

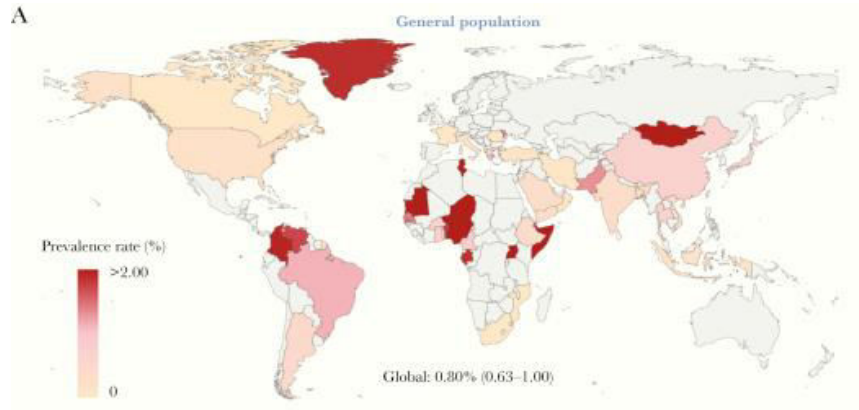
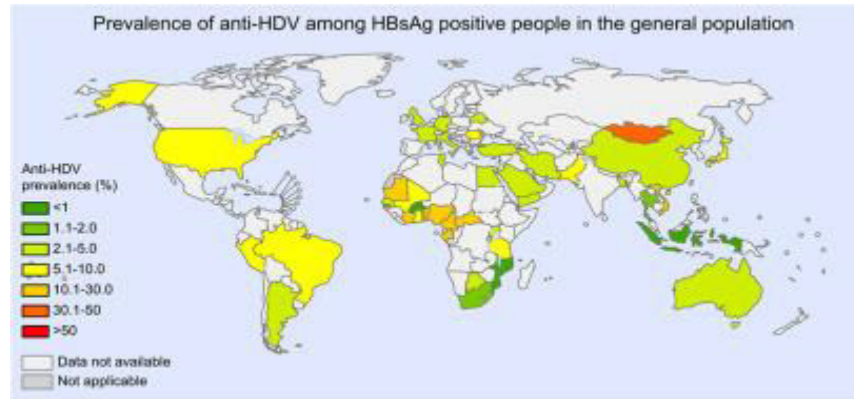
# Diagnosics for HDV: what we have and what we need for improving diagnosis in low-and-middle income countries

*I. Chemin*



*Delta Cure 2024 Milano*

# GLOBAL HDV PREVALENCE WORLDWIDE 2020



JOURNAL  
OF HEPATOLOGY

The Home of Liver Research

EASL

The global prevalence of hepatitis D virus infection:  
Systematic review and meta-analysis

Alexander J. Stockdale • Benno Kreuels • Marc Y.R. Henrion • ... Catherine de Martel • Yvan Hutin •  
Anna Maria Geretti • Show all authors

Open Access • Published: April 23, 2020 • DOI: <https://doi.org/10.1016/j.jhep.2020.04.008>

12 Millions

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA  
Infectious Diseases Society of America

hivma  
HIV medicine association

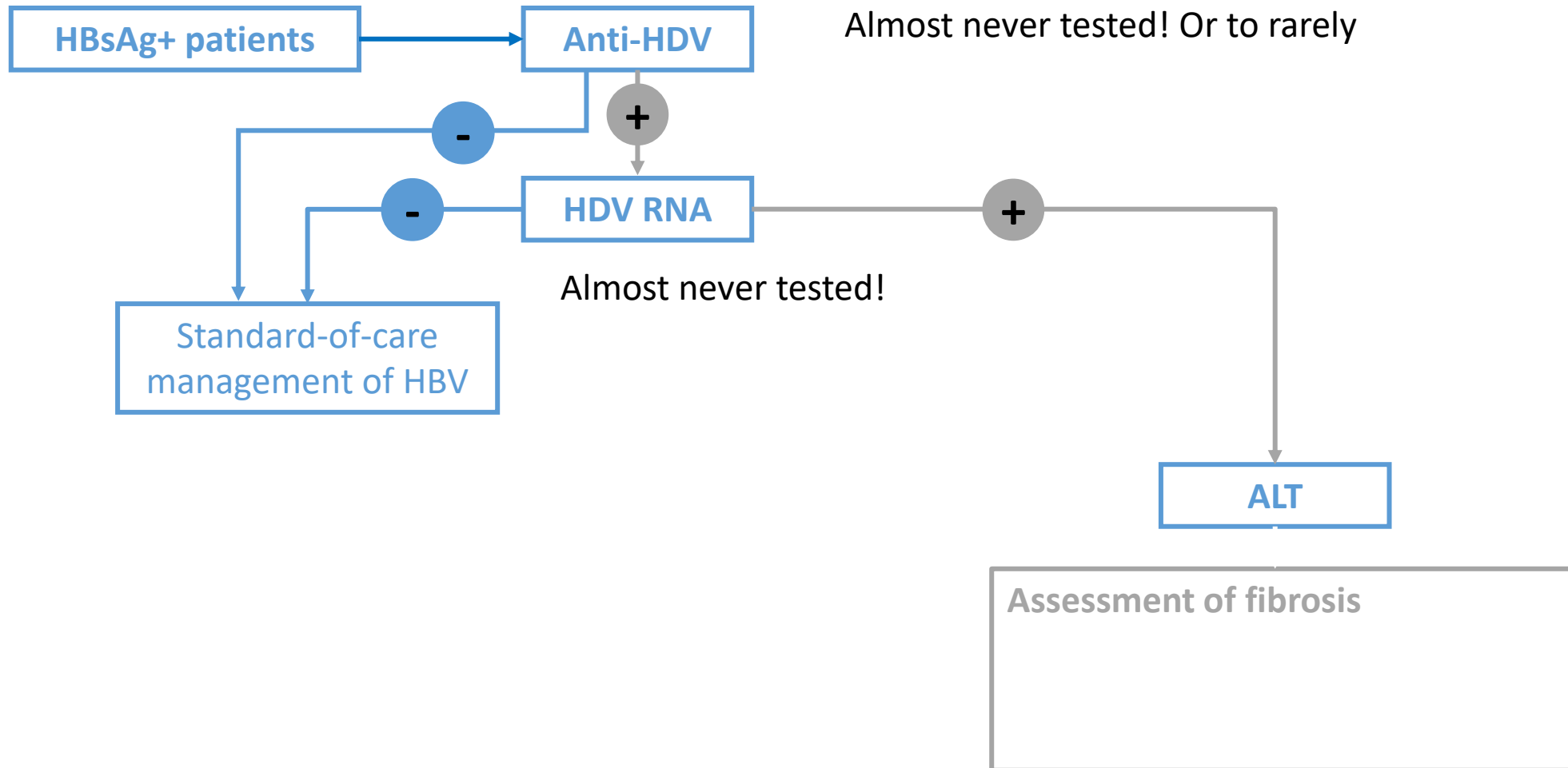
Estimating the Global Prevalence, Disease Progression,  
and Clinical Outcome of Hepatitis Delta Virus Infection

Zhijiang Miao,<sup>1</sup> Shaoshi Zhang,<sup>1</sup> Xumin Ou,<sup>1</sup> Shan Li,<sup>1,2</sup> Zhongren Ma,<sup>3</sup> Wenshi Wang,<sup>1,4</sup> Maikel P. Peppelenbosch,<sup>1</sup> Jiaye Liu,<sup>1</sup> and Qiuwei Pan<sup>1</sup>

48-60 Millions

- **Hepatitis D: a neglected disease**
- **Mongolia display the highest prevalence**
- **Amazonia? Africa?**

# Algorithm for the Evaluation of HDV



# HDV serology

- [ETI-DELTA-IGMK-2 kit](#) (Dia.Pro Diagnostic Bioprobes srl, Sesto San Giovanni, Italy)
- LIAISON® XL MUREX Anti-HDV (CHU Limoges et autres)
- ARCHITECT HDV Ig assay (Abbott Laboratories)
- EIA-ANTI-HDV; Witech Inc., USA, ref# D-152/1.0
- [General Biologicals HDV Ab kit](#) (General Biologicals Corporation, Taiwan, China)
- For research use only : human Hepatitis D virus IgG, HDV IgG ELISA Kit (Clinisciences)

## HDV RNA

Eurobioplex (CNR/CHU)

[In house](#) (several protocols)

HDV RNA test, m2000 RealTime HDV

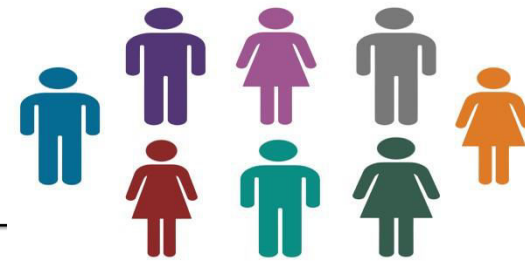
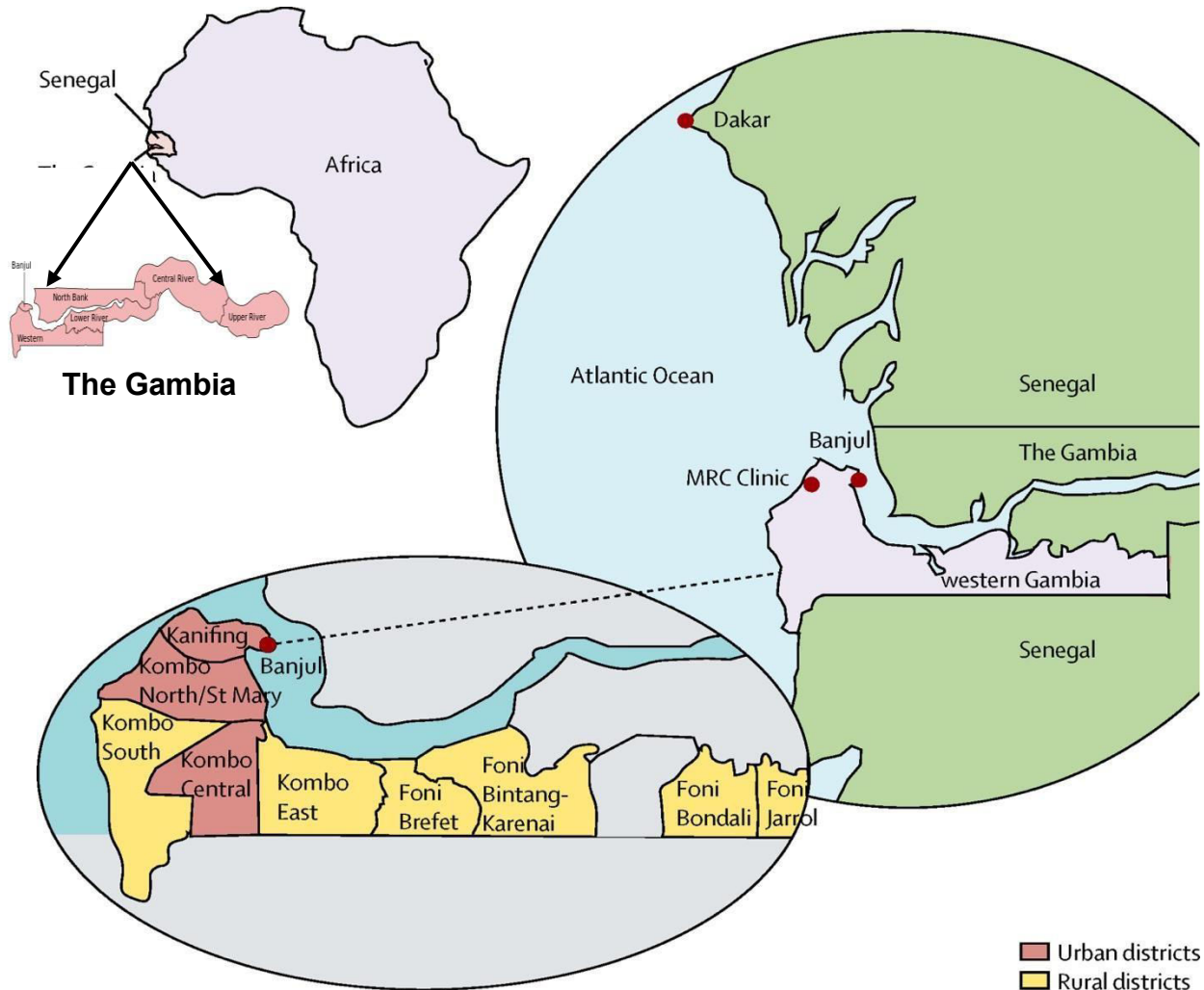
HDV Real-TM Quant (Sacace Biotechnologies, Como, Italy)

AmpliSens® HDV-FEP PCR (Russia)

RealStar® HDV RT-PCR Kit 1.0; Altona, Germany

[RoboGene HDV RNA Quantification Kit 3.0](#) - RUO- IvD labeled, Germany

# PROLIFICA: Study Population



Community Screening (WATCH-B)

Blood Bank Screening (Blood Donors)

705 HBsAg + patients TESTED IN OUR STUDY

Anti-HDV by Diasorin, POC and GB

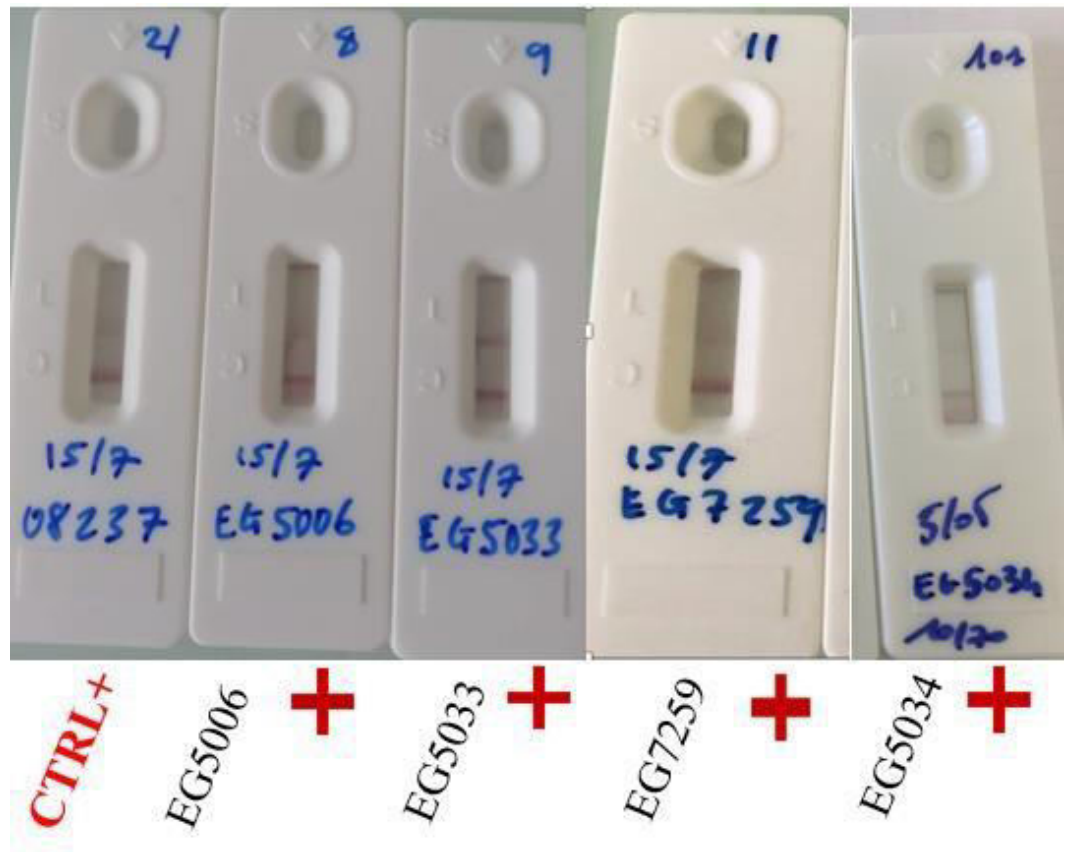
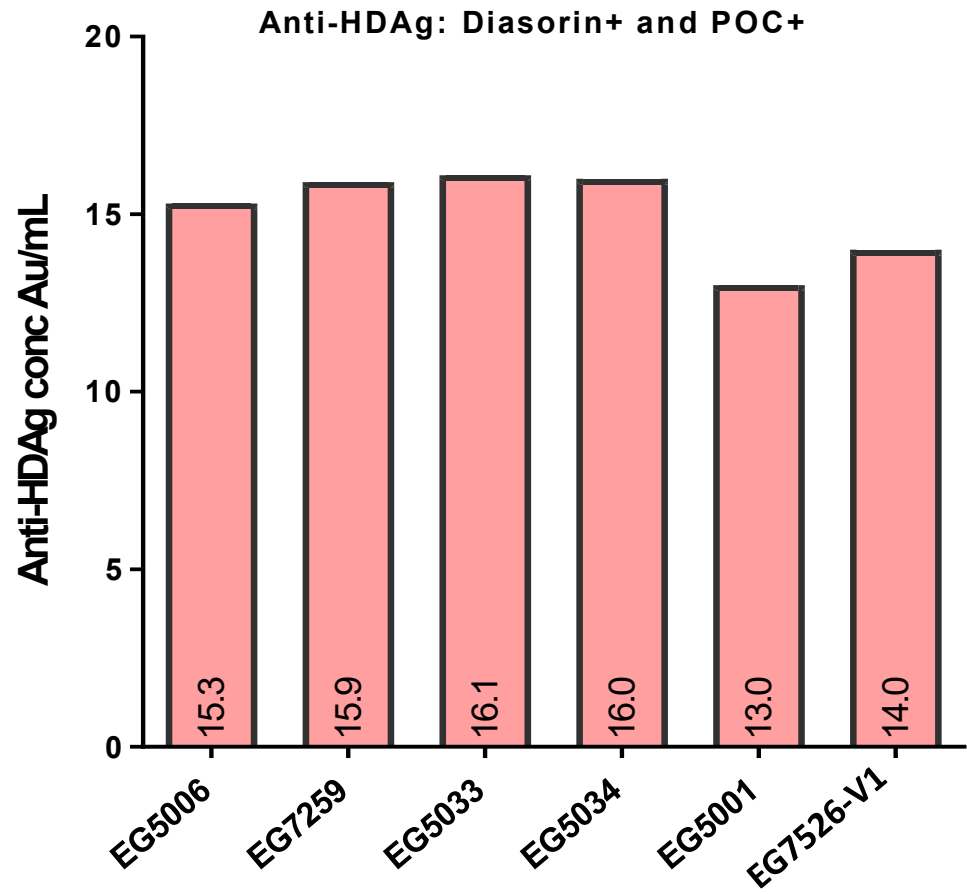
In house RT qPCR, Nested PCR, ddPCR, Roboscreen

HDVAg

Lemoine, M et al 2016:

DOI: 10.1016/S2214-109X(16) *The Lancet Global Health*

# Anti-HDAg positive by both assays



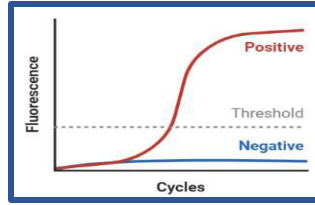
**6/26** (DiaSorin) and **6/11** (POC) were **anti-HDAg positive** by both assays.

- ❖ The POC test detects high anti-HDV levels **13 AU/mL and above**
- ❖ **Overall, high anti-HDV level maybe an active infection**

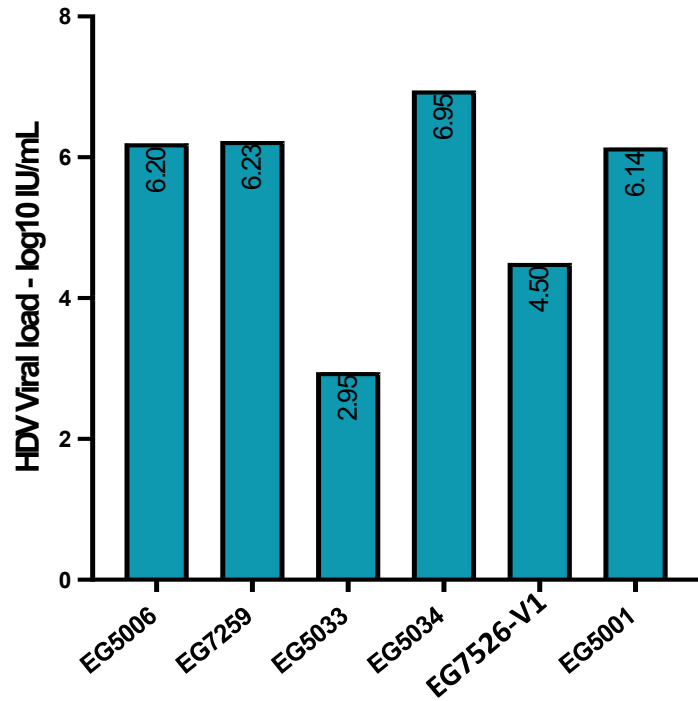
# Anti-HDV + by both tests tends to have higher viral loads

## One step qPCR

Scholtes C.  
*et al.* 2012:

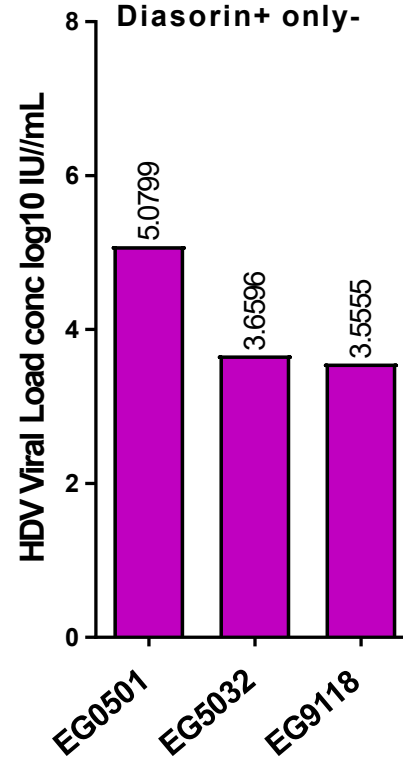


Diasorin + POC +



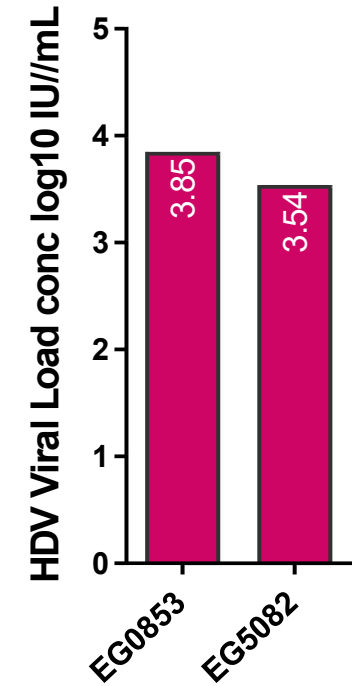
VL ranged Log<sub>10</sub> 3 to 6 IU/mL

Diasorin+ only-



VL ranged log<sub>10</sub> 3 to 6 IU/mL

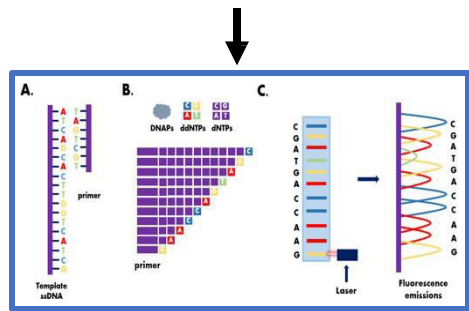
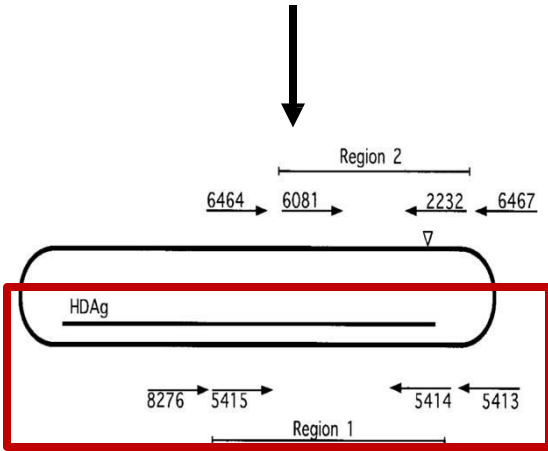
POC+ only:



VL log<sub>10</sub> 3 IU/mL



- **Nested- PCR:**
- Total: 11 samples
  - Targeting HDAg



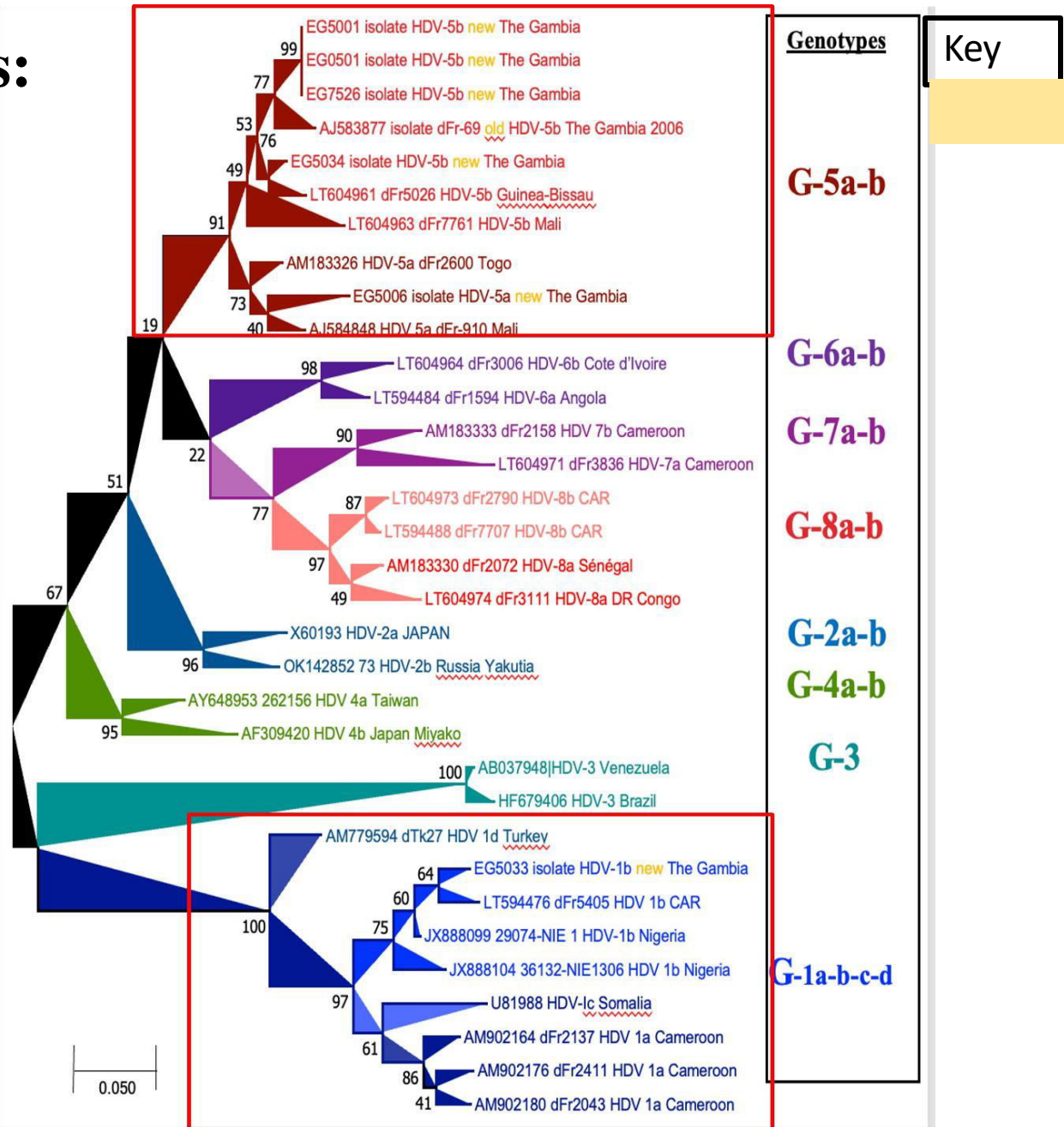
### Sanger Sequencing

GRAZIAA Niro et, al. 1997; HEPATOLOGY Vol. 25, No. 3, 1997

## Sequences Analysis:

- **Phylogenetic Tree:**

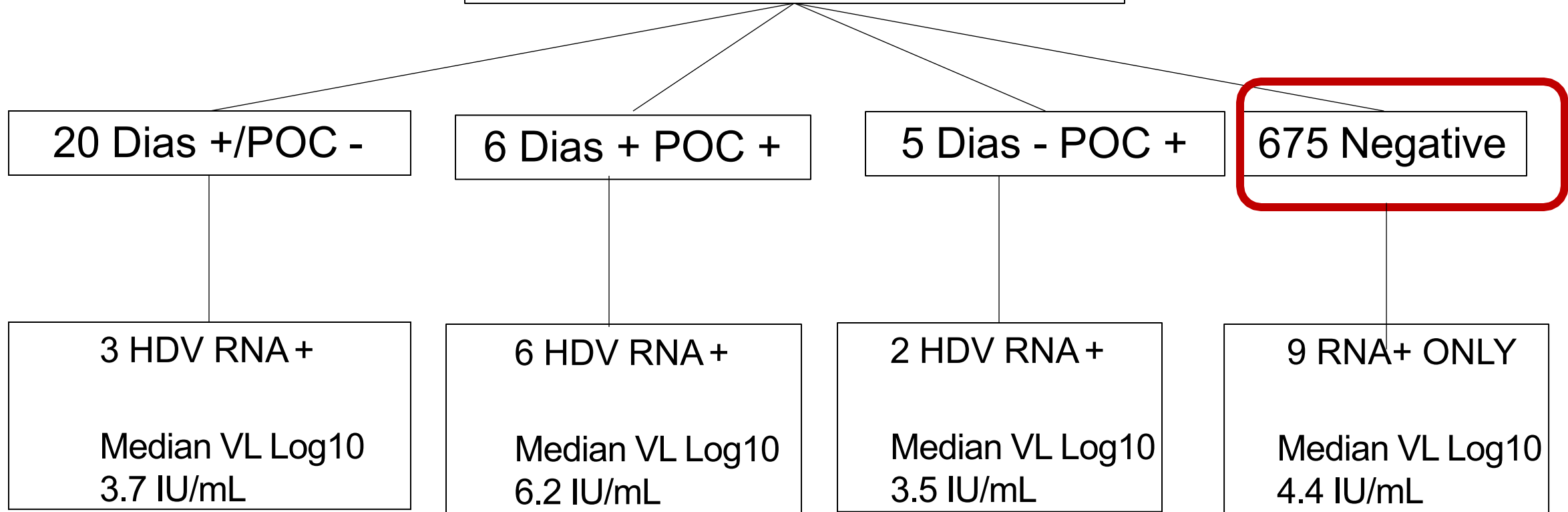
Gambian isolates  
[NEW]





# Summary

**705 Diasorin tested**



# Focus on 52 sera with 3 antibody tests and 2 HDV RNA tests

9 POC + only

2 HDV RNA +  
VL log<sub>10</sub> 3 IU/mL

6 Dias +/-POC  
+/-GB

**15 Dias + GB +**

GB + 11

11 Dias only

6 HDV RNA +  
Median VL Log<sub>10</sub>  
5.8 IU/mL

**13 HDV RNA +**  
  
**Median VL Log<sub>10</sub>  
5.5 IU/mL**

11 HDV RNA +  
Median VL Log<sub>10</sub>  
4.4 IU/mL

3 HDV RNA  
+  
Median VL  
Log<sub>10</sub> 3.5  
IU/mL

**None of the tests are perfect (estimated anti-HDV + 42/705 samples (6.0%))**

# Clinical characteristics of patients depending on anti-HDV status

| HDV Ab+ vs HDV Ab- / POC test in the general cohorts |                                  |                                   |                      |
|--|----------------------------------|-----------------------------------|----------------------|
| Characteristics                                      | Negative =696 <sup>1</sup> (0,N) | Positive = 11 <sup>1</sup> (1,N), | p-Value <sup>2</sup> |
| Age group (years), median (IQR)                      | 40 (36,48)                       | 36(31,37)                         | 0.024                |
| HBsAg, median  | 3,042 (1,337, 4,221)             | 2,560 (2,076, 3,980)              | 0.9                  |
| HBV DNA (IU/L), median (IQR)                         | 213 (10, 2,560)                  | 953 (89, 3,020)                   | 0.3                  |
| HBV DNA categories IU/L                              |                                  |                                   | 0.3                  |
| Jaundice   | 5/694 (0.7%)                     | 1/9 (11%)                         | 0.075                |
| ALT (IU/mL)  | 23 (17, 31)                      | 36 (20, 44)                       | 0.067                |
| AST (IU/mL)  | 27 (22, 35)                      | 34 (25, 73)                       | 0.12                 |
| GGT (IU/mL)  | 28 (20, 40)                      | 61 (31, 195)                      | 0.056                |
| HBeAg  | 45 (122 (37%))                   | 1/ 3 (33%)                        | >0.9                 |
| Liver stiffness (kPa), median (IQR)                  | 5.30 (4.30, 6.60)                | 12.00 (4.70, 41.20)               | 0.11                 |
| METAVIR score, n/N (%)                               | 5.30(4.30, 6.60)                 | 12.00 (4.70, 41.20)               | 0.002                |
| Ascites (Clinic), n/N (%)                            | 3/694 (0.4%)                     | 2/9 (22%)                         | 0.001                |
| Us-Ascite n/N (%)                                    | 4 (694 (0.6%))                   | 3/9 (33%)                         | <0.001               |
| APRI score >2.0                                      | 26/667 (3.9%)                    | 2/8 (25%)                         | 0.04                 |

# Take-home Points

- All patients positive for HBsAg should be tested for hepatitis delta according to the screening algorithm
- Need to compare existing anti-HDV tests including the promising POC
- Anti-HDV testing is probably missing positive patients at least in African context, more studies to be performed
- Any HDV RNA test such as for HBV with GenXpert would be pivotal due to difficult access to molecular testing and HDV flares
- Patients coinfecting with HBV and HDV harbouring the higher risks (viral loads) are seen by antibody testing and should be monitored since they experience more rapid progression vs those with HBV mono-infection
- Reflex anti-HDV testing and other strategies should be employed to increase HDV testing rates and reduce loss to follow-up in persons positive for HBsAg

# ACKNOWLEDGMENTS

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anrs

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Many thanks to Stefan Urban for  
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LOUSTAUD-RATTI for her precious  
advices

# Trying to go Forward with Hepatitis Viruses Enigmas



*microorganisms*



an Open Access Journal by MDPI

## Editorial Board Members' Collection Series: Hepatitis Viruses: Who They Are and Consequences

Guest Editors:

### Dr. Isabelle Chemin

Centre de Recherche en  
Cancérologie de Lyon INSERM  
U1052, CNRS UMR5286,  
Université de Lyon, Lyon, France

### Prof. Dr. Flor Helene Pujol

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Microbiología y Biología Celular  
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Caracas 1020A, Venezuela

Deadline for manuscript  
submissions:

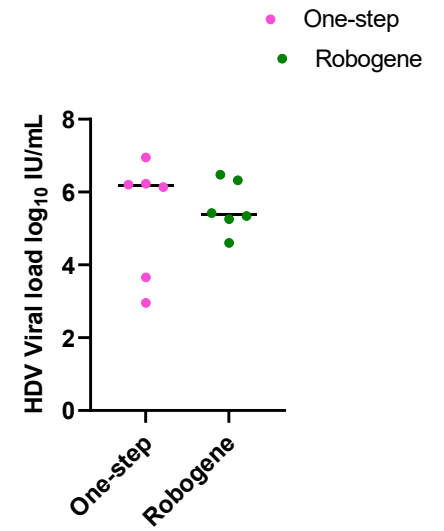
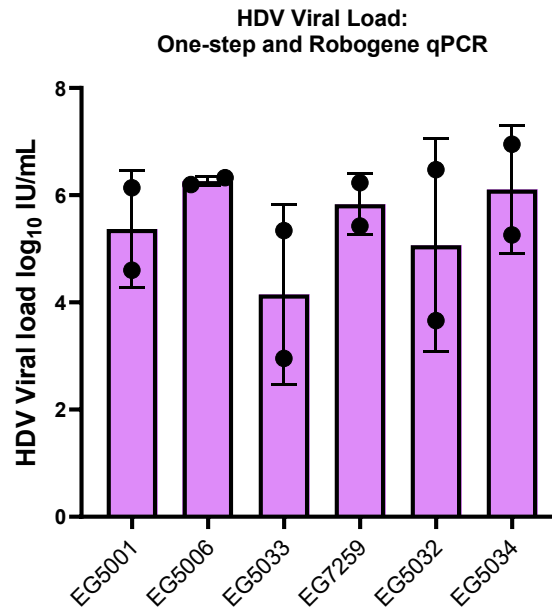
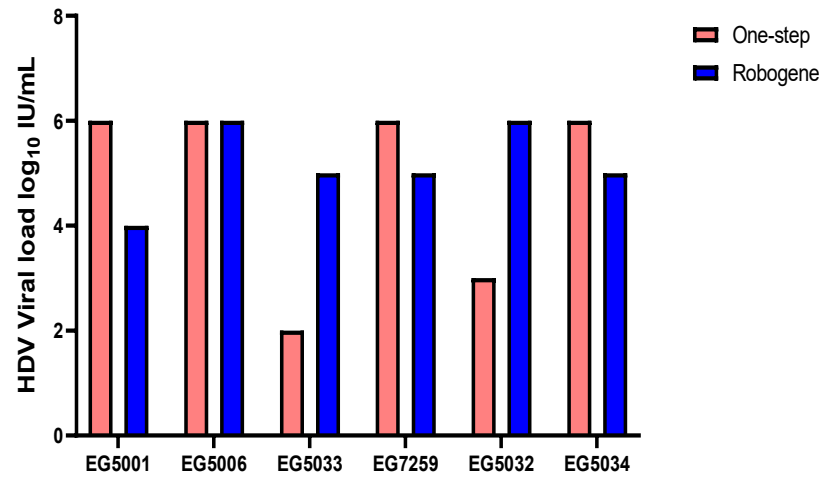
**30 November 2024**

### Message from the Guest Editors

Expected papers:

- Update on the use of the hepatitis A vaccine?
- What are the new data regarding hepatitis E?
- Where is the epidemiology of hepatitis C that can be cured?
- HCV infection and PWID
- Hemodialysis: an HCV redoubt.
- Illustration of the substantial disparities in HBV burden between countries and regions but also within a country or region, income, race or ethnicity, and other social and cultural factors.
- How to improve the management of cirrhosis and liver cancer HBV-related deaths, (acute flares and reactivation, extrahepatic complications, and social stigma)?
- Current programs regarding Universal infant vaccination with timely birth dose and peripartum antiviral prophylaxis in mothers with a high level of

Special Issue Editors

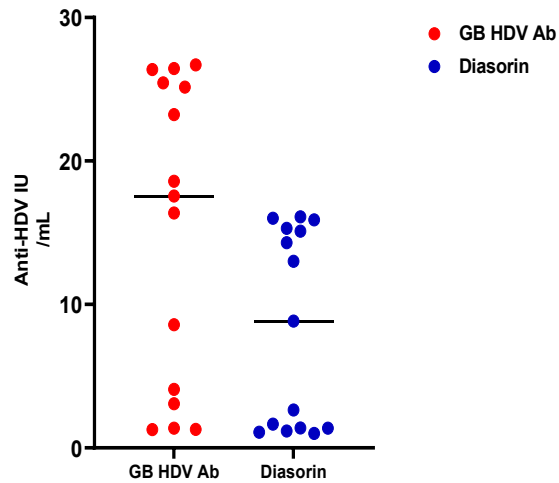
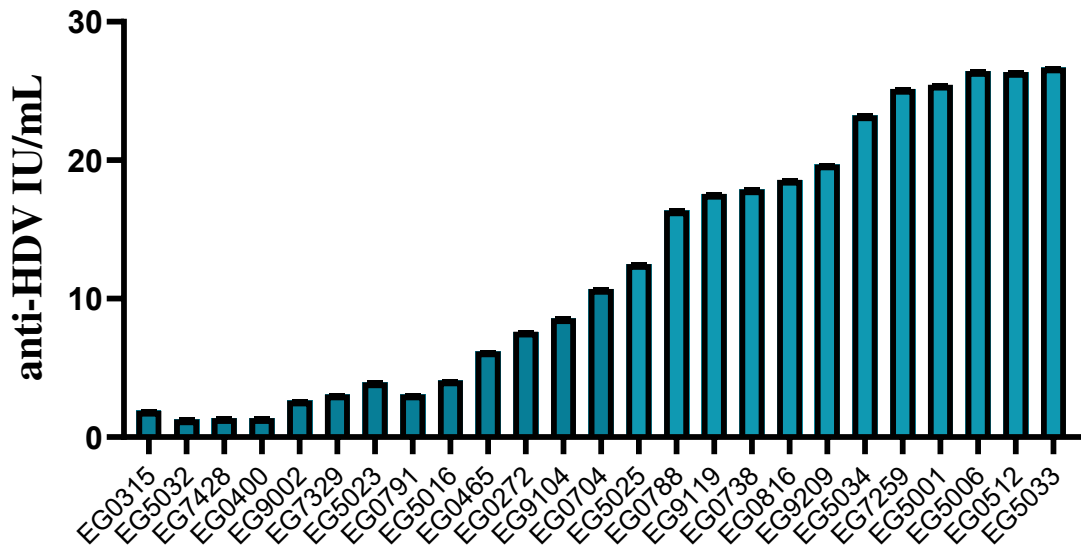
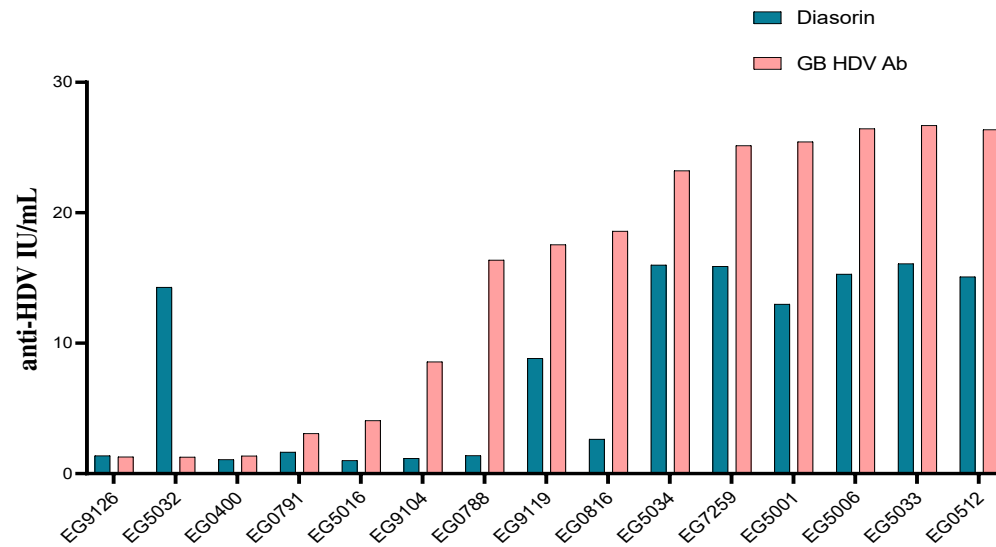
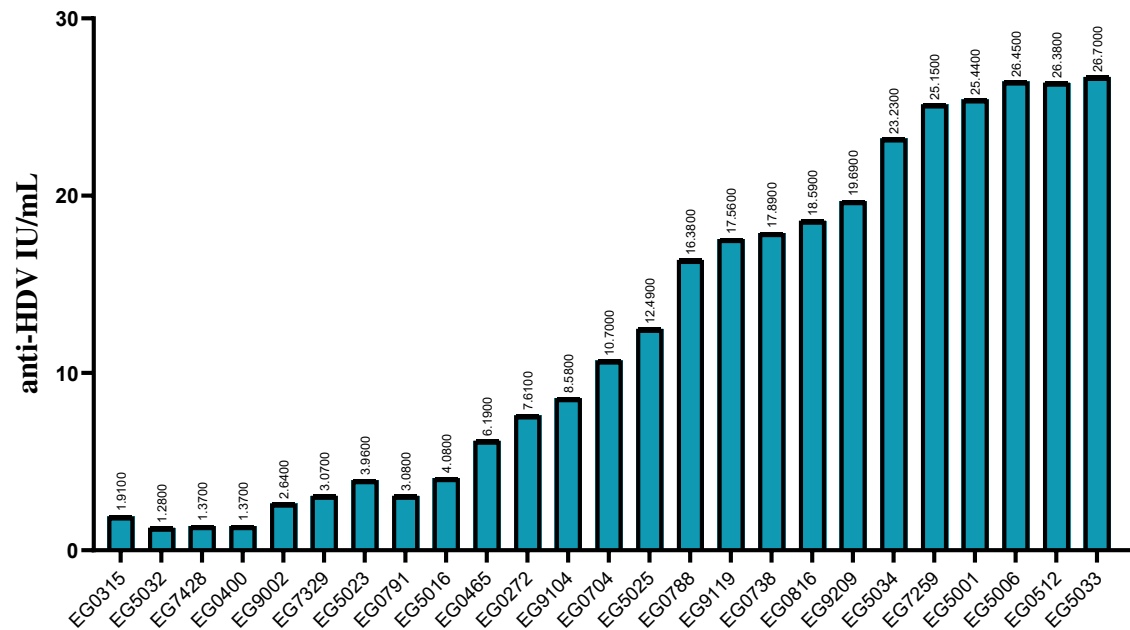




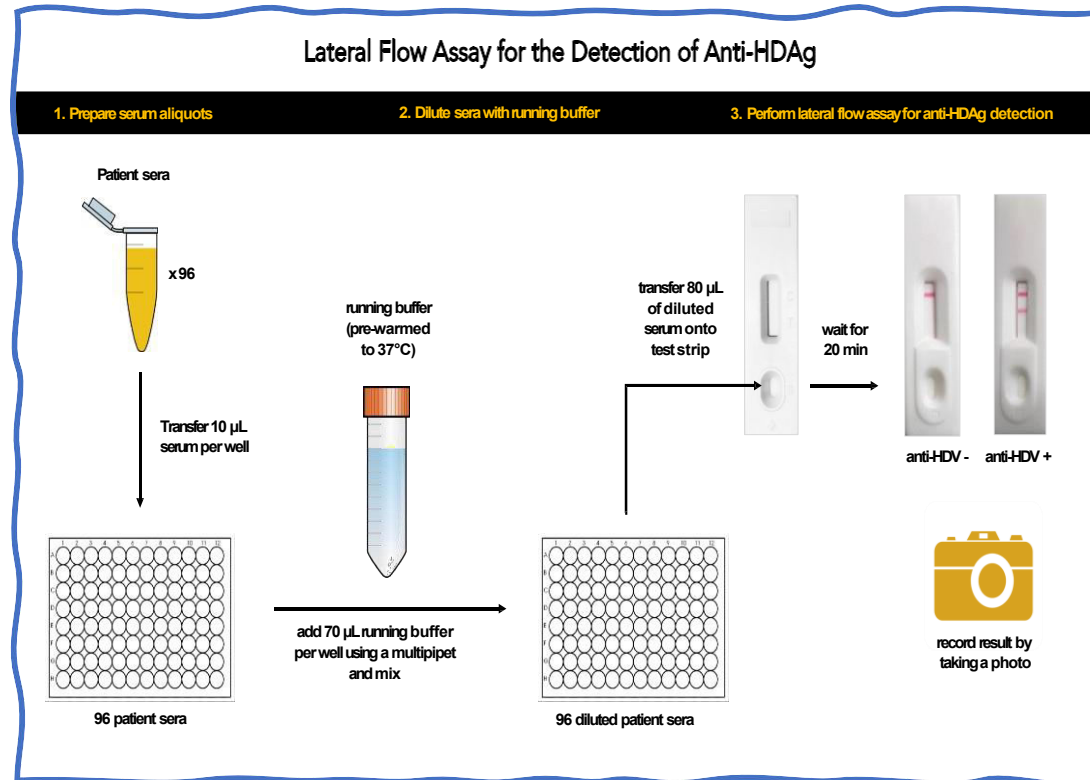
### HDV RNA+ vs RNA- /HDV Ab+ by Diasorin

| Characteristics                     | Negative =17 <sup>1</sup> (0,N) | Positive = 8 <sup>1</sup> (1,N), | p-Value <sup>2</sup> |
|-------------------------------------|---------------------------------|----------------------------------|----------------------|
| Age group (years), median (IQR)     | 42 (40, 43)                     | 43 (33,46)                       | >0.9                 |
| HBsAg, median (IQR)                 | 1,696 (32, 3,337)               | 2,275 (1,541, 4,057)             | 0.5                  |
| HBV DNA (IU/L), median (IQR)        | 10 (10, 755)                    | 3, 020 (10, 37,715,100)          | 0.2                  |
| HBV DNA categories IU/L             |                                 |                                  | 0.03                 |
| Jaundice                            | 0 / 16 (0%)                     | 1 / 7 (14%)                      | 0.3                  |
| ALT (IU/mL)                         | 20 (16, 29)                     | 44 (38, 153)                     | 0.003                |
| AST (IU/mL)                         | 28 (20, 38)                     | 73 (43, 94)                      | 0.007                |
| GGT (IU/mL)                         | 26 (22, 34)                     | 178 (86, 226)                    | 0.002                |
| HBeAg                               | 1 / 1 (100%)                    | 2 / 4 (50%)                      | >0.9                 |
| Liver stiffness (kPa), median (IQR) | 5 (5, 6)                        | 12 (10, 41)                      | >0.001               |
| METAVIR score, n/N (%)              |                                 |                                  | >0.001               |
| Ascites (Clinic), n/N (%)           | 0/16 (0%)                       | 2 / 7 (29%)                      | 0.083                |
| Us-Ascite n/N (%)                   | 0/16 (0%)                       | 3/41 (43%)                       | 0.02                 |
| APRI score >2.0                     | 0/16 (0%)                       | 3/7 (43%)                        | 0.02                 |
| Viral load (median)                 |                                 | log10 5.5 IU/mL                  |                      |

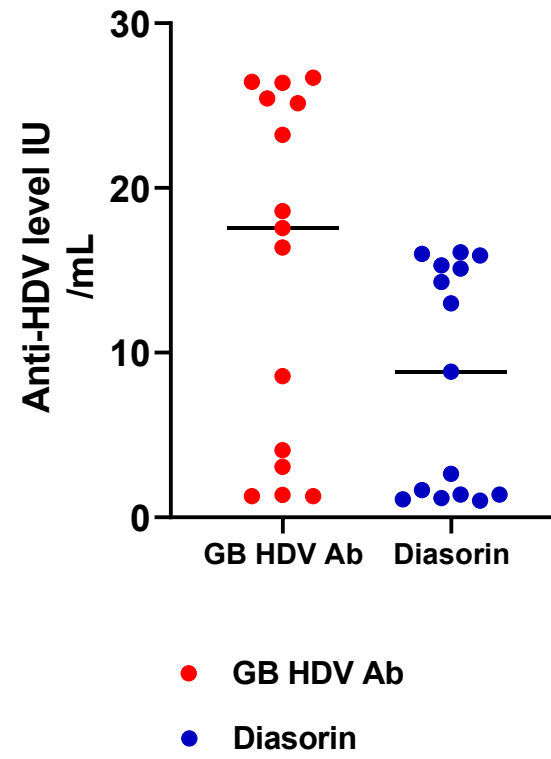
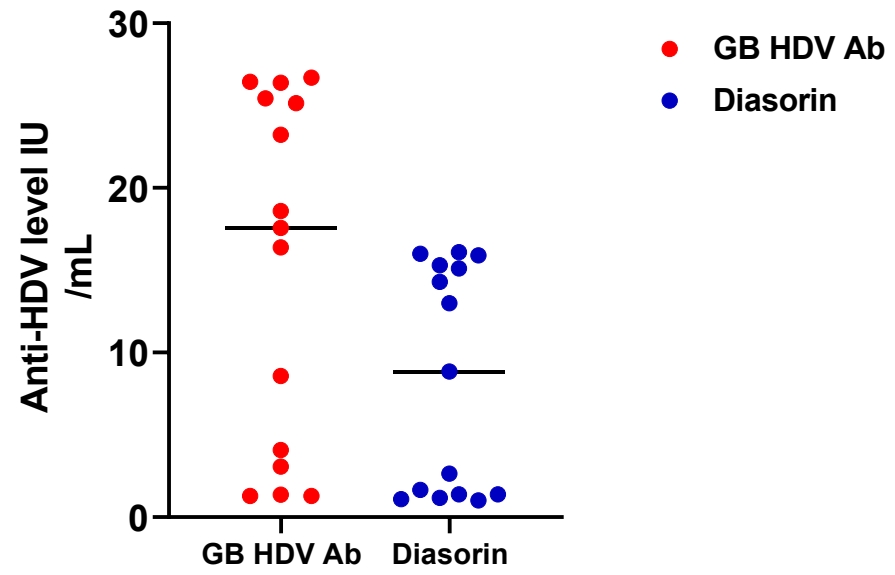
| <b>HDV Ab + vs HDV Ab- /Diasorin Assay in the general cohorts</b> |  |   |                            |
|---|--|---|----------------------------|
| <b>Characteristics</b>  | <b>Negative =682<sup>1</sup> (0,N)</b> | <b>Positive = 25<sup>1</sup> (1,N),</b> | <b>p-Value<sup>2</sup></b> |
| Age group   | 40 (36, 48)                            | 42(38,44)                               | 0.5                        |
| HBsAg, median   | 3,074 (1,529-4,323)                    | 1,987 (161,- 3,912)                     | 0.13                       |
| HBV DNA (IU/L), median (IQR)                                      | 214 (10, 2,560)                        | 10 (10, 4,175)                          | 0.8                        |
| HBV DNA categories IU/L   |  |   | 0.7                        |
| Jaundice  | 5/680 (0.4%)                           | 1/23 (4.3%)                             | 0.2                        |
| ALT (IU/mL)   | 23 (17,31)                             | 22 (19, 39)                             | 0.3                        |
| AST (IU/mL)   | 27 (22,35)                             | 35 (24, 46)                             | 0.073                      |
| GGT (IU/mL)   | 28 (20, 40)                            | 32 (25, 61)                             | 0.062                      |
| HBeAg   | 43/ 120 (36%)                          | 3/5 (60%)                               | 0.4                        |
| Liver stiffness (kPa), median (IQR)                               | 5.3 (4.3, 6.60)                        | 5.70 (4.75, 8.40)                       | 0.2                        |
| METAVIR score, n/N (%)  |  |   | 0.061                      |
| Ascites (Clinic), n/N (%)   | 3/680 (0.4%)                           | 2/23 (8.7%)                             | 0.01                       |
| Us-Ascite n/N (%)   | 4/680 (0.6%)                           | 3/23 (13%)                              | <0.001                     |
| APRI score >0.65  | 122/ 652 (19%)                         | 9/23 (39%)                              | 0.027                      |
| Anti-HDV level (median)   | 12 IU/mL                               |   |                            |
| HDV Viral Load  | Log10 5.5 IU/mL                        |   |                            |

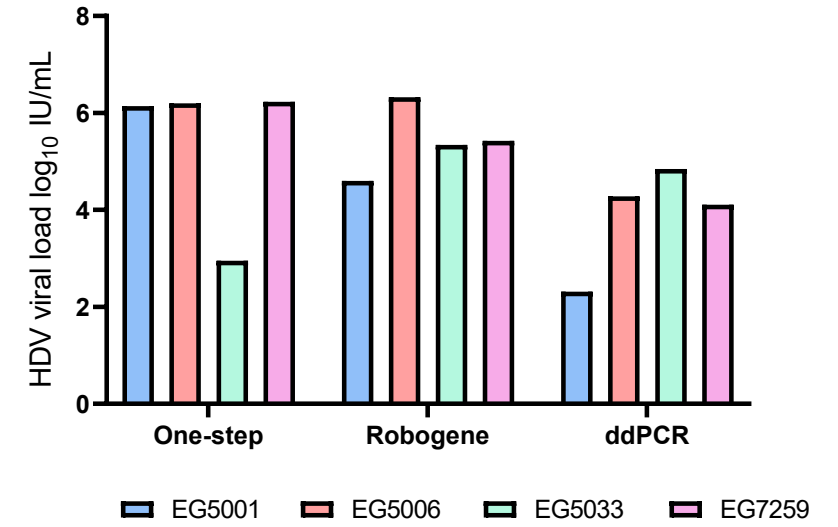
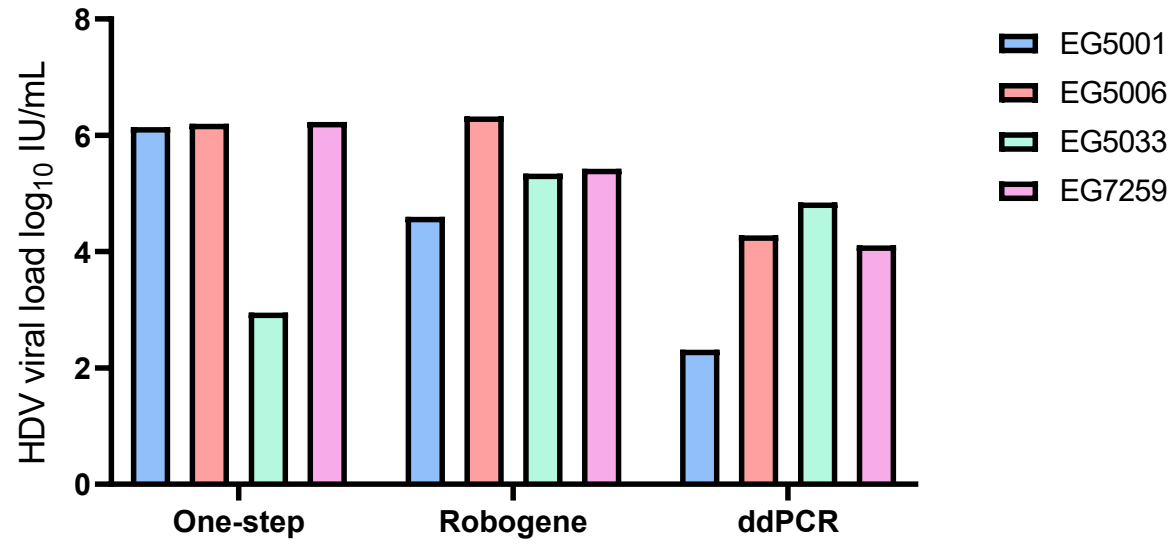


# Pan-Genotypic HDAg POC



Lempp, F.A. et, al. 2021  
<https://doi.org/10.3390/v13122371>





HDV Viral Load:  
One-step and Robogene qPCR

