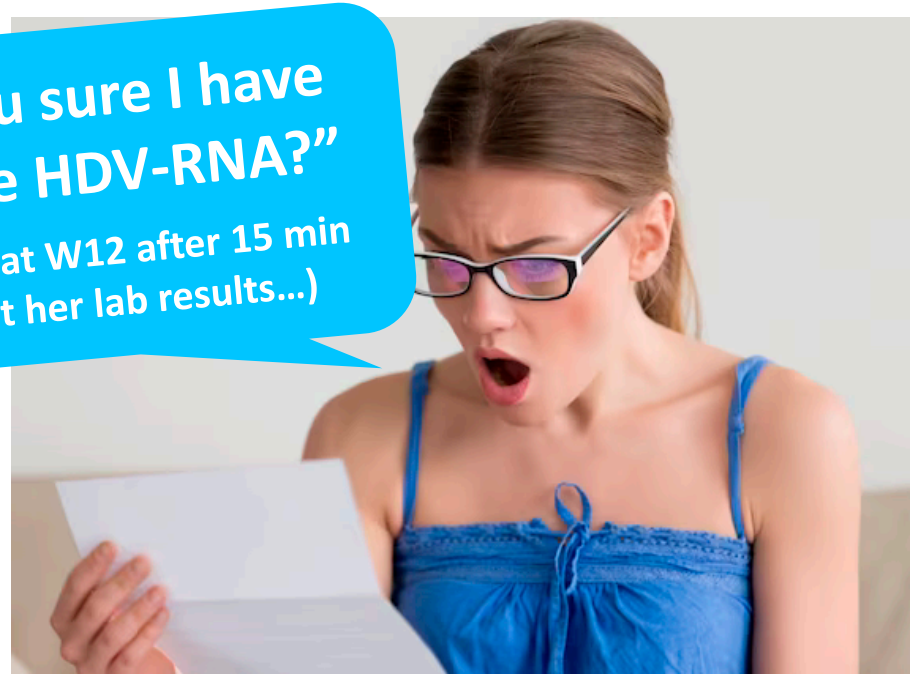
"I feel alive again!"

(Patient #2 at W4 after improvement of ascites and edema)

Patient #5: HDV cirrhosis (recent history of decompensation) and failure to a 8-month bulevirtide treatment

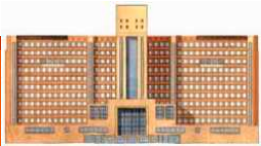
"Are you sure I have negative HDV-RNA?"

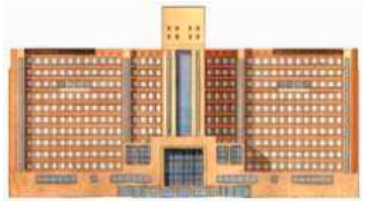
(Patient #5 at W12 after 15 min looking at her lab results…)



Take-home messages

- REP 2139-Mg is a nucleic acid polymer with activity against HBV and HDV
- Complete HDV virological response (TND) and HBsAg loss is achievable in difficult-to-treat CHD patients
- Excellent safety profile and tolerance observed in real life, including CHD patients with decompensated cirrhosis
- Treatment regimen and duration will be probably individualized for optimal virological results

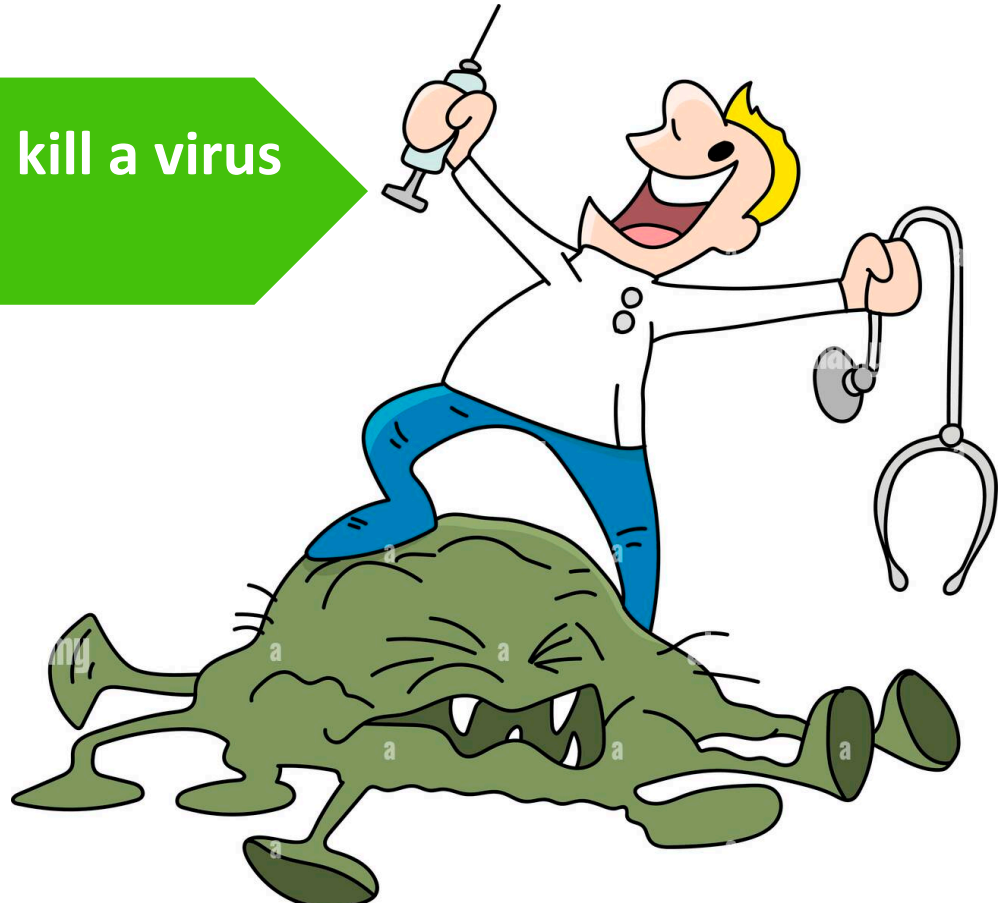




Thanks for your attention!

How to kill a virus in 1923

How to kill a virus in 2023



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