Episode 236: Polymerase inhibitors and immune-virology of COVID and HIV

Dear colleagues,

Searching the scientific literature for new COVID antivirals is a bit frustrating. You find a lot of papers with potential new drugs in a very early phase, but information on drugs that are really in development by pharma companies is very scarce and unclear. It seems they keep their cards hidden, until trials have finished and even then they rather communicate by virtual prees release than in scientific papers. Anyhow, I report on what I find on polymerase inhibitors.

In the second part, there is some exciting (but complicated) immune-virology of COVID and HIV.

Papers see:

## 1) Review

Candidate polymerase inhibitors

Ep 236-1 : Lai Tian Eur J Medic Chem 2021 provides a very broad overview of RNA-dependent RNA polymerase inhibitors (RdRp inh) against various RNA viruses. They conclude that the following drugs have some interest for COVID-19:

- Hypermutation-inducers Ribavirin, Favipiravir, Molnupiravir or EIDD-2801: already discussed earlier.
- Purine nucleosides Remdesivir, Galidesivir, IDX-184 and AT-527
- Pyrimidine nucleoside Sofosbuvir

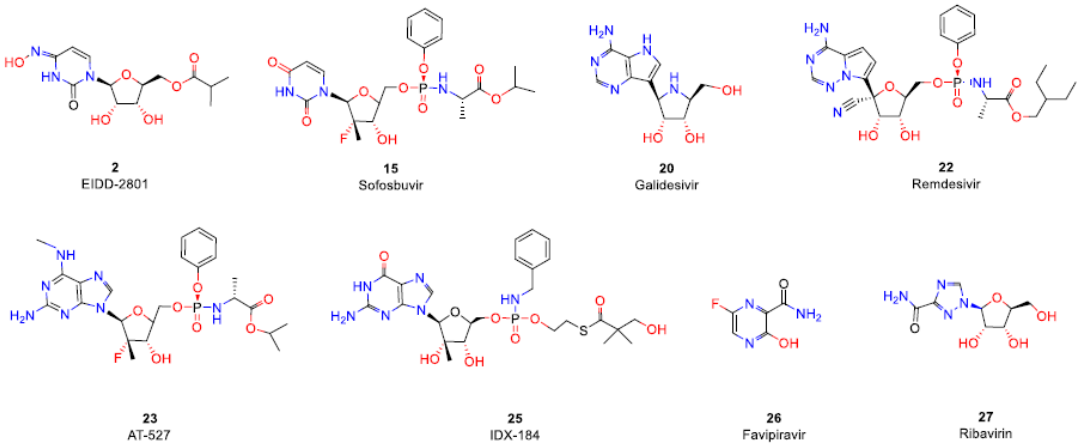



**Fig. 7.** Structure of the RdRp inhibitor repurposing for the COVID-19 pandemic.

## 2) News on Remdesivir

Ep 236-2: Gottlieb NEJM 27 Jan 2022: **Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients**

Remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo intravenous in COVID outpatients with symptom onset within the previous 7 days and who had at least one risk factor for disease progression (age ≥60 years, obesity, or certain coexisting medical conditions)..

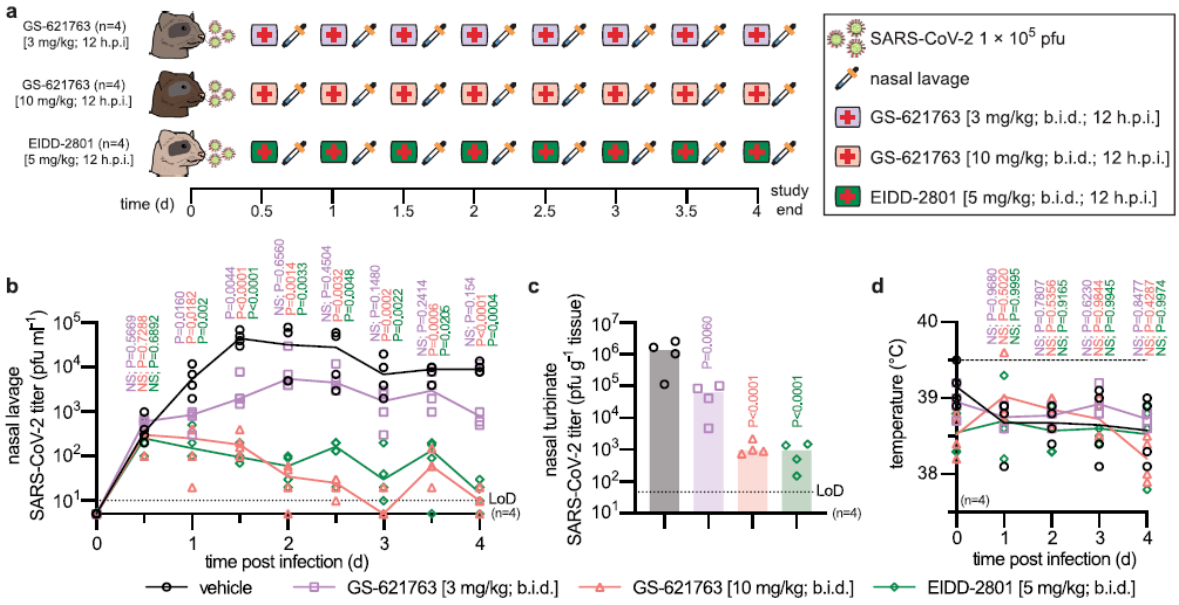
**Covid-19–related hospitalization or death** from any cause:
in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group

(**hazard ratio, 0.13;** CI, 0.03 to 0.59; P = 0.008).

**Covid-19–related medically attended visit**
4 of 246 patients (1.6%) in the remdesivir group and 21 of 252 (8.3%) in the placebo group

Ep 236-3: Cox Nat Comm 2021 Oral prodrug of remdesivir parent GS-441524 is efficacious against SARS-CoV-2 in ferrets;

- Twice-daily oral administration of 10 mg/kg GS-621763 reduces SARS-CoV-2 burden to near-undetectable levels in ferrets. Treatment started 12 hours after infection. Effect similar as Molnupiravir.




- When dosed therapeutically against VOC P.1 gamma, oral GS-621763 blocks virus replication and prevents transmission to untreated contact animals

**This should translate in a feasible human daily dose of approximately 250 mg oral GS-621763.**

Ep 236-4: Press release indicating that Gilead is NOT going to proceed with oral Remdesivir:

*"There are currently **no immediate plans to study GS-621763** in clinical trials; the compound has been used in the preclinical studies as a tool for the design of oral antivirals for COVID.*

*"Gilead is working with Georgia State because of their extensive expertise in animal models for SARS-CoV-2 infection that are suitable for testing the preclinical efficacy of new investigational antiviral agents," the company said in a statement.*

### 3) Galidesivir

Ep 236-5: Ray Viruses Dec 2021 **Activity of Galidesivir in a Hamster Model of SARS-CoV-2**

Treatment with galidesivir, if started 24 h before infection, reduced lung pathology

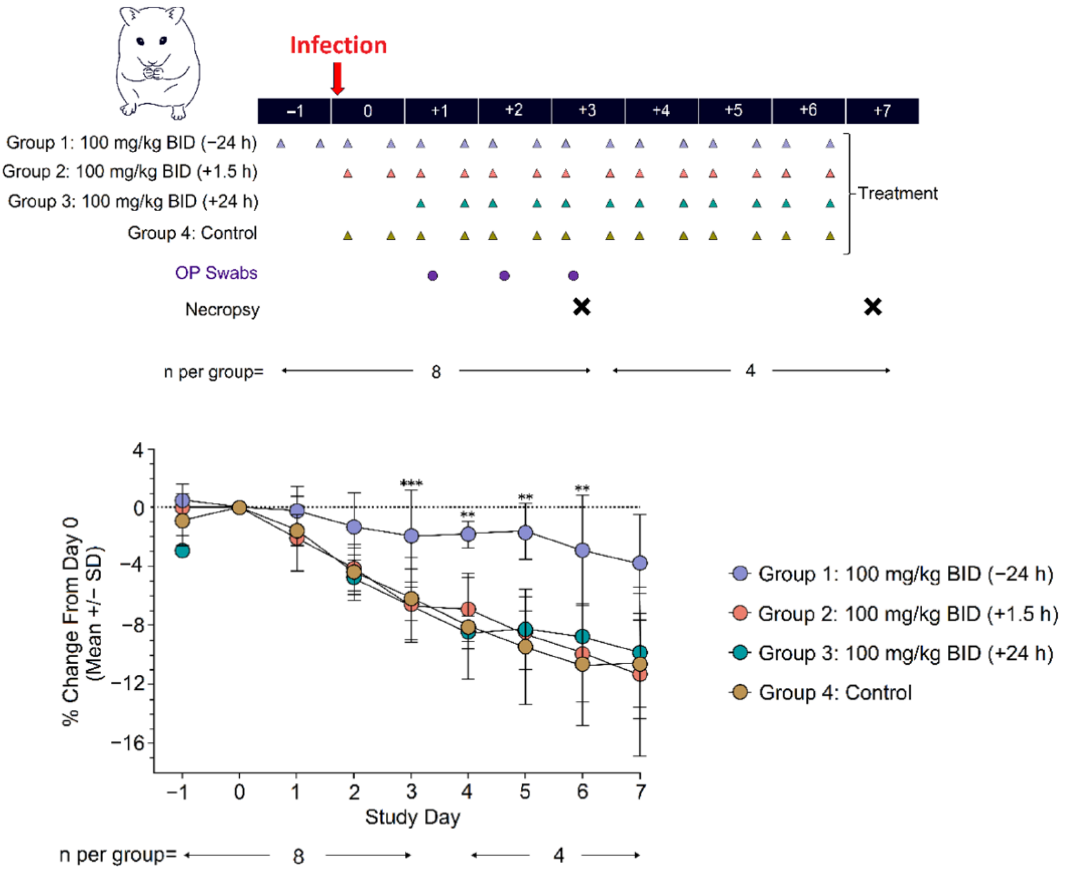



**Figure 2.** Mean weight change from Day 0 through Day 7. Statistical analysis was conducted u

**Table 2.** Mean difference ($log_{10}$) in viral burden at Day 3 post infection in caudal lung, cranial lung, and turbinate tissues between groups receiving active galidesivir treatment and the vehicle control.

| | Group | n | Mean (PFU/100 mg, $log_{10}$) | Difference vs. Control | 95% CI for Treatment Difference | *p*-Value [1] |
|---|---|---|---|---|---|---|
| Caudal lung | Group 1: 100 mg/kg BID (−24 h) | 4 | 4.86 | −1.53 | (−2.68, −0.38) | <0.05 |
| | Group 2: 100 mg/kg BID (+1.5 h) | 4 | 4.42 | −1.97 | (−3.12, −0.81) | <0.05 |
| | Group 3: 100 mg/kg BID (+24 h) | 4 | 5.74 | −0.65 | (−1.80, 0.51) | NS |
| | Group 4: control | 4 | 6.39 | NA | NA | NA |
| Cranial lung | Group 1: 100 mg/kg BID (−24 h) | 4 | 5.03 | −1.42 | (−2.22, −0.61) | <0.05 |
| | Group 2: 100 mg/kg BID (+1.5 h) | 4 | 4.75 | −1.70 | (−2.50, −0.89) | <0.05 |
| | Group 3: 100 mg/kg BID (+24 h) | 4 | 5.68 | −0.77 | (−1.57, 0.04) | NS |
| | Group 4: control | 4 | 6.45 | NA | NA | NA |
| Turbinates | Group 1: 100 mg/kg BID (−24 h) | 4 | 6.51 | −0.31 | (−1.47, 0.86) | NS |
| | Group 2: 100 mg/kg BID (+1.5 h) | 4 | 5.96 | −0.85 | (−2.02, 0.31) | NS |
| | Group 3: 100 mg/kg BID (+24 h) | 4 | 6.83 | 0.01 | (−1.15, 1.18) | NS |
| | Group 4: control | 4 | 6.81 | NA | NA | NA |

[1] Dunnett's test for mean differences. CI, confidence interval; NA, not applicable; NS, not significant; PFU, Plaque Forming Units; BID, twice daily dosing.

Ep 236-6: Julander Antiviral Res Nov 2021.

- Moderate in vitro activity against SARS-CoV-2 EC50 = 57.7 µM

*Results from the initial dose-ranging part of the trial in COVID-19 subjects showed that galidesivir was* ***safe*** *and generally well tolerated across tested dose levels and that the therapy was associated with a* ***dose-dependent decline in viral levels of SARS-CoV-2 in the respiratory tract****. However, the trial was not designed or sized to demonstrate clinical efficacy.*
***Further development of galidesivir for COVID-19 will not be pursued at this time***

4) **<u>IDX-184 and Sofosbuvir</u>**: polymerase inhibitors, used against hepatitis C.

- No data on IDX-184

<u>Ep 236-7</u>: Abdel-Salam medRxiv May 2021 **Single blinded efficacy of Sofosbuvir plus Ledipasvir (SL) in Egyptian patients with COVID-19 in about 250 hospitalized patients**

*The inclusion criteria were pneumonic patients with SARS-COV-2 infection confirmed to be positive by RT-PCR. They demonstrated moderate cases criteria: fever (measured temperature of at least 38 °C), respiratory symptoms (cough, shortness of breath), and imaging-confirmed pneumonia.*
*Control treatment =* Oseltamivir, Hydroxychloroquine, and Azithromycin

**Cure rate:** 71 % in SL vs 41 control
**Deaths:** 0 in SL vs 6 in control
**ICU rate = similar**

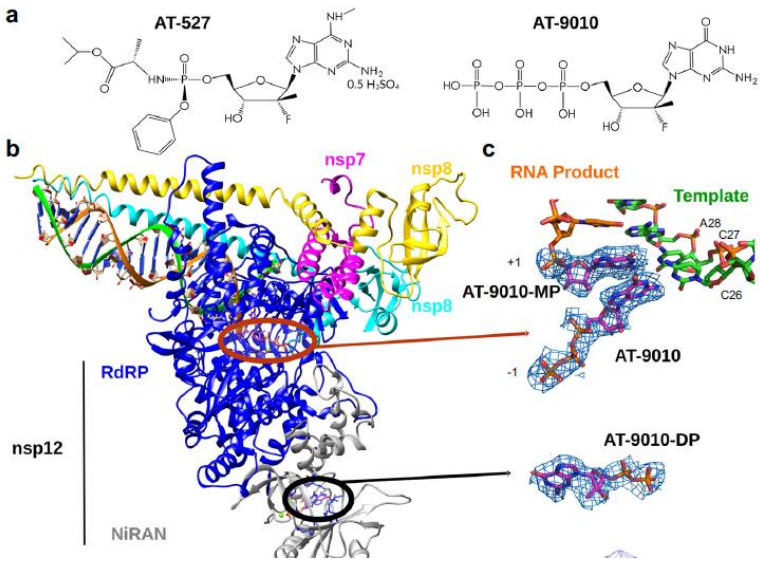
<u>Ep 236-8</u>: Sara Mobara JAC Oct 2021**: DISCOVER phase 3 double blind trial with Sofosbuvir + Daclatasvir** in > 500 hospitalized COVID patients: *with clinically diagnosed COVID-19 by either PCR positivity or COVID-19-compatible chest CT scan findings were considered, for inclusion if they were >18 years old and provided written informed consent. Individuals were required to have an oxygen saturation <95% and at least one symptom of fever (oral temperature > 37.8_C), dry cough, severe fatigue or dyspnoea.*

→ **no significant effect on hospital discharge or survival**.

**5) <u>AT-527</u>**

<u>Ep 236-9:</u> Shannon Nat Comm 2021: Dual mechanism of action of AT-9010 (active metabolite of AT-527):

1) **Chain termination** of newly formed genomic RNA in the RNA-dependent RNA polymerase(RdRp) site (by incorporation of 2 molecules of AT-9010- monophosphate)
2) **Blocking of NiRAN** activity (Nidovirus RdRp-Associated Nucleotidyltransferase) by AT-9010 monophosphate: this is a very conserved function, since mutations at this site are lethal



*Such AT-9010 pleiotropic action should **attenuate the chance of simultaneous resistance** mutations, and be an important asset in the control of the expanding genetic pool of SARS-CoV-2 variants observed in the pandemic.*

Ep 236-10: Good AAC April 2021 **AT-527, a Double Prodrug of a Guanosine Nucleotide Analog, Is a Potent Inhibitor of SARS-CoV-2 In Vitro and a Promising Oral Antiviral for Treatment of COVID-19**

- **EC90** (90 % inhibitory conc) in human airway epithelial cells against SARS-CXoV-2 = **0.47 µM**
- Pharmacokinetic studies predict that **twice daily oral doses of 550 mg AT-527** will result in trough concentrations in human lung that exceed the EC90

Ep 236-11: Tribulations, yet continuation

- Press release 20 Oct: AT-527 fails to meet primary goal. Yet a reduction of viral load by 0.50 log was reported.
- Press release 17 Nov: ATEA terminates deal with Roche, but continues clinical development of AT-527 alone.

The ongoing phase II and III clinical trials (NCT04709835, NCT04396106, NCT04889040) of AT- 527 for the treatment of both out and in patients with COVID-19 are expected to be completed at the end of 2021 or mid 2022?

**CONCLUSIONS on candidate polymerase inhibitors**

1) **Remdesivir**: despite encouraging data on outpatient IV treatment and favorable oral treatment in animal models, the development of an oral treatment for humans has been halted. It is not clear on which oral alternative Gilead will work. See https://www.gilead.com/purpose/advancing-global-health/covid-19
2) **Galidisevir** has a rather moderate in vitro potency and needs to be administered already before infection to have an effect on SARS-CoV-2 in the hamster model Development stopped.
3) **Sofosbuvir:** results of clinical trials unclear.
4) **AT-527**: interesting compound with good potency in vitro and a double mechanism of action, which may reduce chances on resistance. After "failed" phase 2, Roche has withdrawn, but ATEA continues development

**IMMUNO-VIROLOGY of COVID and HIV**

Ep 236-12: Zicheng Hu Res Square Feb 22: Prognostic value of early (innate) immune markers on COVID disease progression and response to RNA vaccination

Increased risk of disease progression: early transcriptomic signatures of Type I IFN and RIG-I signaling, interferon induced chemokines (CXCL10, CXCL11) and CCR 2 ligands (MCP-1, MCP2 MCP3) positively associated with subsequent progression.
Viral load:

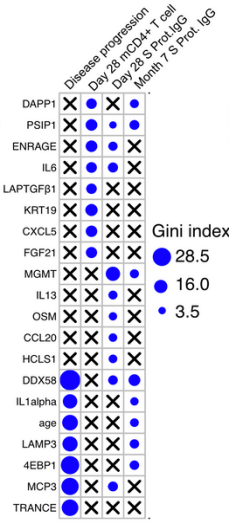
- Inverse association with early RIG-I plasma levels
- Direct association with C-Type Lectin Domain Family 4 Member C (CLEC4C, expressed by plasmacytoid dendritic cells), and TNF-related apoptosis inducing ligand (TRAIL),

T cell and antibody responses to COVID: positively associated with RIG-I

Similar trajectories of immune responses induced by SARS-CoV-2 infection and mRNA vaccine

- First 7 days after 1st vaccine: IFN-gamma,type-1 IFN signature (CXCL-1O and -11) as well as MCP1 and MCP2.
- Later markers in vaccination or infection: SLAMF1, TNFRSF9, CCL3, CCL4, TGFα, TNFSF14 and B

Identified set of markers



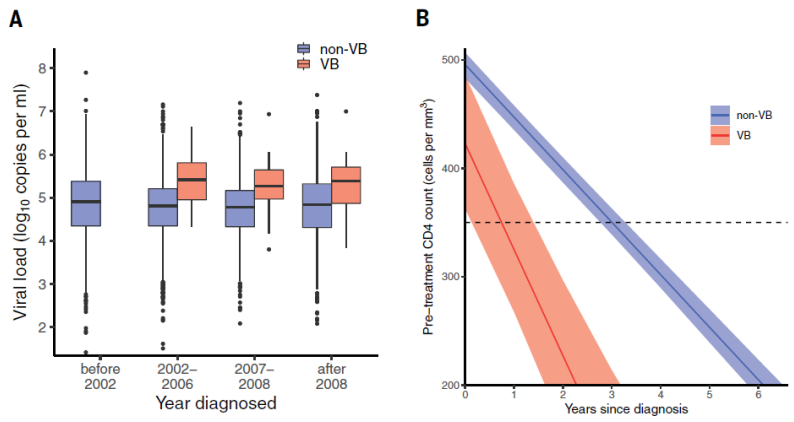

Potential application: these markers can be used to predict disease progression and early identification of poor response to vaccine

**HIV**

Ep 236-13: Chris Wymant Science 4 Feb ’22: A highly virulent variant of HIV-1 circulating in the Netherlands

A virulent variant of subtype-B HIV-1 in 109 subjects with:

- 3.5-5.5 fold increase in viral load
- Twice as fast CD4 T decline: would reach < 350 /µL within 9 months without treatment
- Arose in the nineties and is highly transmissible
- Bad evolution can be stopped with appropriate anti-viral treatment

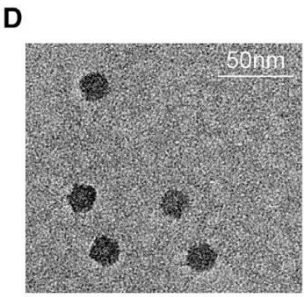


→ Emphasizes importance of early diagnosis and treatment.

Ep 236-14: Announcement of collaboration IAVI and Moderna to develop an mRNA vaccine to generate broad HIV-neutralizing antibodies, based on VRC-01 eOF-GT8 immunogen

Ep 236-15: Melo Mol Therapy 2021: Proof of principle in mice:

- **The eOD-GT8 immunogen** is a germline-targeting antigen designed to prime human B cells capable of evolving toward VRC01-class broadly neutralizing antibodies
- **Self-amplifying RNA** = alphavirus replicon expressing a self-assembling protein nanoparticle immunogen, the glycoprotein 120 (gp120) germline-targeting engineered outer domain (eOD-GT8) 60-mer.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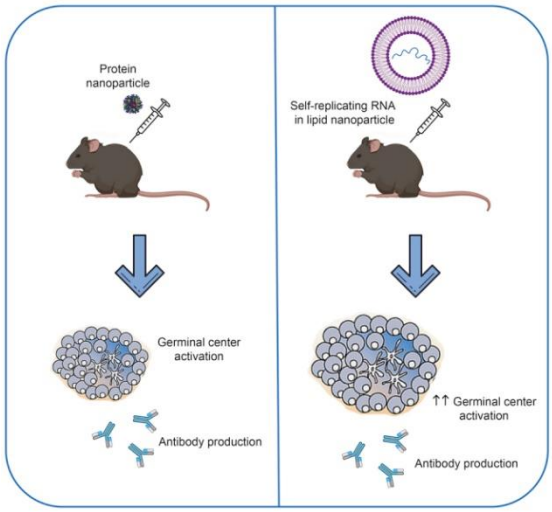
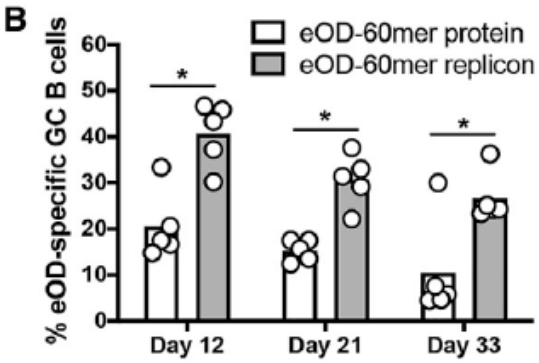
- A single injection in mice of this saRNA eODGT8 60-mer-encoding replicons elicited
    - high titers of gp120-specific antibodies
    - and increased levels of antigen-specific germinal center B cells

  as compared with protein immunization.
- Immunization of transgenic mice expressing human inferred-germline VRC01 heavy chain B cell receptors that are the targets of the eOD antigen led to priming of B cells and somatic hypermutation consistent with VRC01-class antibody development




**CONCLUSIONS on immune-virology**

1) **Early innate markers could be used prognostically in COVID:**

- To predict disease progression, T and B immune responses and viral load decline

- To predict the response to mRNA vaccination

**2)** A more **pathogenic and transmissible HIV subtype B** has been discovered in the Netherlands. It can and has been contained, however, by early testing and treatment.

**3)** There is progress in the development of **an RNA based HIV vaccine, based on self-replicating RNA and an particular gp120 immunogen**, which can stimulate the maturation of VRC01-like broad neutralizing antibodies.

Best wishes,

Guido