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**HBV Forum 2**  
**April 18<sup>th</sup> 2017**  
**Hilton Amsterdam**

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# HDV RNA and Anti-HDVAg Testing in Europe

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Avicenne Hospital



*French National Reference Laboratory  
For Hepatitis Delta virus*



# HDV-RNA and anti-HDV-Ag Testing in Europe

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**French National Reference Laboratory for HDV**

**Clinical Microbiology Laboratory**

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**INSERM U955 Team 18 – Creteil, France**

- **FNRL for HDV**

**Emmanuel Gordien (MD, PhD)**

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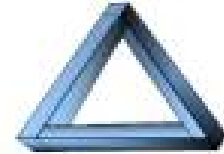
**Athenais Gerber (M2/Ing.)**

**Samira Dziri (M2/Tech.)**

**Zahia Ben-Abdesselam (M2/CRA)**

**Chakib Alloui (MD)**

**Dominique Roulot (MD, PhD)**



**Avicenne Virology Unit**  
*French National Reference Laboratory  
For Hepatitis Delta virus*



**Avicenne Hospital**



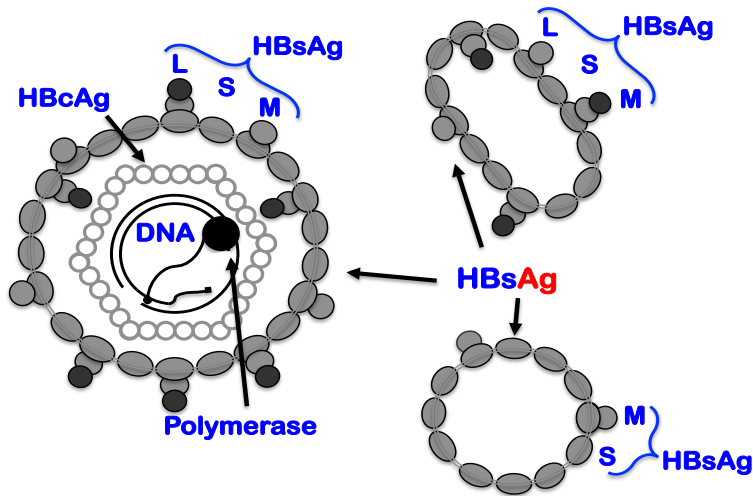
# Disclosures

- **Speakers on a time-time basis for:**
  - **BMS, Gilead, Qiagen, Siemens**
- **Invitation to scientific congress:**
  - **BMS, Gilead, Qiagen, Eurobio**
- **Consulting & scientific assistance :**
  - **Bioactiva diagnostics GmbH**
  - **Eurobio**

# HDV Infection

Occurs only in  
patients infected  
with HBV

# Viral particles

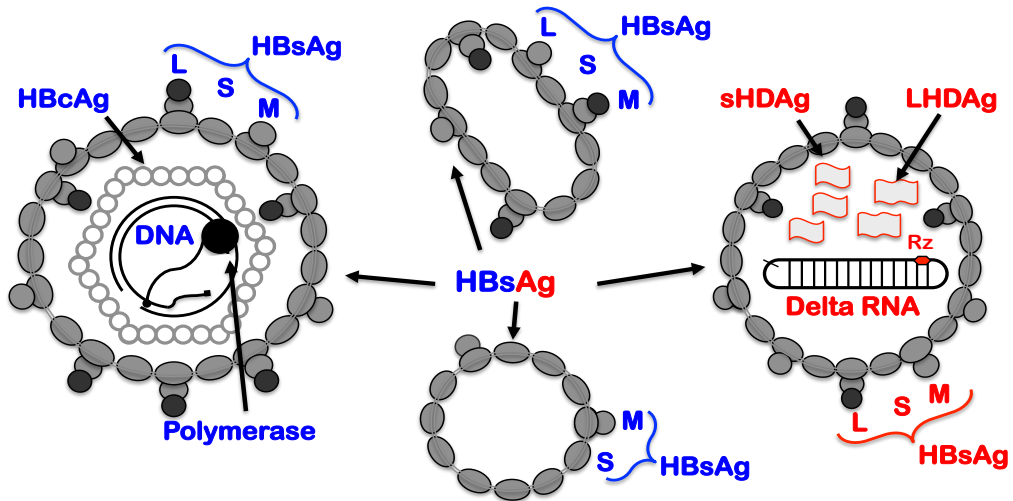


42 nm  
Hepatitis B Virus

19 - 22 nm  
Empty particles

# Viral particles

## HDV Satellite of HBV



42 nm  
Hepatitis B Virus

19 - 22 nm  
Empty particles

35 - 37 nm  
Hepatitis Delta Virus



# Main characteristics of HDV

- HDV belongs to the satellite virus family
- **Genome: negative circular single stranded RNA of  $\approx$  1.7 Kb with 60% of GC content  $\rightarrow$  high intramolecular base pairing (74%)**
- **Replication by a double rolling circle mechanism, involving a ribozyme region in its genome & host RNA polymerases (RNA Pol I, II & III)**
- **Only one coding ORF situated on the antigenome,**
- **One mRNA**
- **Two Proteins : sHDAg and LHDAg  $\rightarrow$  *Editing* mechanism of the antigenome involving the human ADAR-1**
- **Its envelope is provided by HBV, involving an isoprenylation of the LHDAg by a cellular farnesyl transferase**
- **HDV is characterized by a high genetic variability (8 (sub)genotypes)**

# Epidemiology

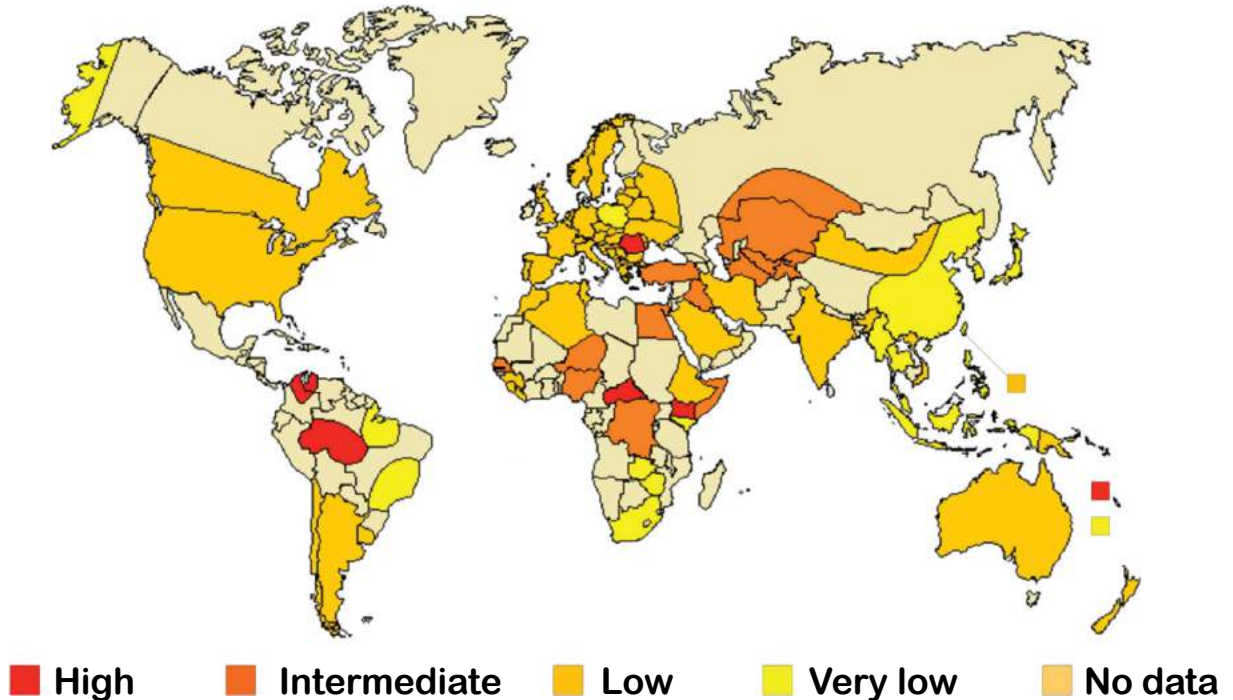
# Delta Viral Hepatitis:

## A Worldwide Healthcare Problem?

- **2 Billion individuals have been infected with HBV**
  - Among them : 240 millions chronically infected
  - Risk of developing cirrhosis and HCC X 100
  - 1 million deaths per year
- **≈10 to 20 millions chronic carriers of HDV**
- **In Europe → 4 to 10% of HBV positive patients**



# HDV worldwide epidemiology

Rizzetto M., 2015



# HDV in Europe

Rizzetto M., 2015

-  HDV endemic in the general population
-  HDV in drug addicts and immigrants

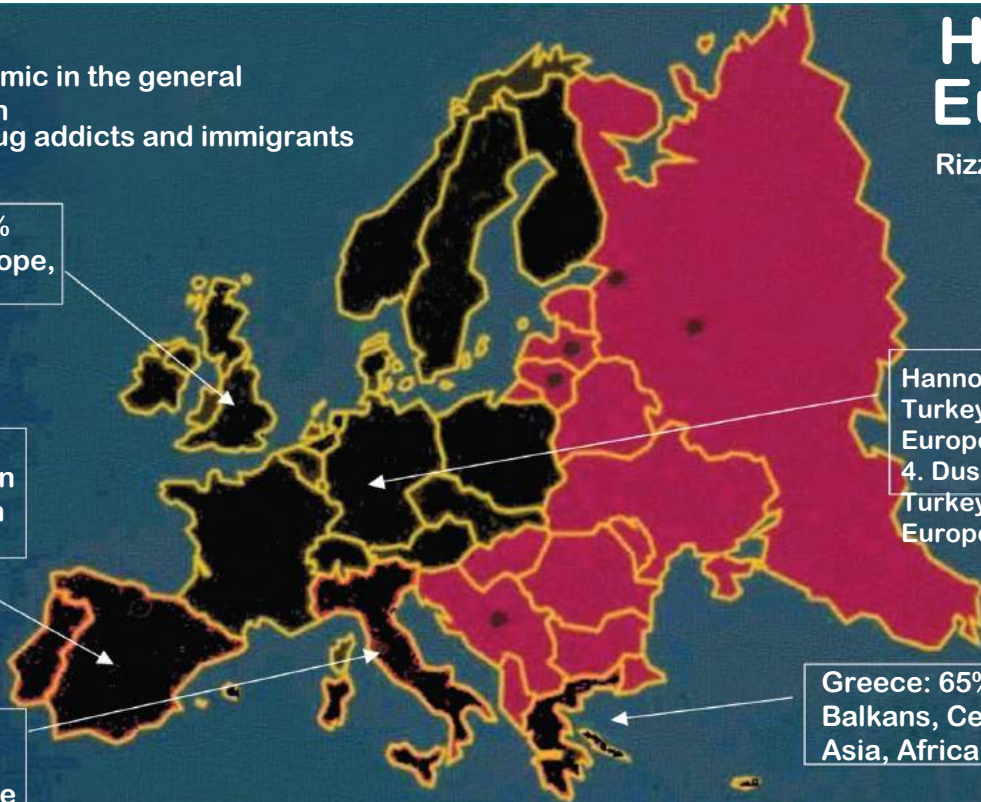
London: 85%  
Eastern Europe,  
Asia, Africa

Spain: 28%  
Africa, Eastern  
Europe, South  
America

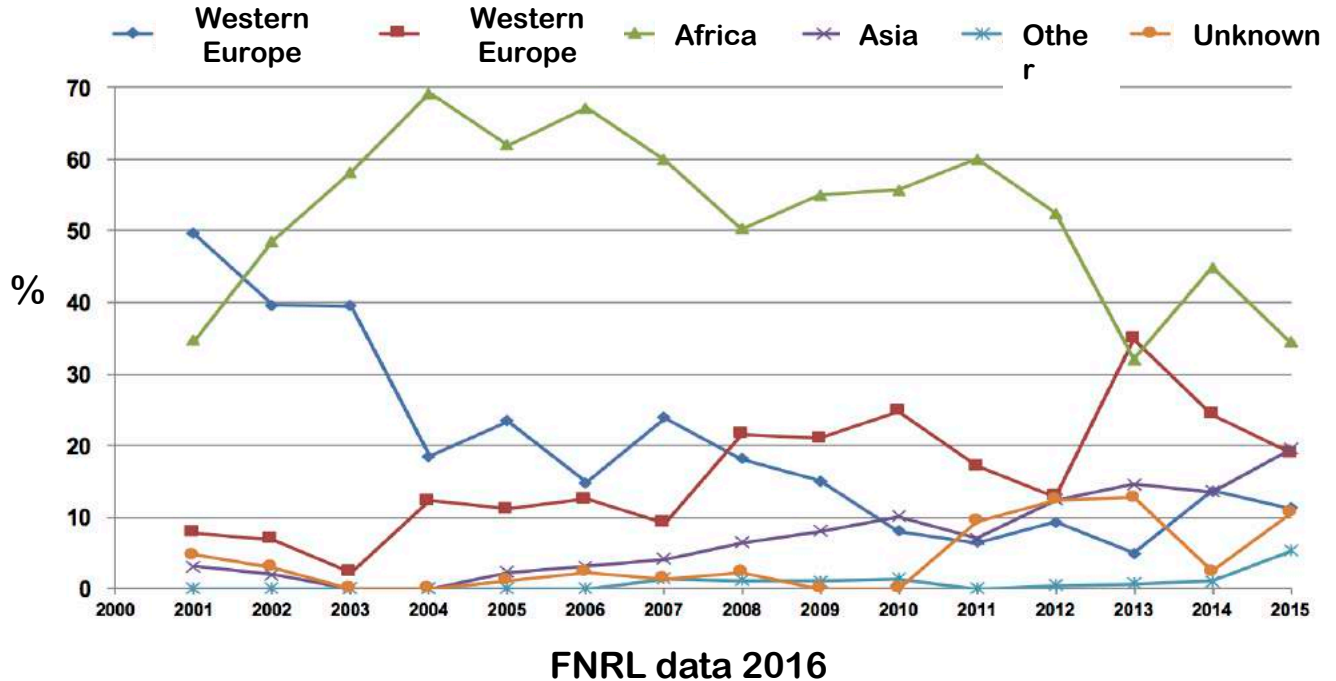
Italy: 40%  
Romania,  
Eastern Europe

Hannover: 80%  
Turkey, Eastern  
Europe  
4. Dusseldorf: 56%  
Turkey, Eastern  
Europe

Greece: 65%  
Balkans, Central  
Asia, Africa



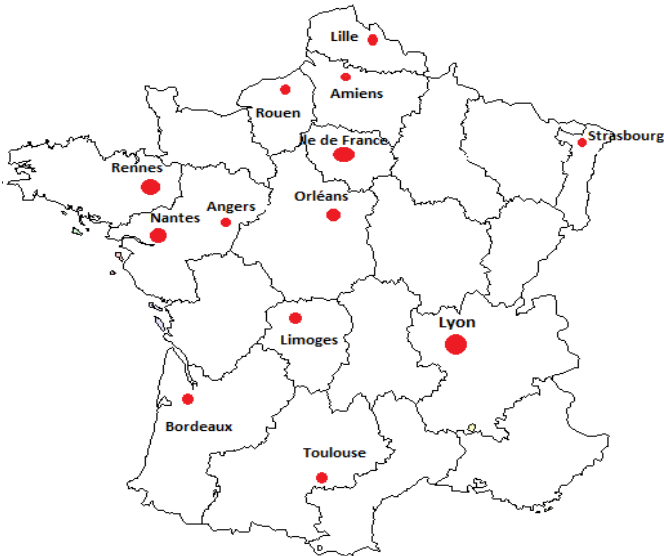
# HDV Epidemiology in France



**Clinical aspects**

# The Deltavir study

EASL 2015



**35 Centers**

**anRS** France  
REcherche  
Nord & sud  
Sida-hiv  
Hépatites  
Agence autonome de l'Inserm

**Hepatology Unit**

Dominique Roulot

**FNRL for HDV**

Emmanuel Gordien

Ségolène Brichler

Frédéric Le Gal

**Biostatistics**

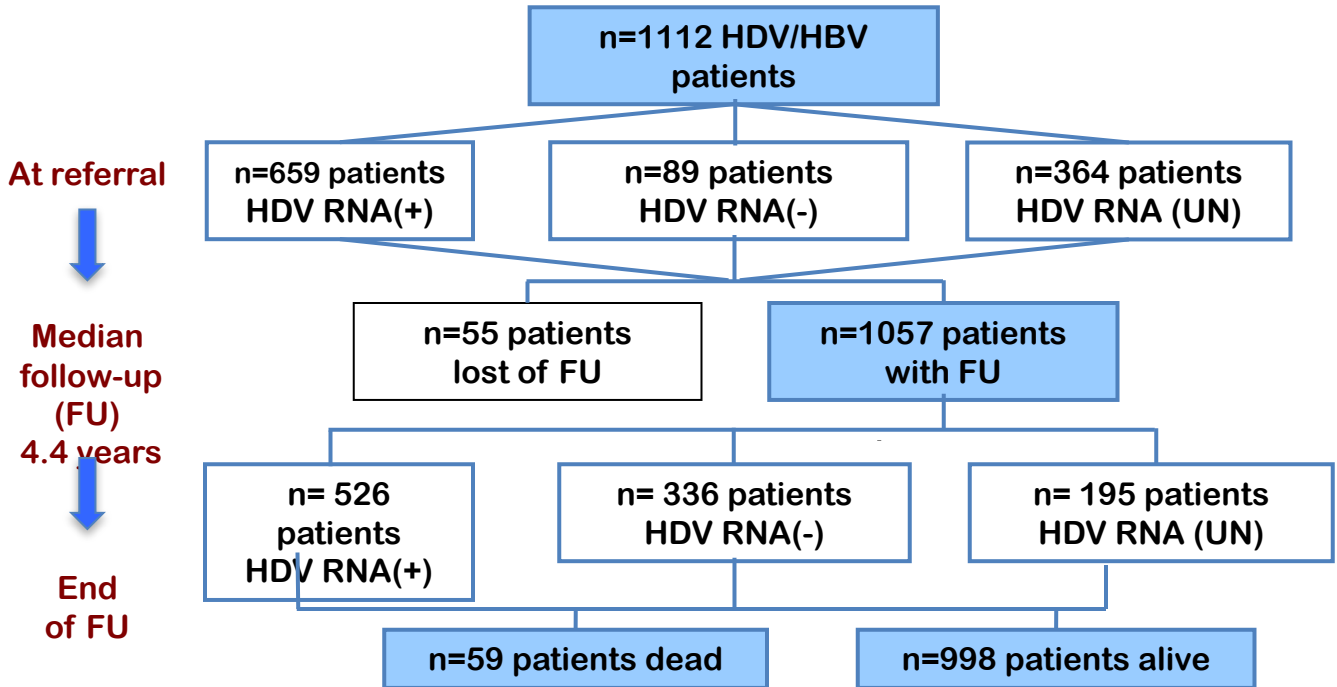
Françoise Roudot-Thoraval



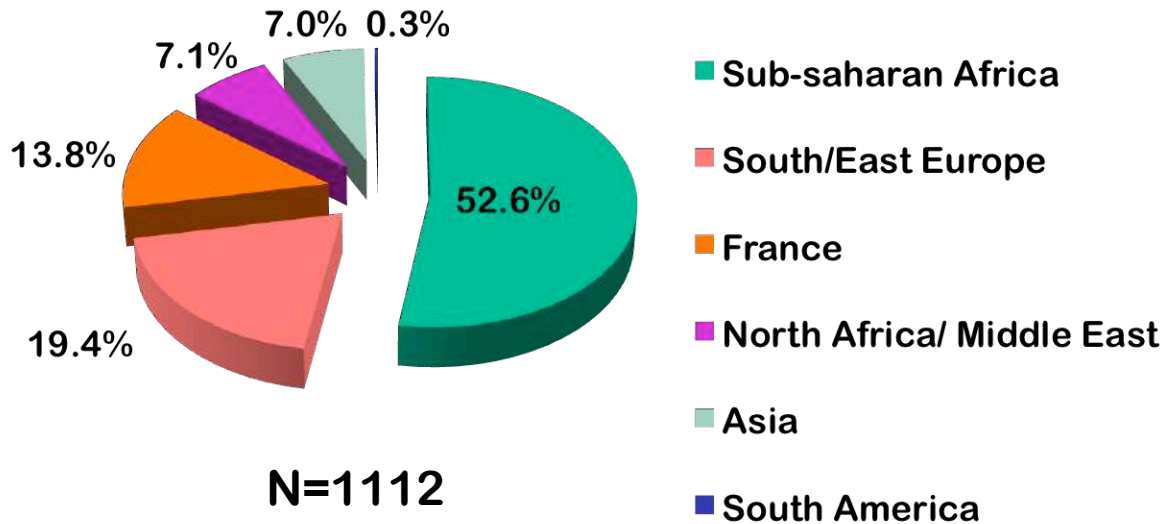
Unité de Virologie Avicenne  
*Virus de l'Hépatite Delta*  
Laboratoire associé au  
CNR des Hépatites B, C et Delta



# The Deltavir study



# Geographic origin of the patients



# Evolution and severity of the liver disease

Median of follow-up (FU): 4.4 years [0.8 - 8,9]

Clinical Status	At referral	At end of FU
Cirrhosis	28.3%	48.8%
Liver Decompensation	14.8%	24.2%
HCC	2.7%	9.2%
Death or Liver Transplantation	-	19.1%

At the end of follow-up:

- 584 were treated with IFN or  $\alpha$ PegIFN
- 33% of whom being HDV-RNA negative

# Liver events: incidence at 10 years

Event	Cirrhosis	Hepatic decompensation	HCC	Death or Liver Transplantation
Incidence at 10 yrs [95% IC]	57.3 % [53.2 - 61.4]	31.0 % [27.3 - 35.2]	15.3 % [12.1 - 19.3]	25.1 % [21.6 - 28.9]

# HDV infection

- HDV infection usually results in an inhibition of its helper HDV and by a much more severe liver disease
- ... and must be systematically screened in all HBV-infected patients

**Diagnosis**

# HDV infection diagnosis

- Total HDV Abs : key marker
- IgM HDV Abs
  - Persist in chronic infection +++
  - But can lack in African patients \*
- Delta Ag

2524 positive = 0.28% (FNRC)

→ Between 1996 et 2004 : 7 /

- Delta ARN +++
  - Qualitative RT-PCR ( $\approx$  60 IU/mL) \*\*
  - Quantitative real-time RT-PCR +++ (2 to 8 log IU/mL) \*\*\*

\* Lunel F, Mansour W et al., *J Infect.* 2013

\*\* Radjef N. et al., *J. Virol.* 2004

\*\* Legal F. et al., *J. Clin. Microbiol.* 2005

# HDV Diagnosis Algorithm (1)

1 Marker

**Total HDV Abs**

ELISA assays :

Diasorin<sup>\*</sup>; EIAGEN (Adaltis);  
Dia.Pro (Ingen, BioEvolution)



Neg



Neg

Plasma → False positivity +++



# HDV Diagnosis Algorithm (2)

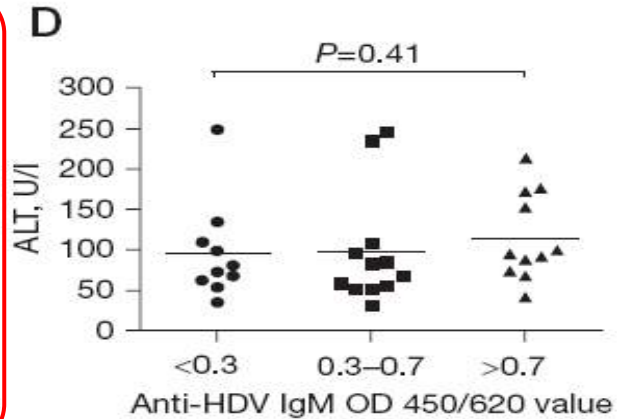
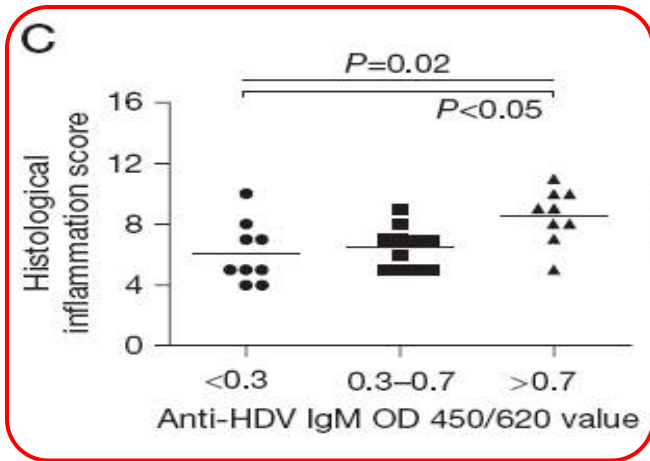
Total HDV Abs : Pos



IgM Abs (ELISA) ?

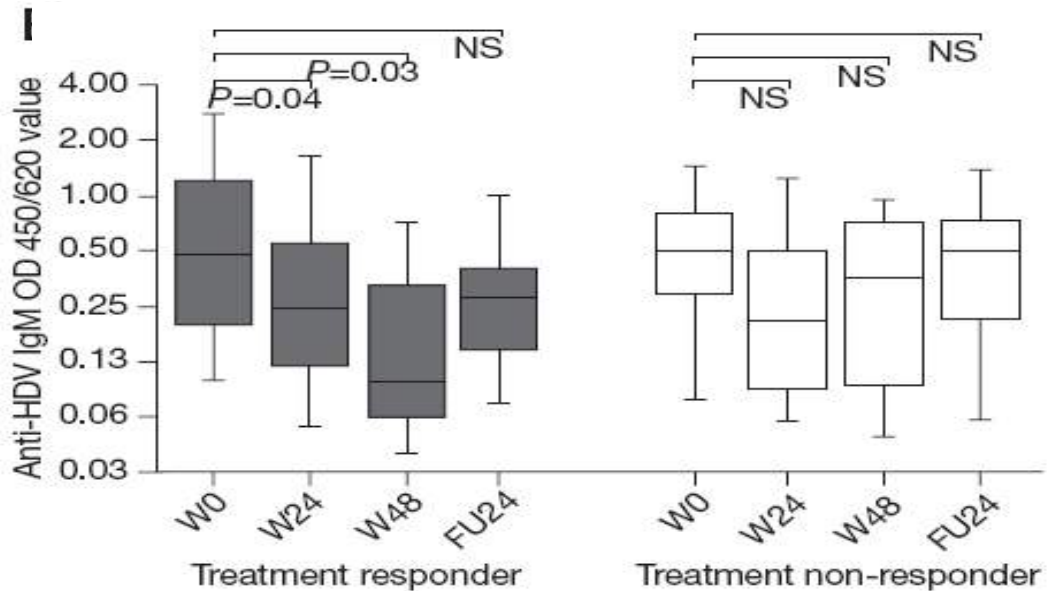
# Interest of HDV IgM Ab(1)

(Wedmeyer H., 2011; Mederacke I. 2012)



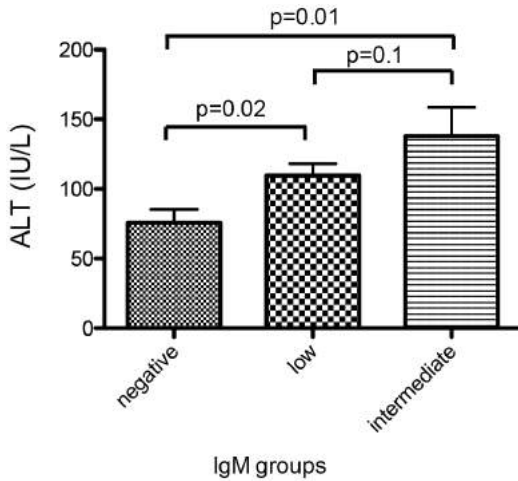
# Interest of HDV IgM Abs (2)

(Wedmeyer H., 2011; Mederacke I. 2012)

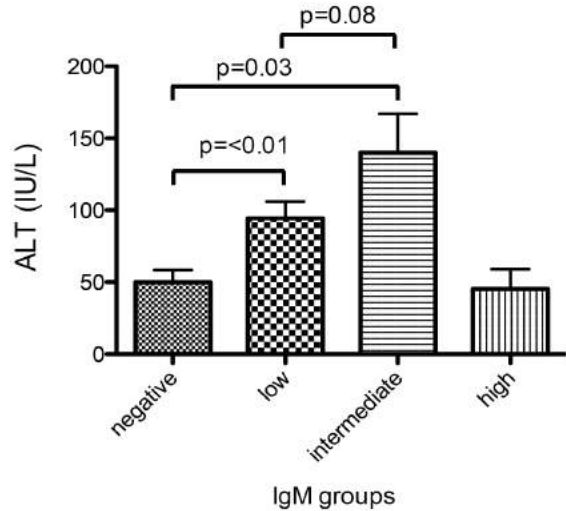


# Interest of HDV IgM Abs (3)

(Wranke A., 2014)



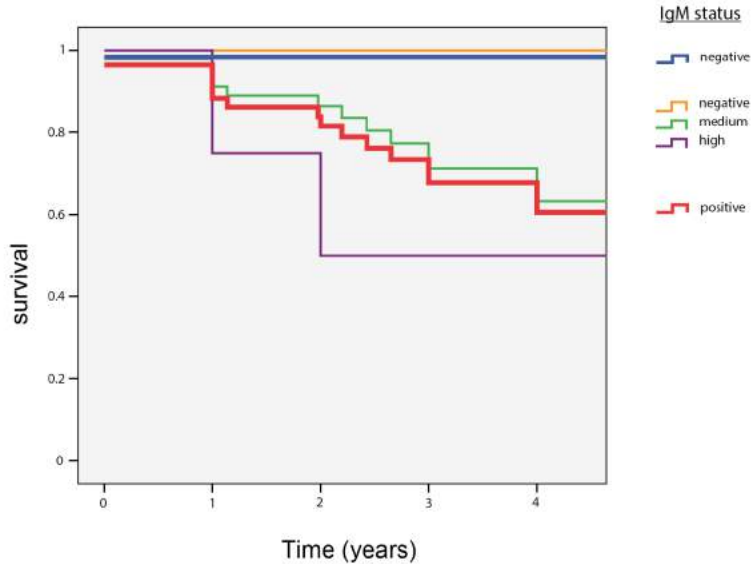
HIDIT-2 Cohort



MHH Cohort

# Interest of HDV IgM Abs (4)

Cumulative event free survival



Number at risk	0	1	2	3	4	5
IgM negative	11	8	6	5	3	2
IgM positive	67	48	37	27	19	13

(Wranke A., 2014)

# IgM Abs Assays

## French national quality control (2012)

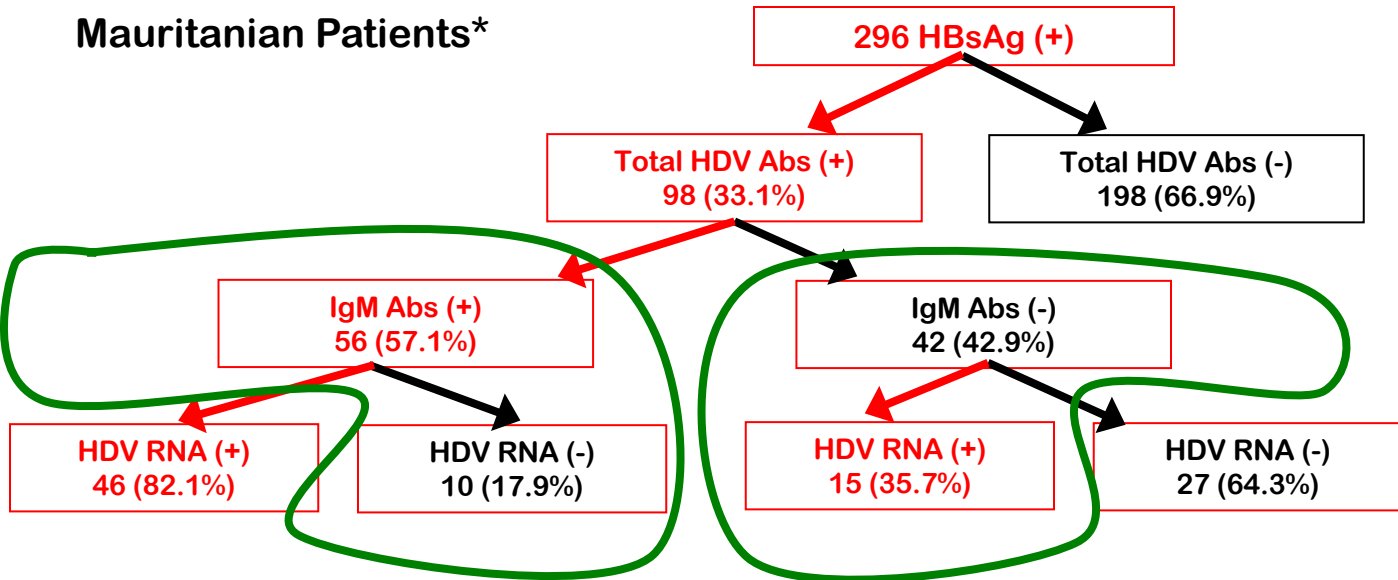
- IgM anti-HDV Abs

(14 Labs using Diasorin kit®)

Samples (n=4)	S3583	S3850	S4203	S2012
Expected Results	w POS	POS	w POS	NEG
Results				
Pos	5	14	8	
D	2		1	
Neg	7		5	14
Concordance	35.7%	100%	57.1%	100%

# HDV IgM Abs in African patients

Mauritanian Patients\*



\*Lunel F, Mansour W et al., *J Infect.* 2013 Jun

# HDV Diagnosis Algorithm (3)

Total HDV Abs (IgG) : Pos

HDV IgM Ab ?

HDV RNA +++

RT-PCR Quantitative+++ (Qualitative)

IgM (-) et ARN(-)

Efficient treatment  
Resolute Infection

IgM (-) et ARN(+)

Acute or Chronic  
replicative infection

IgM (+) et ARN(+)

Acute or Chronic  
replicative infection



# HDV Diagnosis Algorithm (4)

Total HDV Abs (IgG) : Pos

HDV IgM Ab ?

HDV RNA +++

RT-PCR Quantitative+++ (Qualitative)



IgM (-) et ARN(-)

Efficient treatment  
Resolute Infection

IgM (-/+ ) et ARN(+)

Acute or Chronic  
replicative infection

# Major clinical interests of HDV Viral load quantification

- Identification of patients with a replicative HDV infection : viral replication is associated with a poor outcome of the hepatic disease
- **Decision to treat**
- Evaluation of treatment efficiency and virological response under treatment
- Decision to stop the treatment
- Evaluation of new anti-HDV compounds

**HDV genetic variability**

**& D E T E C T I O N /**

**QUANTIFICATION of HDV**

**R N A V i r a l L o a d**

# HDV Genetic Diversity

Nadjia RADJEF : D (2001), (P. DÉNY et E. GORDIEN)

Mathieu TAMBY : M1 (2001) (E. GORDIEN)

Frédéric LE GAL : D (2007) (P. DÉNY)

**From 3 to ... 8 genotypes !**

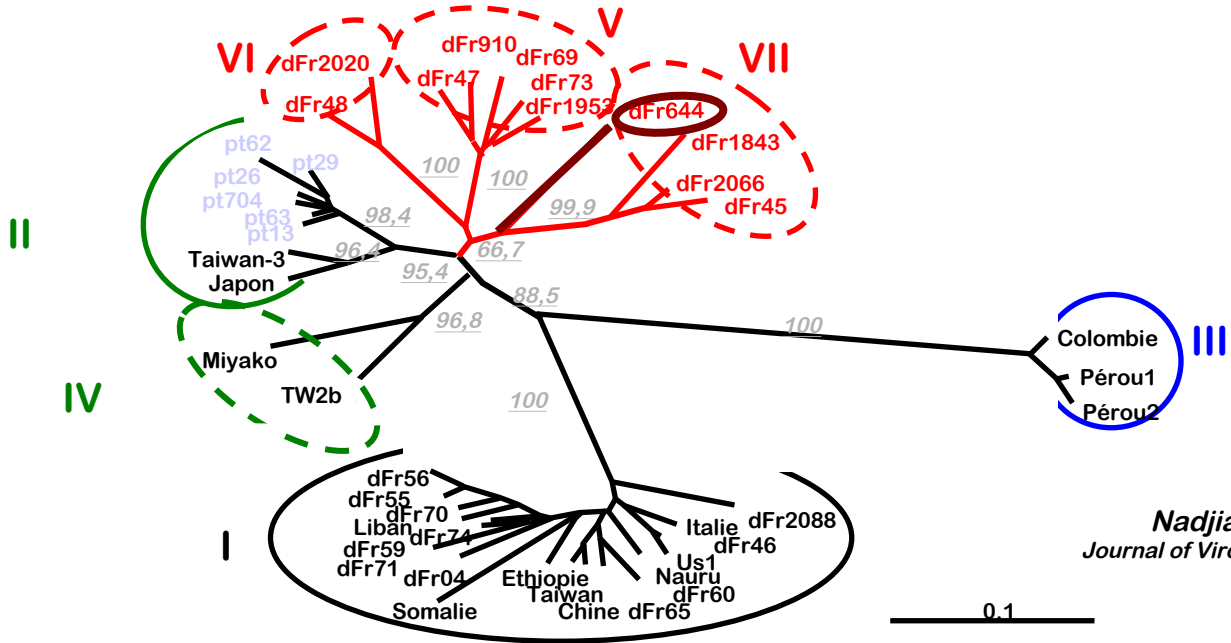
*Radjef N. et al, Journal of Virology 2004*

*Le Gal F. et al, Emerging Infectious Diseases 2006*

*Dény P., Curr Top Microbiol Immunol. 2006*

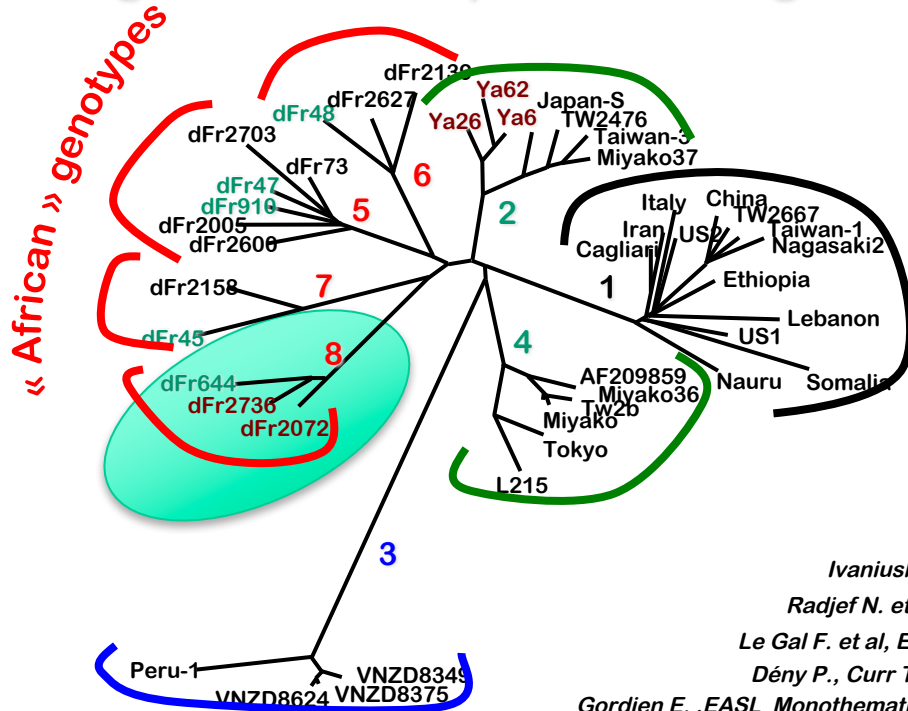
*Gordien E, EASL monothematic conference (2010) and manuscript submitted 2013*

# HDV Genotypes



Nadjia Radjef.  
Journal of Virology 2004

# HDV genus is composed of 8 genotypes



Ivaniushina et al., J Gen Virol, 2001

Radjef N. et al, Journal of Virology 2004

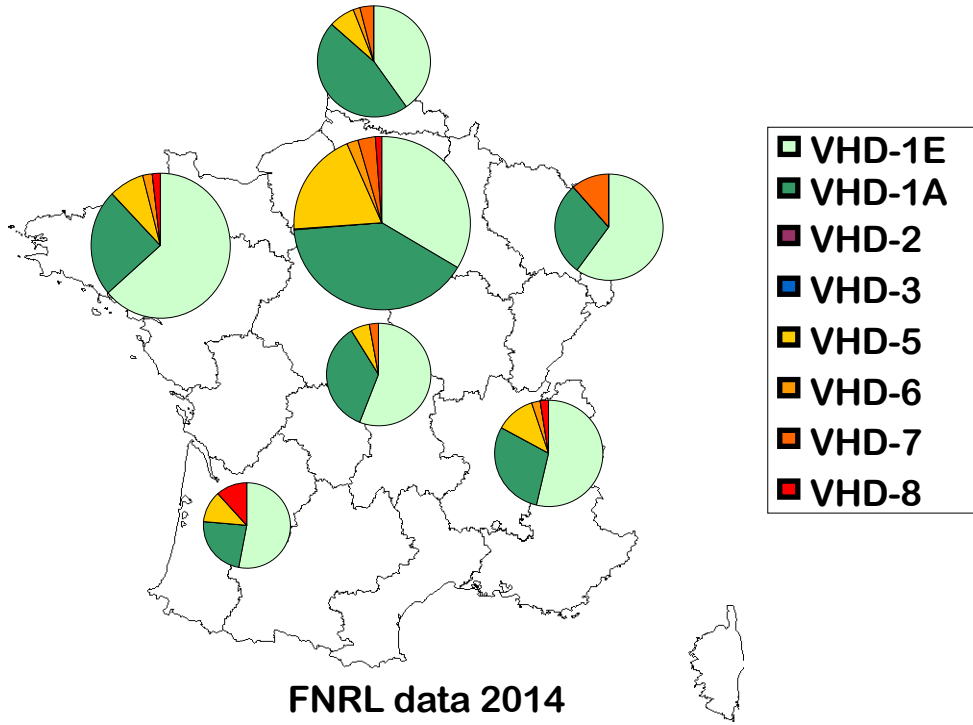
Le Gal F. et al, Emerg. Infect. Diseases 2006

Dény P., Curr Top Microbiol Immunol. 2006

Gordien E., EASL Monothematic conference, Istanbul 2010



# HDV genotypes in France





# Molecular tools for HDV ARN VL Quantification

# « In house » assays

- Yamashiro T, et al.; 2004. Quantitation of the level of hepatitis delta virus RNA in serum, by real-time polymerase chain reaction--and its possible correlation with the clinical stage of liver disease. *J Infect Dis.* Apr 1;189(7):1151-7.
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- Hofmann, J., K. et al., 2010. Quantitative detection and typing of hepatitis D virus in human serum by real time polymerase chain reaction and melting curve analysis. *Diagn Microbiol Infect Dis* 67:172-9
- Mederacke, I., et al.; 2010. Establishment of a novel quantitative hepatitis D virus (HDV) RNA assay using the Cobas TaqMan platform to study HDV RNA kinetics. *J Clin Microbiol* 48:2022-9.
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- Scholtes, C., et al., 2012. Standardized one-step real-time reverse transcription-PCR assay for universal detection and quantification of hepatitis delta virus from clinical samples in the presence of a heterologous internal-control RNA. *J Clin Microbiol* 50:2126-8.
- Shang, D., et al., 2012. Development and validation of an efficient in-house real-time reverse transcription polymerase chain reaction assay for the quantitative detection of serum hepatitis delta virus RNA in a diverse South London population. *J Virol Methods* 184:55-62.
- Kodani, M., A. et al., 2013. One-step real-time PCR assay for detection and quantitation of hepatitis D virus RNA. *J Virol Methods* 193:531-5.
- Katsoulidou, A., et al., 2013. Development and assessment of a novel real-time PCR assay for quantitation of hepatitis D virus RNA to study viral kinetics in chronic hepatitis D. *J Viral Hepat* 20:256-62.
- Botelho-Souza LF, et al., 2014. Development of a reverse transcription quantitative real-time PCR-based system for rapid detection and quantitation of hepatitis delta virus in the western Amazon region of Brazil. *J Virol Methods.* 2014 Mar;197:19-24.
- Karayatalyi E. et al., 2014. A one step real time PCR method for the quantification of hepatitis delta virus RNA using an external armored RNA standard and intrinsic internal control. *J. Clin. Virol.* 2014 May; 60 (1): 11-15.

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# Commercial assays

- Roche® Lightmix HDV kit (Germany)
- AJ-Roboscreen® (Germany)
- DiaPro® HV-RNA Quantification kit (Italy)
- Lipsgene □ HDV Kit (Germany)
- HDV Real-TM Quant Sacace® (Italy)
- Liferiver™ HDV-Real Time RT-PCR Kit (China)
- Amplisens® HDV-Monitor-FRT PCR Kit (Slovakia)
- Fast Track Diagnostics™ (Luxemburg)
- Primerdesign™ Ltd United Kingdom)
- Ecoli ® (Russia)
- Bosphore HDV Quantification-Detection Kit v1 (Turkey)

# Commercial assays

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**Performances  
of these assays**



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**Clinical Gastroenterology and Hepatology**  
[Volume 11, Issue 6](#), Pages 734-740, June 2013

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## Commercial Real-Time Reverse Transcriptase PCR Assays Can Underestimate or Fail to Quantify Hepatitis Delta Virus Viremia

[Ségolène Brichler](#), [Frédéric Le Gal](#), [Afifaa Butt](#), [Sylvie Chevret](#), [Emmanuel Gordien](#) 

published online 04 February 2013.

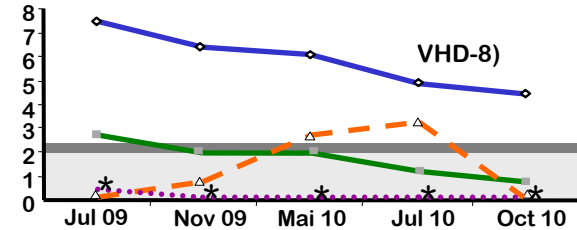
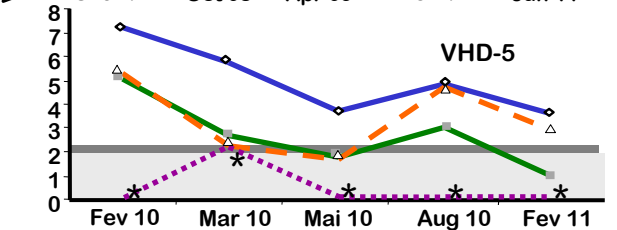
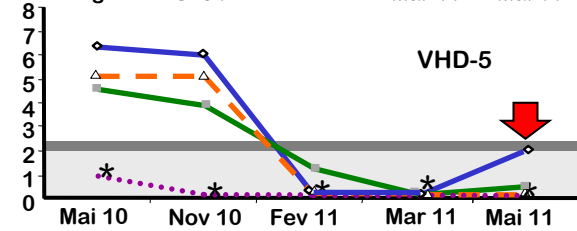
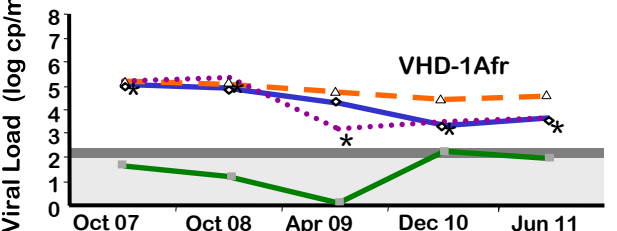
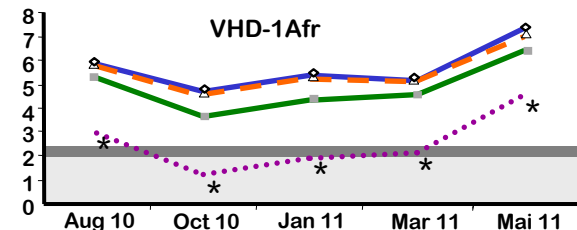
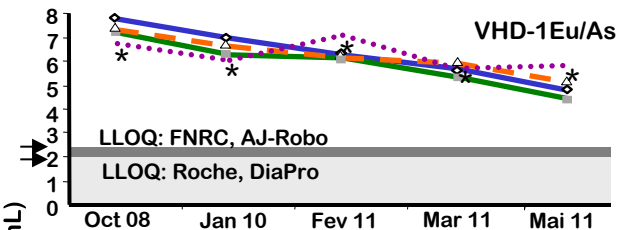
# Longitudinal Study of 6 Patients

FNRC-HDVQ

AJ-Roboscreen

DiaPro

Lightmix Roche







Avicenne  
Hospital,  
Bobigny France



**Virology Unit**

*French National Reference Laboratory  
For Hepatitis Delta virus*



# 1<sup>st</sup> International quality Control for HDV RNA Viral Load Quantification



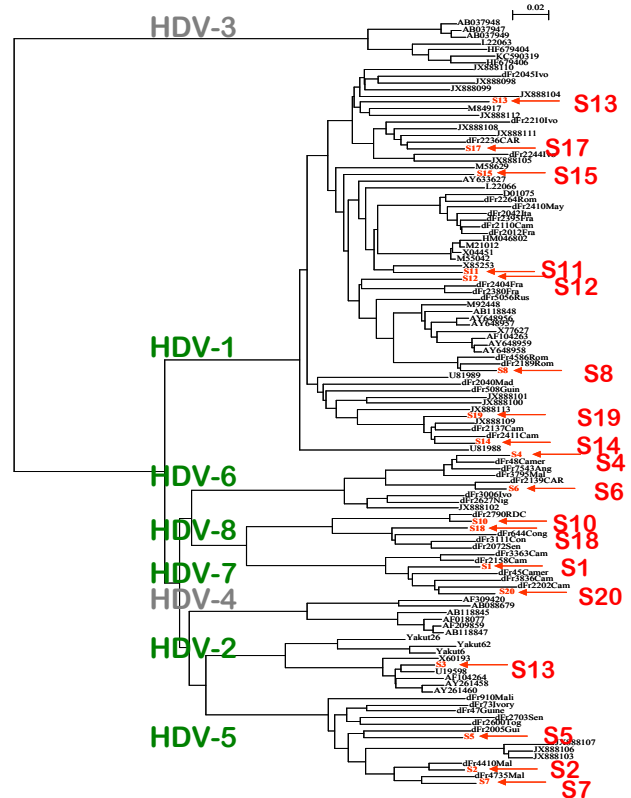
# 28

## Participant Laboratories

CONTACTS	INSTITUTION / ADDRESSES	PAYS
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Dr Henrik B. Krarup	Section of Molecular Diagnostics Department of Clinical Biochemistry Aalborg University Hospital	Denmark
Dr Maria Buti Ferret/ Dr M. Homs / F. Rodriguez-Frias	Hospital Universitario Valle Hberon Barcelona	España
Dr Vincent Thibaut	Laboratoire de virologie, hôpital La Pitié Salpêtrière, Paris	France
Pr. Sophie Alain	Service de bactériologie virologie hygiène, Limoges	France
Dr Emmanuel Gordien	CNR associé Delta	France
Pr Marianne Coste-Burel	Laboratoire de virologie CHU de Nantes	France
Pr Patrice Hervé / Dr Scholtès Caroline	Laboratoire de virologie Centre de biologie Nord, CHU Lyon Sud	France
Dr Jean Dominique Poveda	Laboratoire CERBA	France
Pr Wedemeyer / Dr Birgit Bremer	Department of Gastroenterology, Hepatology and Endocrinology Hannover Medical School;	Germany
Dr Bernhard Miller	MVZ Labor Prof. Seelig GbR Brauer	Germany
Dr Michael Chudy	Molekulare Virologie / Molecular Virology / Paul-Ehrlich-Institut	Germany
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Dr Ada Katsoulidou	Department of Hygiene and Epidemiology Athens University Medical School	Greece
Dr Antonella Olivero	Laboratorio di Fisiopatologia Epatica e Digestiva;	Italy
Dr Teresa Pollicino	Laboratorio di Biologia Molecolare	Italy
Dr Garbuglia Anna Rosa	Laboratory of Virology, INMI L Spallanzani	Italy
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Dr Rory N Gunson	West of Scotland Specialist Virology Centre	Scotland
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Dr Jeremy Garson/ Dr RB Ferns	Clinical Microbiology and Virology UCLH NHS Foundation Trust	United Kingdom
Dr Tonya Mixson-Hayden/ Dr M. Kodani	Associate Service Fellow Division of Viral Hepatitis Assay Development and Reference Laboratory	USA

# 1. HDV-IQC panel

- **20 Samples**  
→ including 2 negative controls
- **Viral loads:**  
→ 3.5 et 7.5 log (copies/ml)
- **Genotypes :**
  - HDV-1Afr (N=4)
  - HDV-1Eu/As (N=4)
  - HDV-2 (N=1)
  - HDV-5 (N=3)
  - HDV-6 (N=2)
  - HDV-7 (N=2)
  - HDV-8 (N=2)



# 2. HDV-WHO Standard

- **Dilutions: 1:10 et au 1:100 (× 3)**
- **+ 2 negative controls**

# « In house » assays

- Yamashiro T, et al.; **2004**. Quantitation of the level of hepatitis delta virus RNA in serum, by real-time polymerase chain reaction--and its possible correlation with the clinical stage of liver disease. *J Infect Dis.* Apr 1;189(7):1151-7.
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# Commercial assays

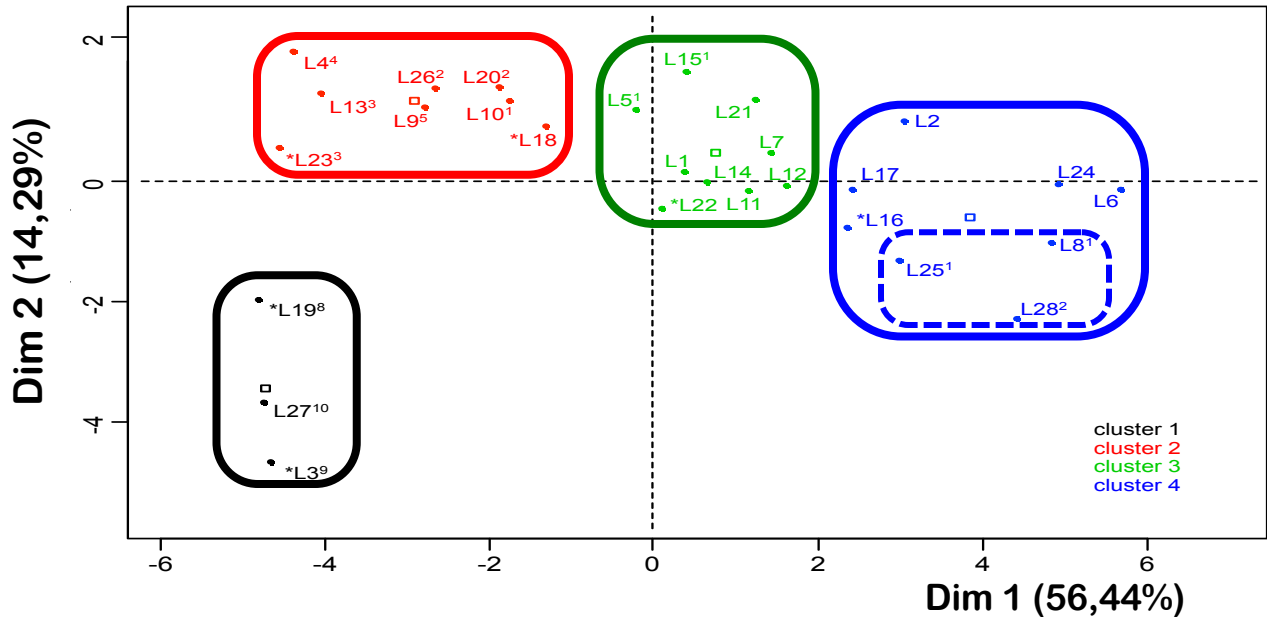
- Roche® Lightmix HDV kit (Germany)
- AJ-Roboscreen® (Germany)
- DiaPro® HV-RNA Quantification kit (Italy)
- Lipsgene □ HDV Kit (Germany)
- HDV Re~~X~~-TM Quant Sacace® (Italy)
- Liferiver™ HDV-Real Time RT-PCR Kit (China)
- Amplisens® HDV-Monitor-FRT PCR Kit (Slovakia)
- Fast Track Diagnostics™ (Luxemburg)
- Primerdesign™ Ltd United Kingdom)
- Ecoli® (Russia)
- Bospho~~X~~re HDV Quantification-Detection Kit v1 (Turkey)

**Results (IU/mL)**



# Labs can be classified into 4 « clusters »

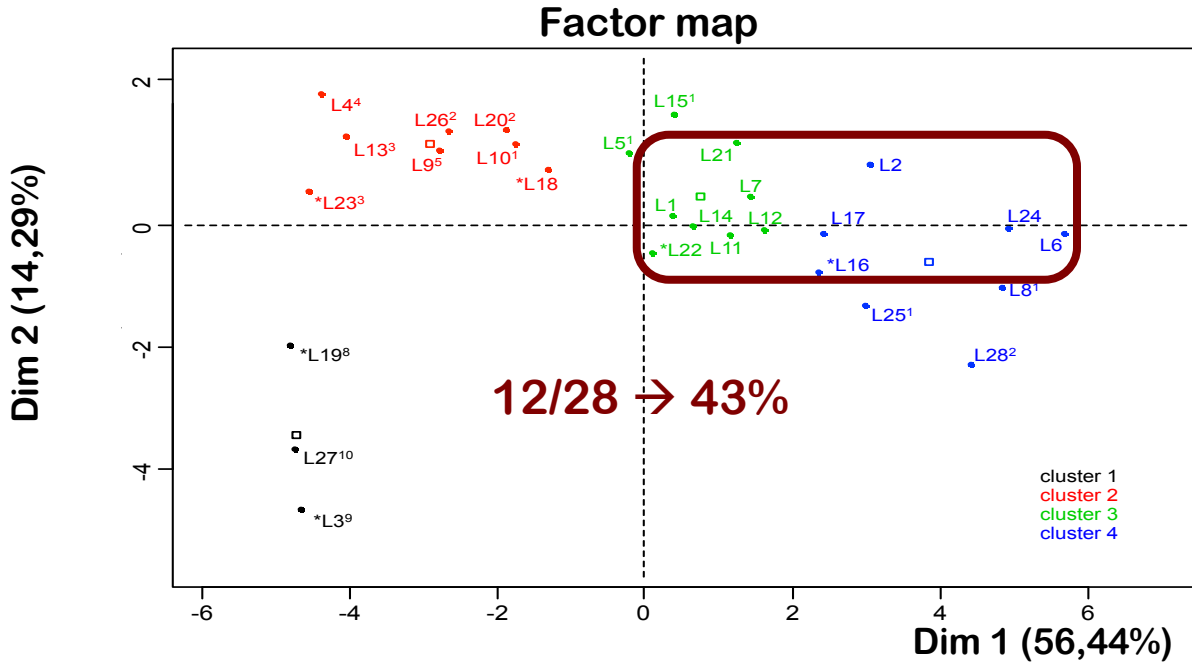
Factor map



*F. Le GAL, S. Brichler, R Sahli, S. Chevret and E. Gordien: Hepatology 2016*



# Labs can be classified into 4 « clusters »



The first Results of the  
1<sup>st</sup> International Quality Control:

**Most available assays  
underestimate or Fail to  
quantify HDV RNA VL**

**HDV Variability  
seems to be of  
major  
concern**



# A new kit: the *Eurobioplex* HDV Kit®

*(Le Gal F. et al., J. Clin. Microbiol., 2017)*

# A new kit: the *Eurobioplex* HDV Kit ®

(Le Gal F. et al., *J. Clin. Microbiol.*, 2017)

Performance comparisons with the FNRL assay results (N = 611)

HDV FNRL assay result	Eurobioplex HDV kit result	
	Positive	Negative
Positive	389	9 <sup>a</sup>
Negative	14 <sup>a</sup>	198

<sup>a</sup>Sample with a very low HDV viral load (<3 log IU/ml).

**Sensitivity: 98.8%**

**Specificity: 100%**

# A new kit: the *Eurobioplex* HDV Kit ®

(Le Gal F. et al., *J. Clin. Microbiol.*, 2017)

## Performance Comparisons with the FNRL assay results (N = 151)

- 33 HDV-1Afr ; 61 HDV-1Eur/As
- 1 HDV-2, -3, -4\*
- 22 HDV-5 ; 7 HDV-6 ; 10 HDV-7 ; 3 HDV-8
- 12 negative controls

Test type	Median viral load by genotype(s) (log IU/ml)			HDV-5 to HDV-8
	All	Europe/Asia	Africa	
Eurobioplex kit	5.05	5.87	4.36	4.74
HDV FNRL	5.16	5.61	4.11	5.38
Difference between results	-0.11	+0.26	+0.25	-0.64

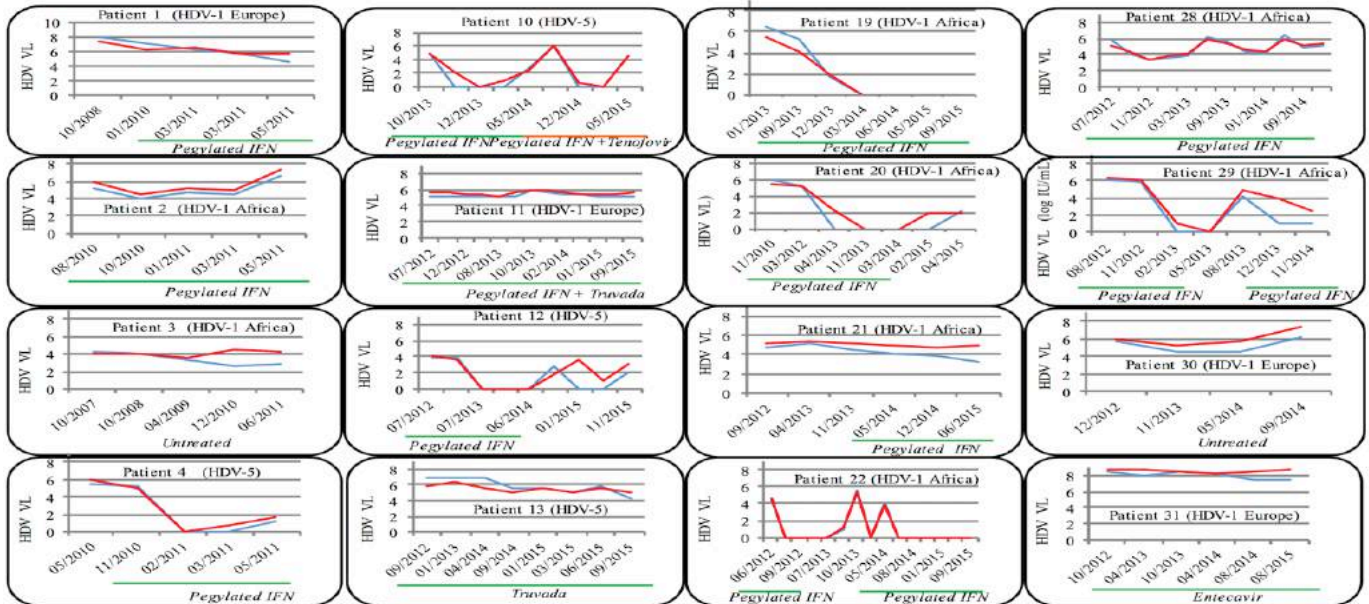
# A new kit : the *Eurobioplex* HDV Kit ®

(Le Gal F. et al., *J. Clin. Microbiol.*, 2017)

FNRC —————

————— Eurobioplex ®

Performance Comparisons with the FNRL assay results (N=36)



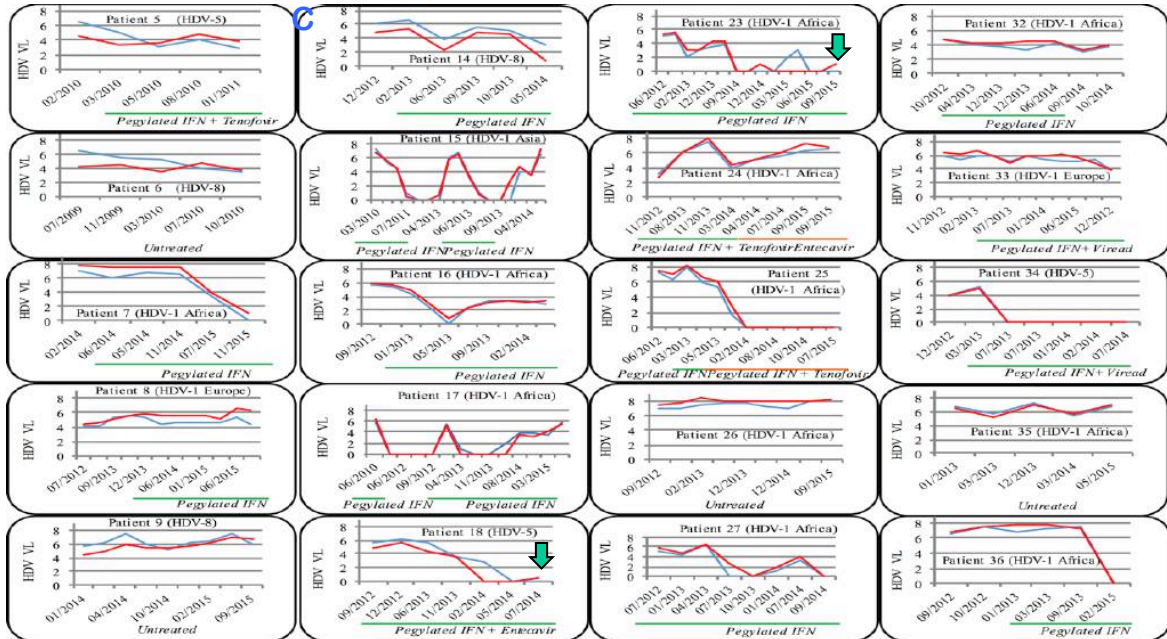
# A new kit : the *Eurobioplex* HDV Kit <sup>®</sup>

(Le Gal F. et al., J. Clin. Microbiol., 2017)

FNR



*Eurobioplex* <sup>®</sup>





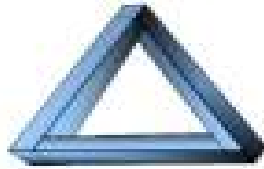
# Summary

- Eurobioplex HDV® kit was very satisfactory on this large panel of samples with good repeatability, specificity and sensitivity, both in serum and plasma samples.
- All samples of all genotypes were well detected and quantified in comparison to the FNRC assay.
- The kit is easy to use and is a suitable tool for monitoring HDV-infected patients.

# Conclusions

- HDV is an unique and amazing virus still understudied
- Is responsible for a much more serious liver disease
- **Its diagnosis must be systematic in all HBV positive, and patients and relies mainly upon:**
  - **HDV total Abs**
  - **Quantitative HDV RNA (Qualitative)**
- HDVL quantification assays need further development
- **Diagnostic algorithms and guidelines for management of patients remain to be better defined**
- **Active basic and clinical research is absolutely needed to better understand the fundamental biology of HDV and to provide molecular diagnostic tools and specific treatments**

# Thank you for your attention !



**Avicenne Virology Unit**  
*French National Reference Laboratory  
For Hepatitis Delta virus*  
*Associated to the National Reference Centre  
for Hepatitis B, C and Delta*

Berkeley

 School of  
Public Health



**FORUM**  
for Collaborative  
**RESEARCH**

A large, light grey circular graphic in the background, containing a white geometric pattern of overlapping squares and lines, similar to the Forum logo icon. A small orange square is positioned within the pattern.

# Discussion

[www.forumresearch.org](http://www.forumresearch.org)