

Origin of Hepatitis Delta Virus (HDV)

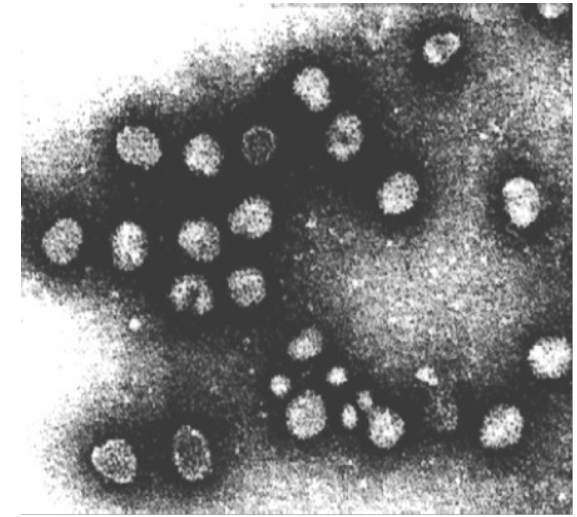
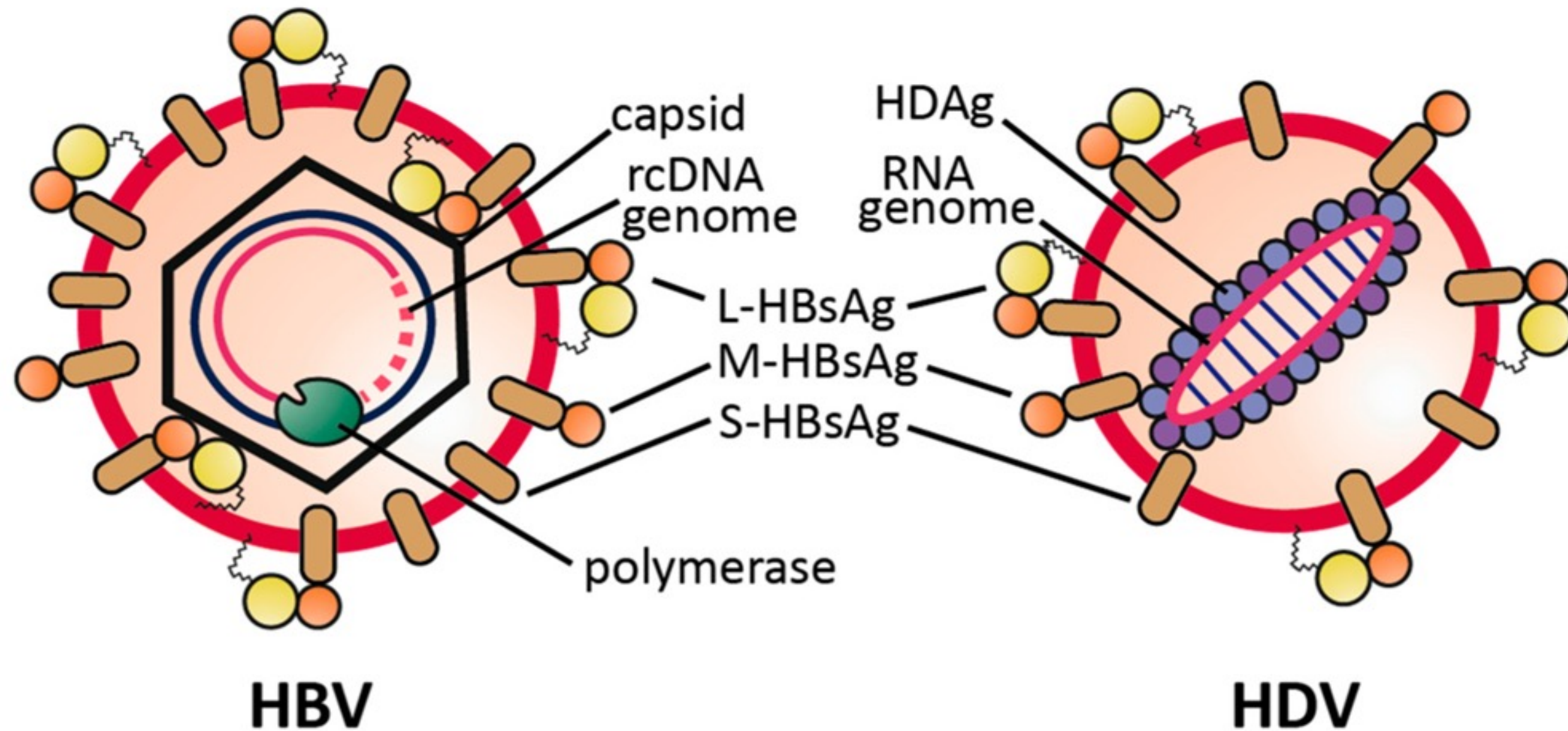
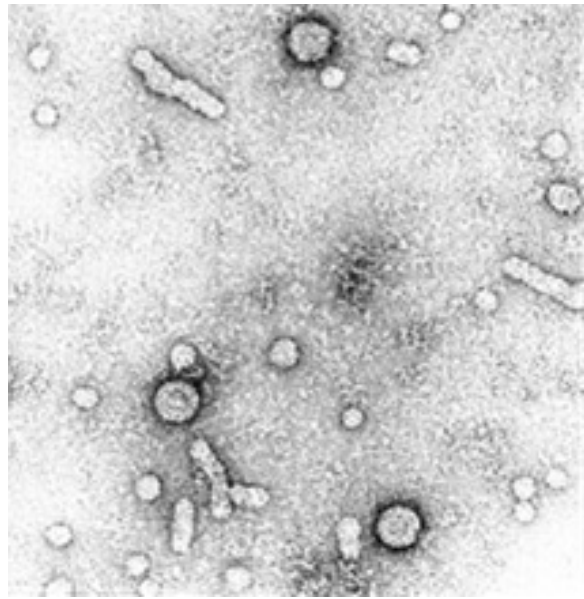
Centre National de Référence Hépatite Delta - Hôpital Avicenne
& INSERM U955, équipe n°18, Université Paris Est, Créteil

Disclosures : None

Endorsed by



Hepatitis Delta Virus (HDV)



- **Viroid of the Kolmioviridae family**
- **First detected in Italy in 1977**
- **Requires Hepatitis B Virus (HBV) for its replication**

Epidemiology of HDV

- **Affects nearly 5% to 10% of people with chronic HBV infection globally**
- **Decreasing incidence since the global HBV vaccination programme (1980's)**
- **Heterogeneous prevalence and unknown in some geographical zones**

Hepatology

ORIGINAL ARTICLE

Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis

Hai-Yan Chen,¹ Dan-Ting Shen,¹ Dong-Ze Ji,² Pei-Chun Han,¹ Wei-Ming Zhang,² Jian-Feng Ma,¹ Wen-Sen Chen,³ Hemant Goyal,⁴ Shiyang Pan,¹ Hua-Guo Xu¹

Research Article
Viral Hepatitis

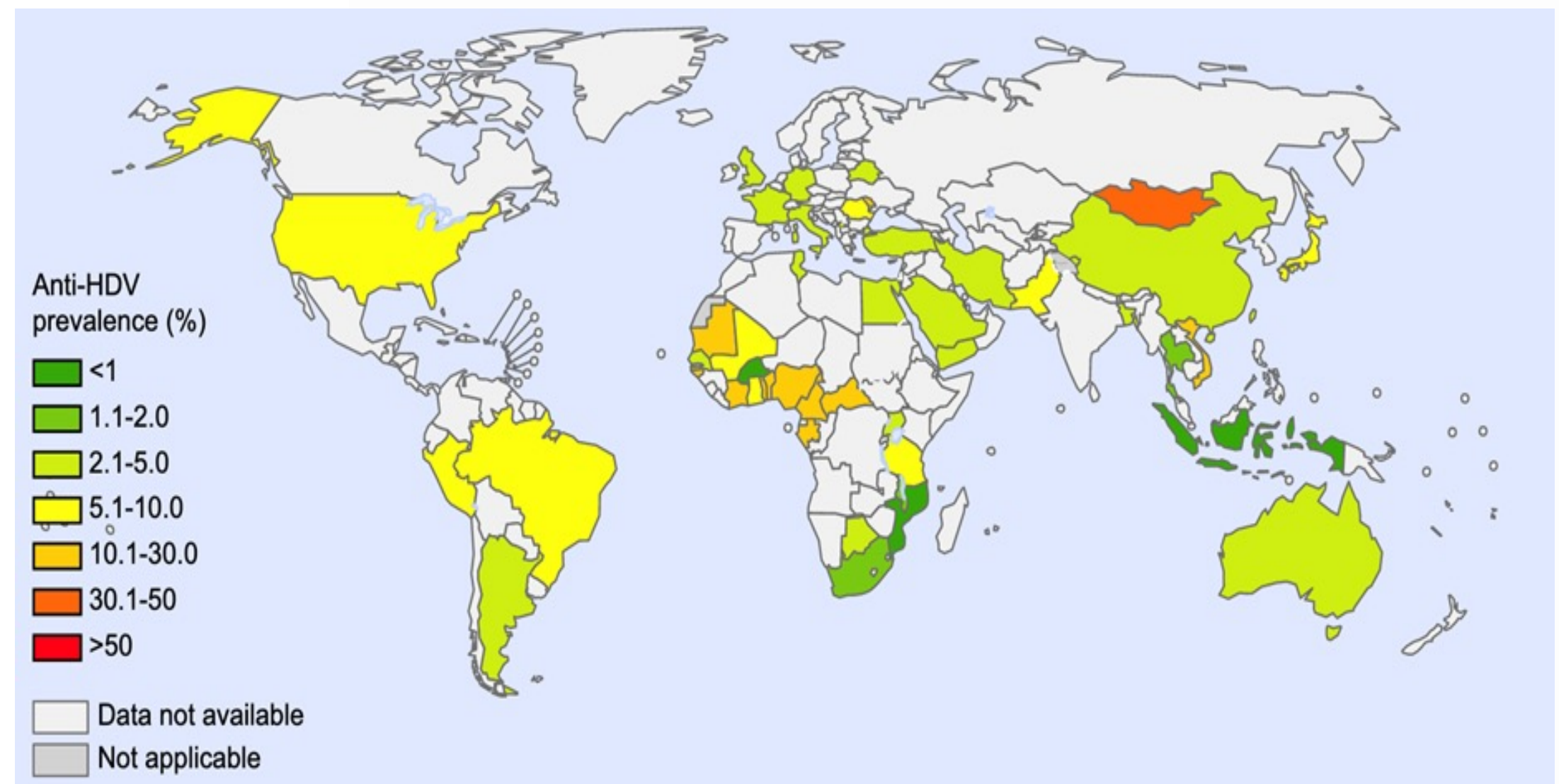


JOURNAL
OF HEPATOLOGY

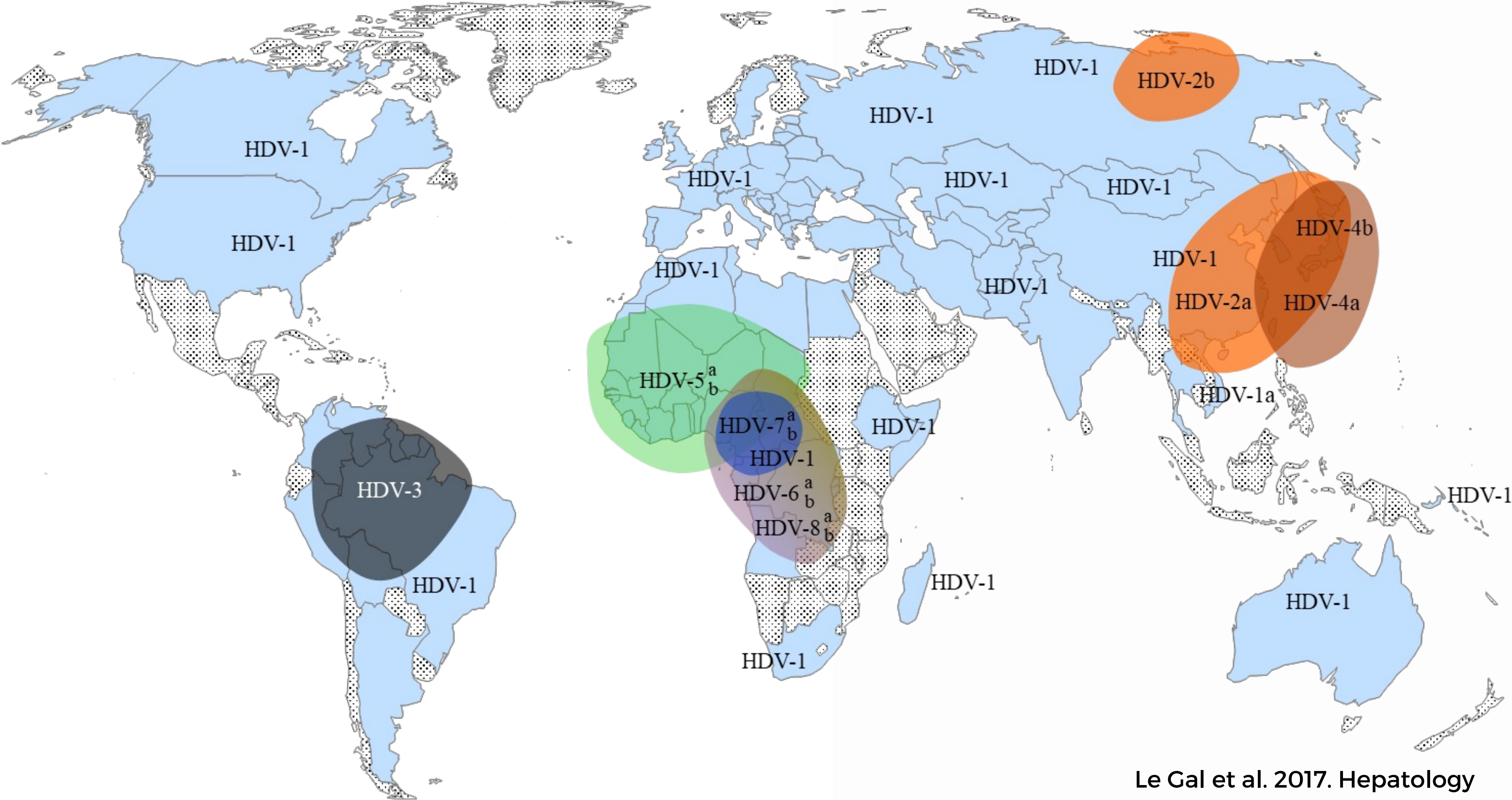
The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis

Alexander J. Stockdale^{1,2}, Benno Kreuels^{3,4}, Marc Y.R. Henrion^{2,5}, Emanuele Giorgi⁶, Irene Kyomuhangi⁶, Catherine de Martel⁷, Yvan Hutin⁸, Anna Maria Geretti^{1,*}

¹Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom; ²Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi; ³College of Medicine, Blantyre, Malawi; ⁴University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; ⁵Liverpool School of Tropical Medicine, Liverpool, United Kingdom; ⁶Centre for Health Informatics, Computing, and Statistics, University of Lancaster, Lancaster, United Kingdom; ⁷International Agency for Research on Cancer, Lyon, France; ⁸World Health Organization, Geneva, Switzerland



Geographical distribution of the 8 HDV species



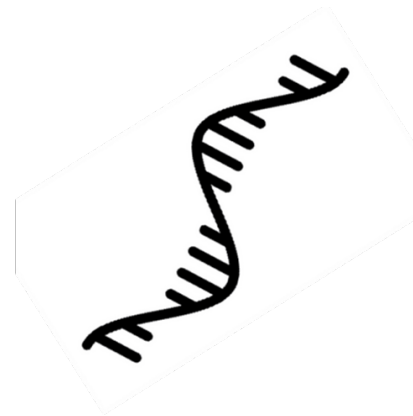
Le Gal et al. 2017. Hepatology

HDV origins ?

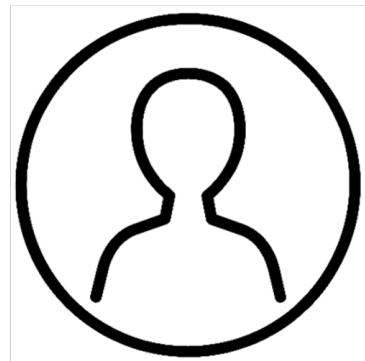
Who ?



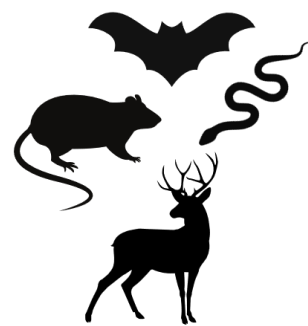
Evolution from **plant** viroids or retroviroids



Evolution from a host **mRNA** precursor with ribozyme activity

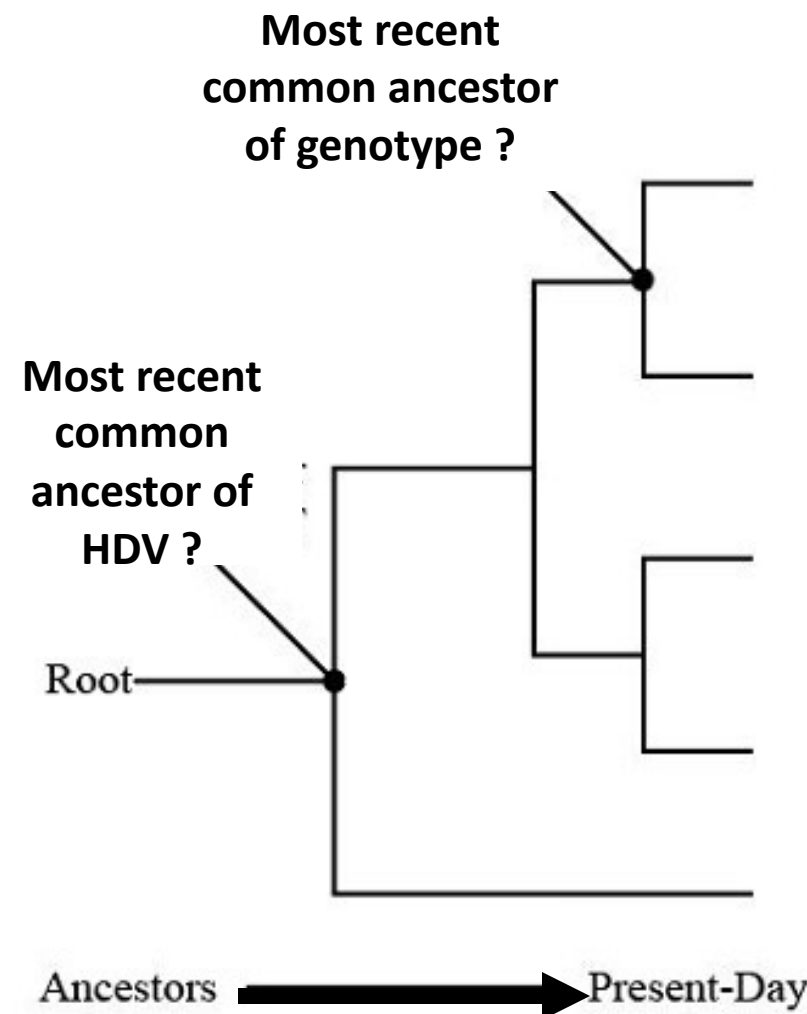


Combination of viroid and **human gene** (DIPA)



HDV-like genomes found in vertebrates and invertebrates

When ?



Where ?



Objective: To date and determine the origin of HDV and the timing of divergence events within HDV

Project ANRS ECTZC133140

EPHYD

EVOLUTIONARY HISTORY, **PHY**LOGEOGRAPHY and PHYLODYNAMIC, **D**ELTAVIRUS

- Collaboration

Hôpital Avicenne AP-HP (France)



London School of Hygiene & Tropical Medicine (UK)



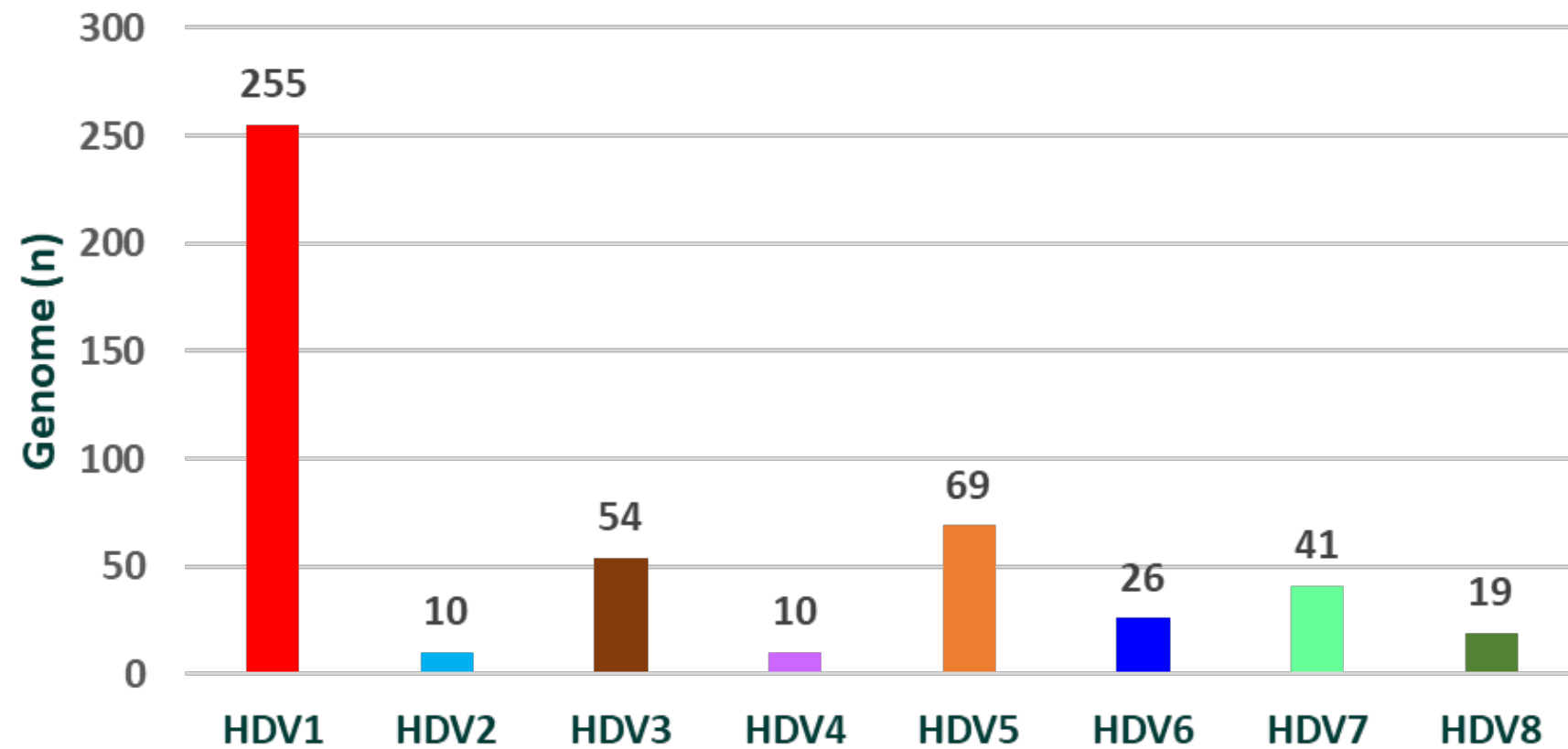
Hôpital H. Mondor AP-HP (France)



- Duration : 2 years (01-2022 to 12-2023)

A Genomic approach

Genotypes distribution

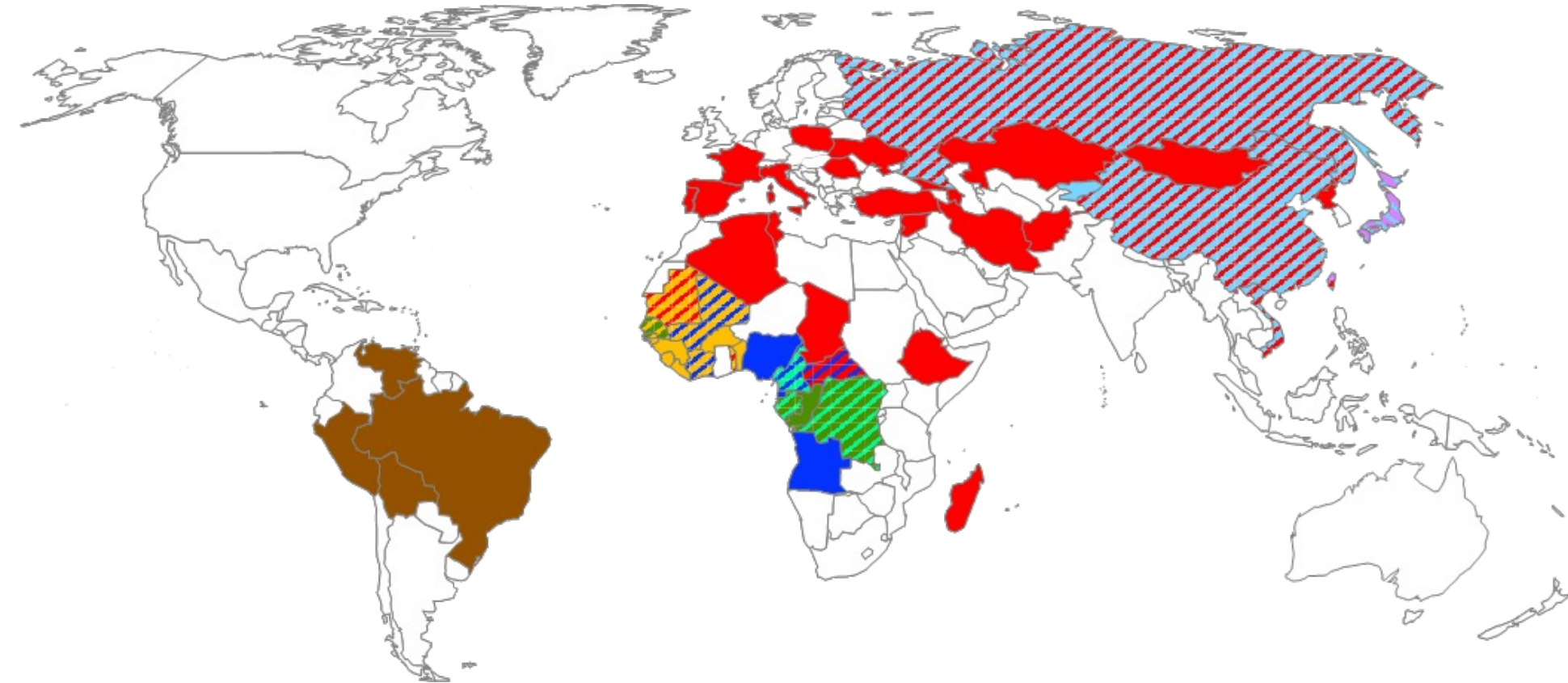


482 complete genomic sequences

HDV

(Sampling date: 1976-2021)

Geographical distribution of HDV



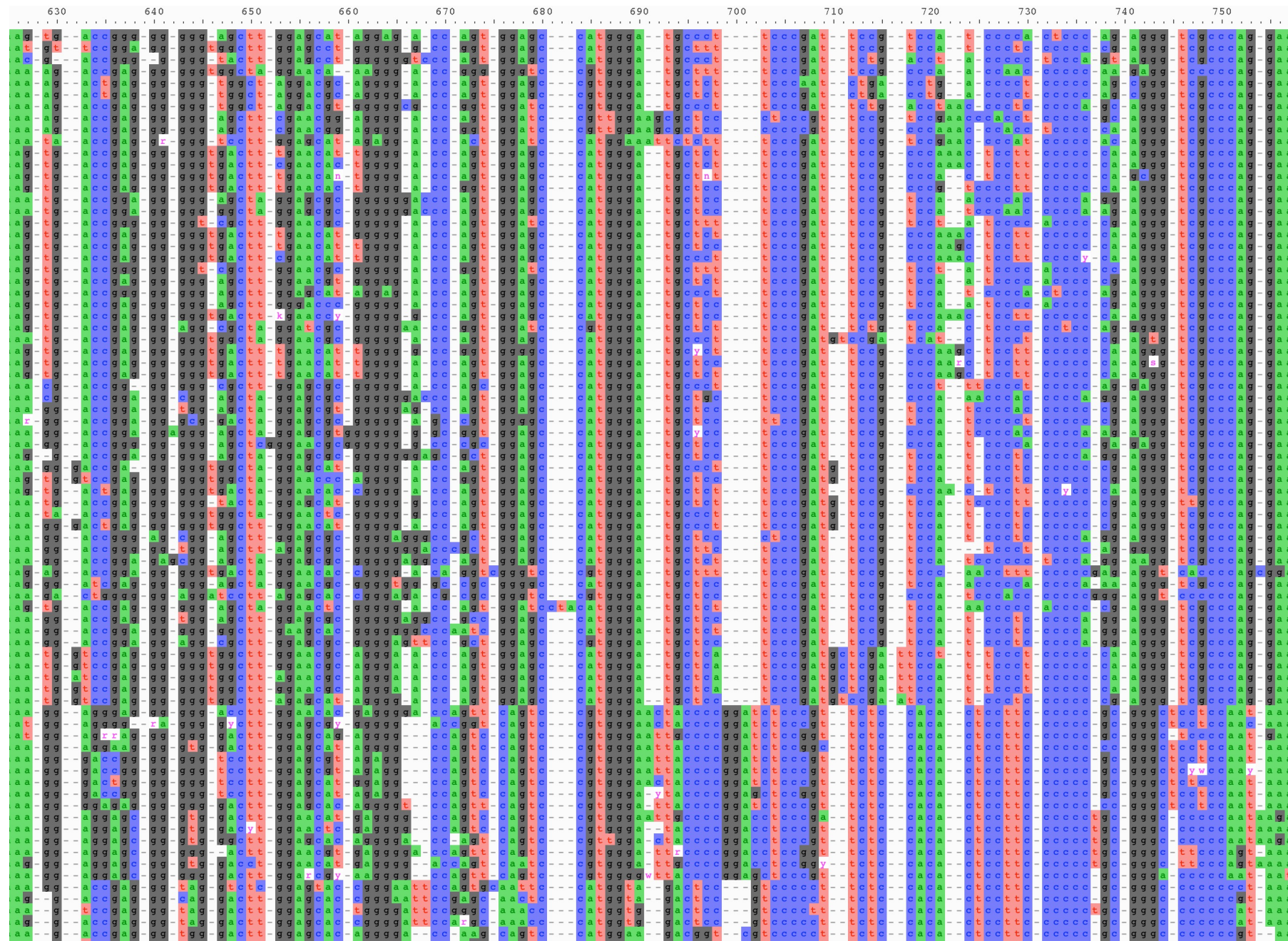
Sampling locations : 15 geographical zones
(United Nations geoscheme)

**HDV Sequences from French Delta
National Reference Center (FDNRC):**

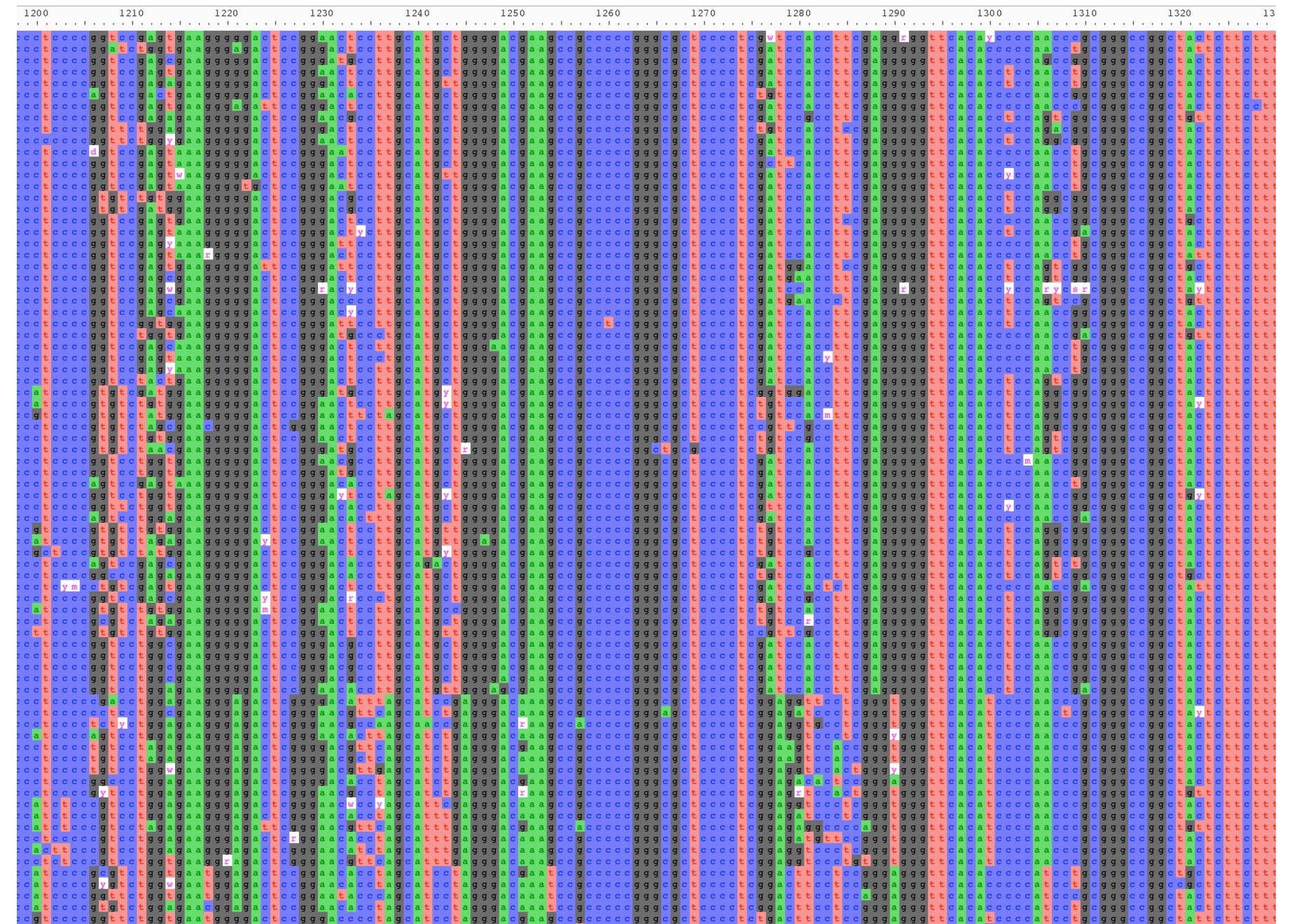
233/482 Newly HDV genomes sequences

HDV molecular clock analysis

Full length genomes vs LHD gene



Hyper variable regions (prone to estimation biases)



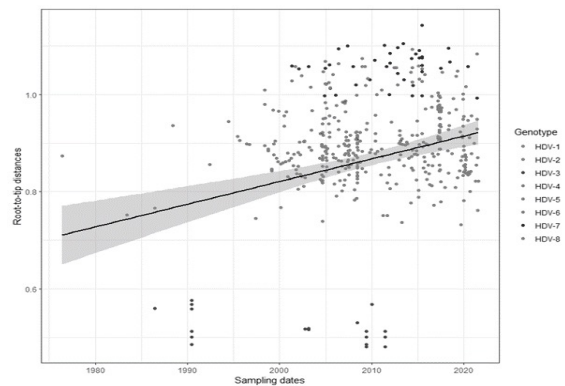
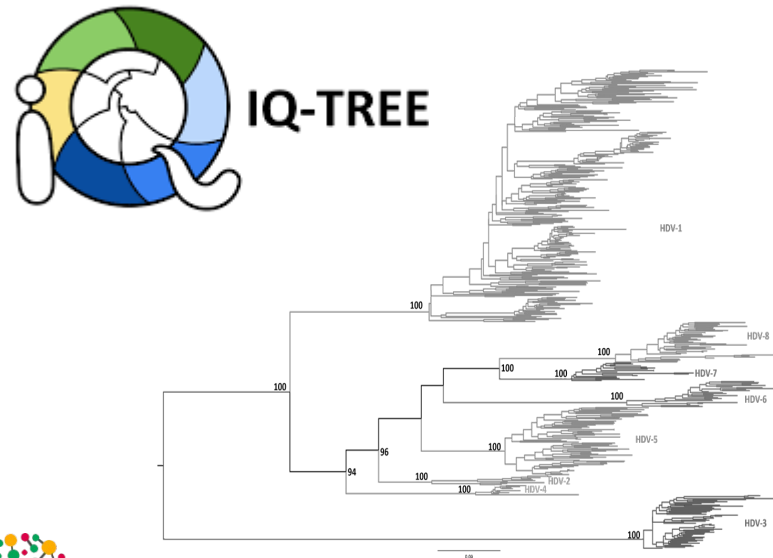
Conserved regions of the LHD gene (reliable but representative)

Methodology

Dataset L-HDAg (n=482)

Phylogenetic analysis

Maximum likelihood (ML)



Evolutionary analyses

Coefficient of linear regression :
 $R^2 = 0,0625$

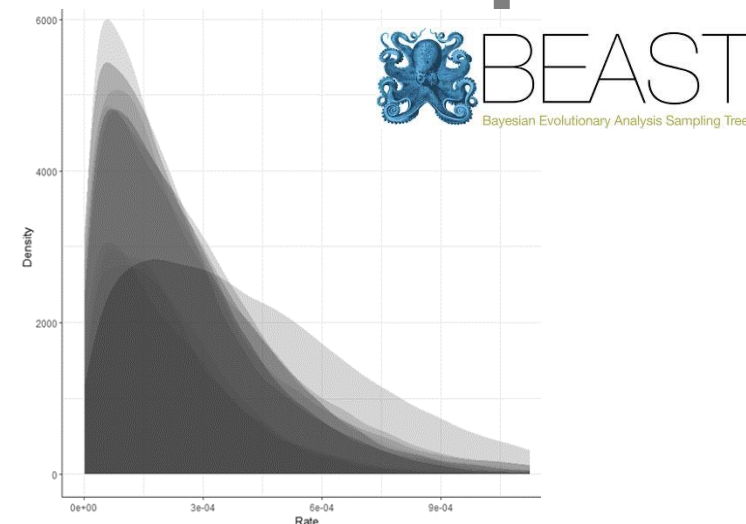
No genetic recombination

Bayesian estimates of evolutionary rate :

(Dataset n=90)x3

(Dataset n=120)x3

(Dataset n=160)x4



Molecular clock dating

Phylogeographic reconstruction



✓ Substitution model :

GTR+Γ+I

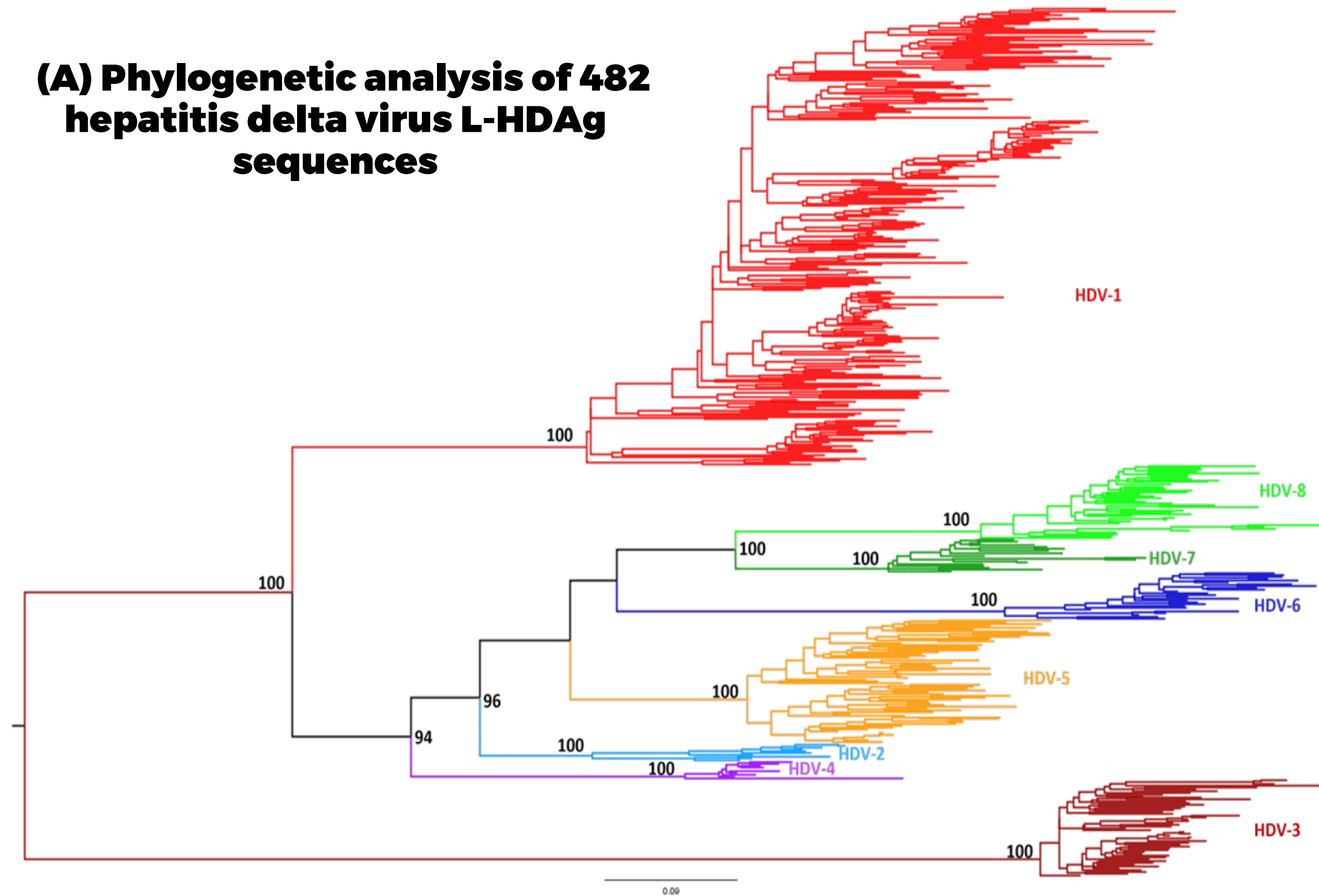
✓ Molecular clock :

Uncorrelated relaxed clock

✓ Distribution model :

Uniform

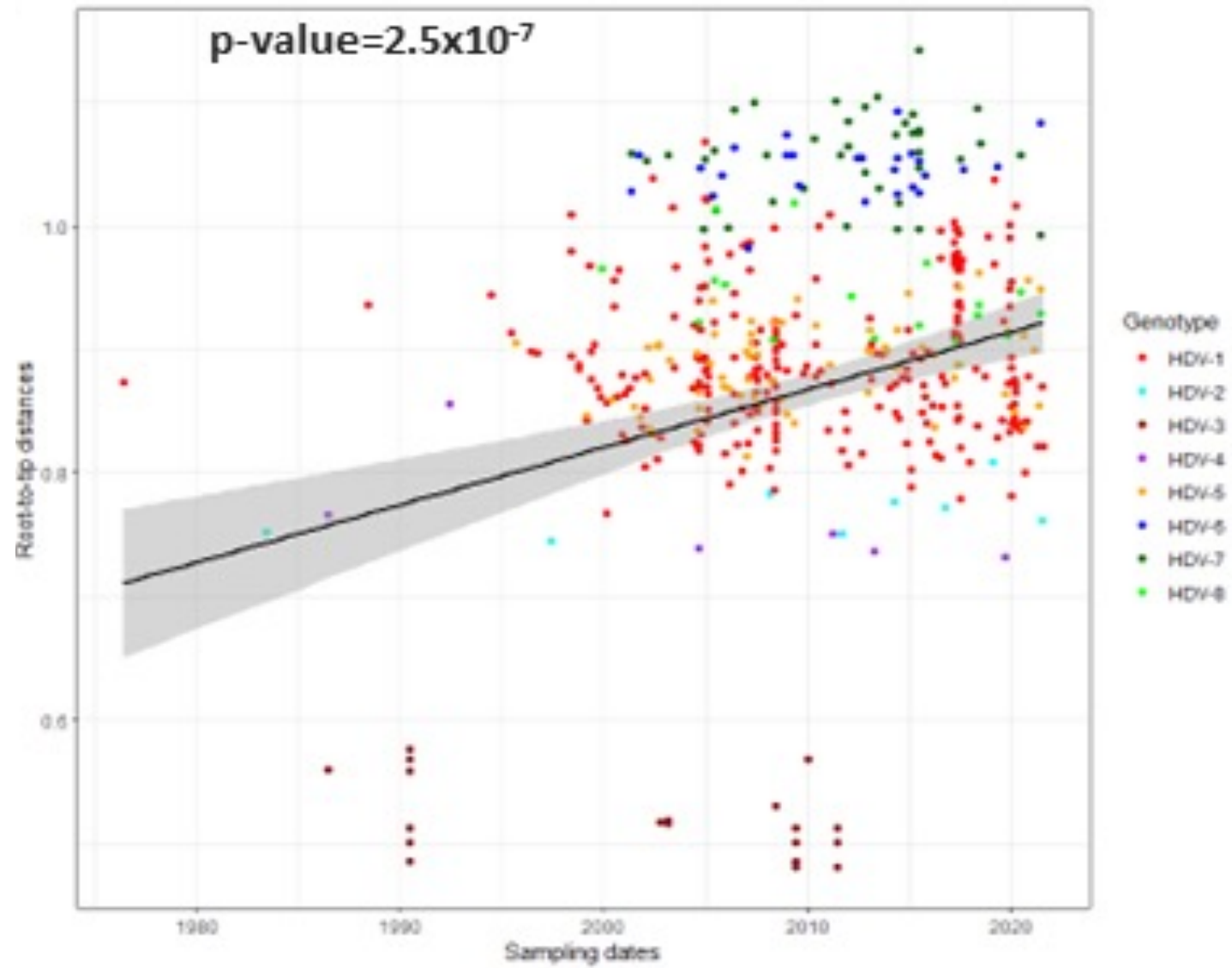
(A) Phylogenetic analysis of 482 hepatitis delta virus L-HDAg sequences



Phase - 2

Dataset L-HDAg (n=482)

(B) Evolutionary rate ?



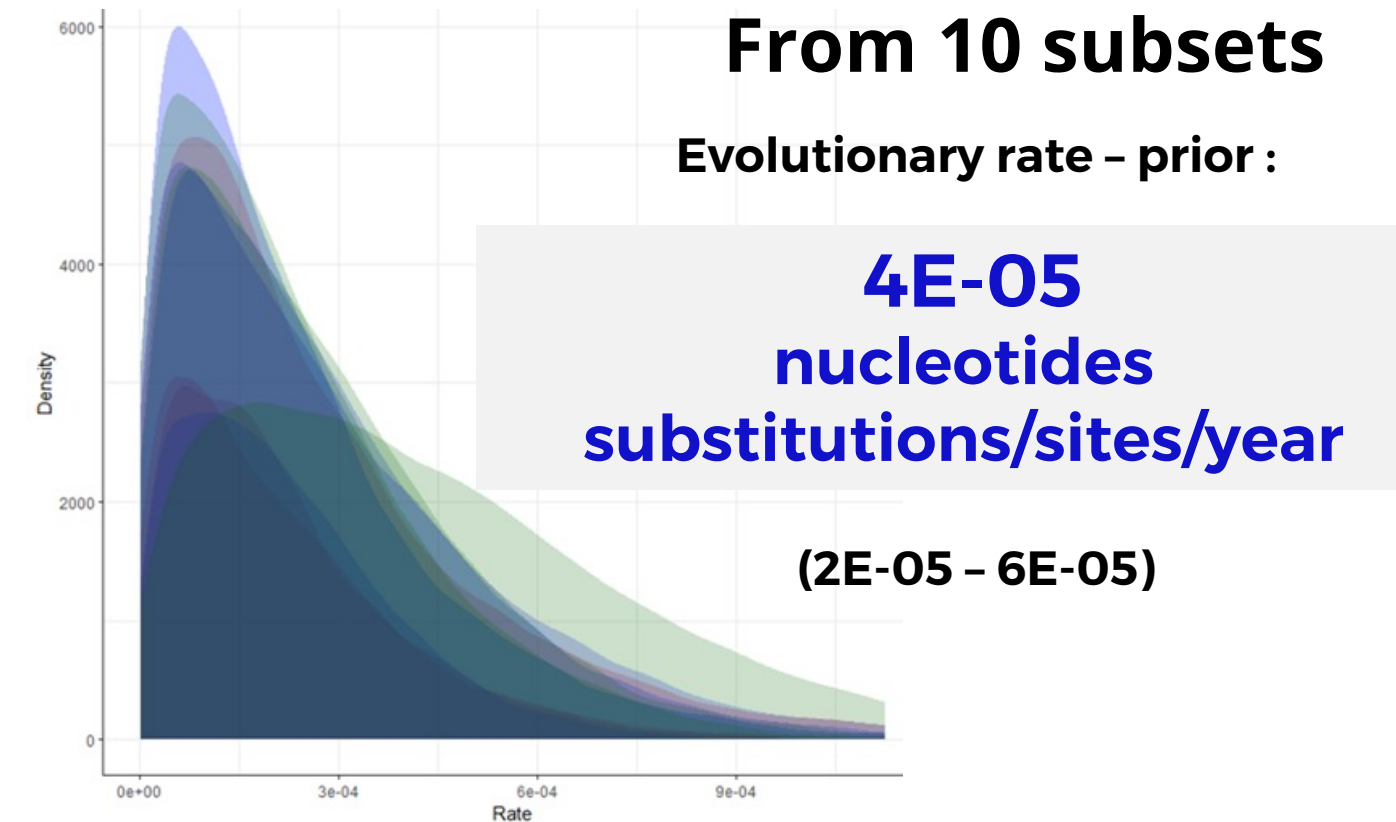
Bayesian estimates

(Subset n=90)x3

(Subset n=120)x3

(Subset n=160)x4

(B) Bayesian estimates of evolutionary rate



Phase - 3

Dataset L-HDAg (n=482)

Parameters



✓ Substitution model :

GTR+ Γ +I

✓ Molecular clock :

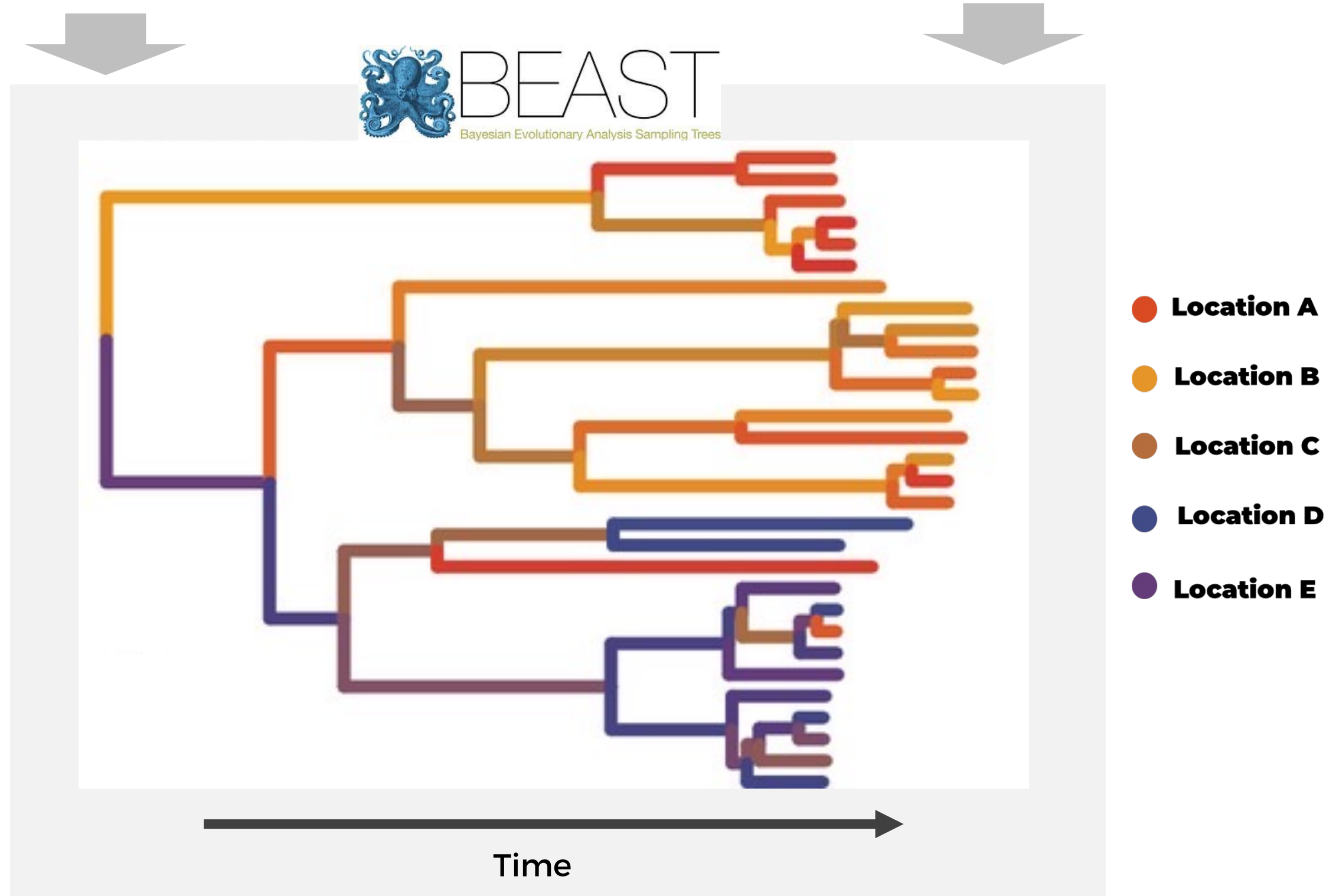
Uncorrelated relaxed clock

✓ Distribution model :

Uniform

Molecular clock dating

Phylogeographic reconstruction



Where?

Location

- Africa - Eastern
- Africa - Middle
- Africa - Northern
- Africa - Western
- America - Southern
- Asia - Eastern
- Asia - Middle
- Asia - South-eastern
- Asia - Southern
- Asia - Western
- Europe - Eastern
- Europe - Northern
- Europe - Southern
- Europe - Western
- Oceania

WESTERN ASIA

Introduction of HDV-1 to Western Asia

3,878 yrs BCE

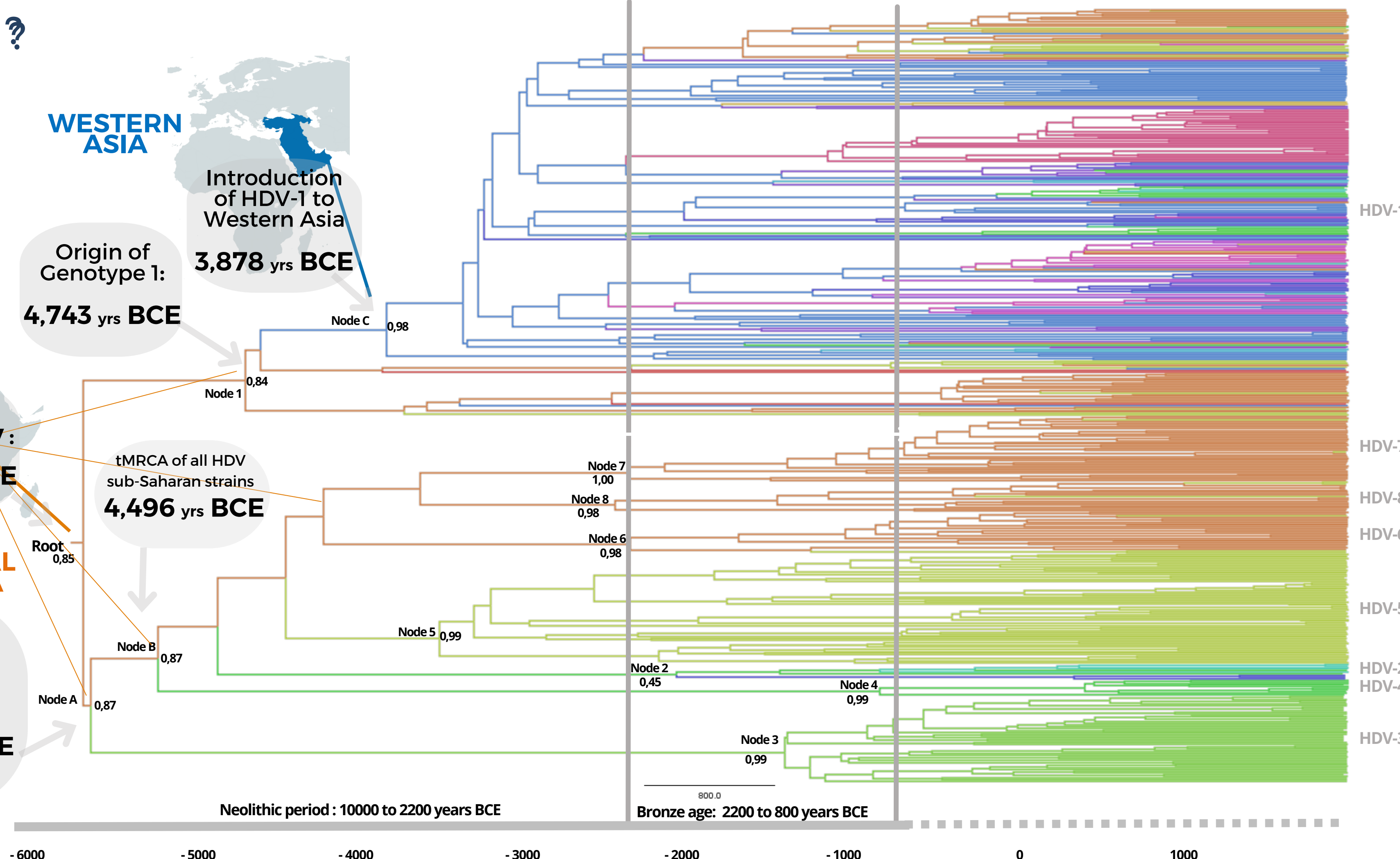
Origin of Genotype 1:
4,743 yrs BCE

Origin of Human HDV:
5,741 yrs BCE

CENTRAL AFRICA

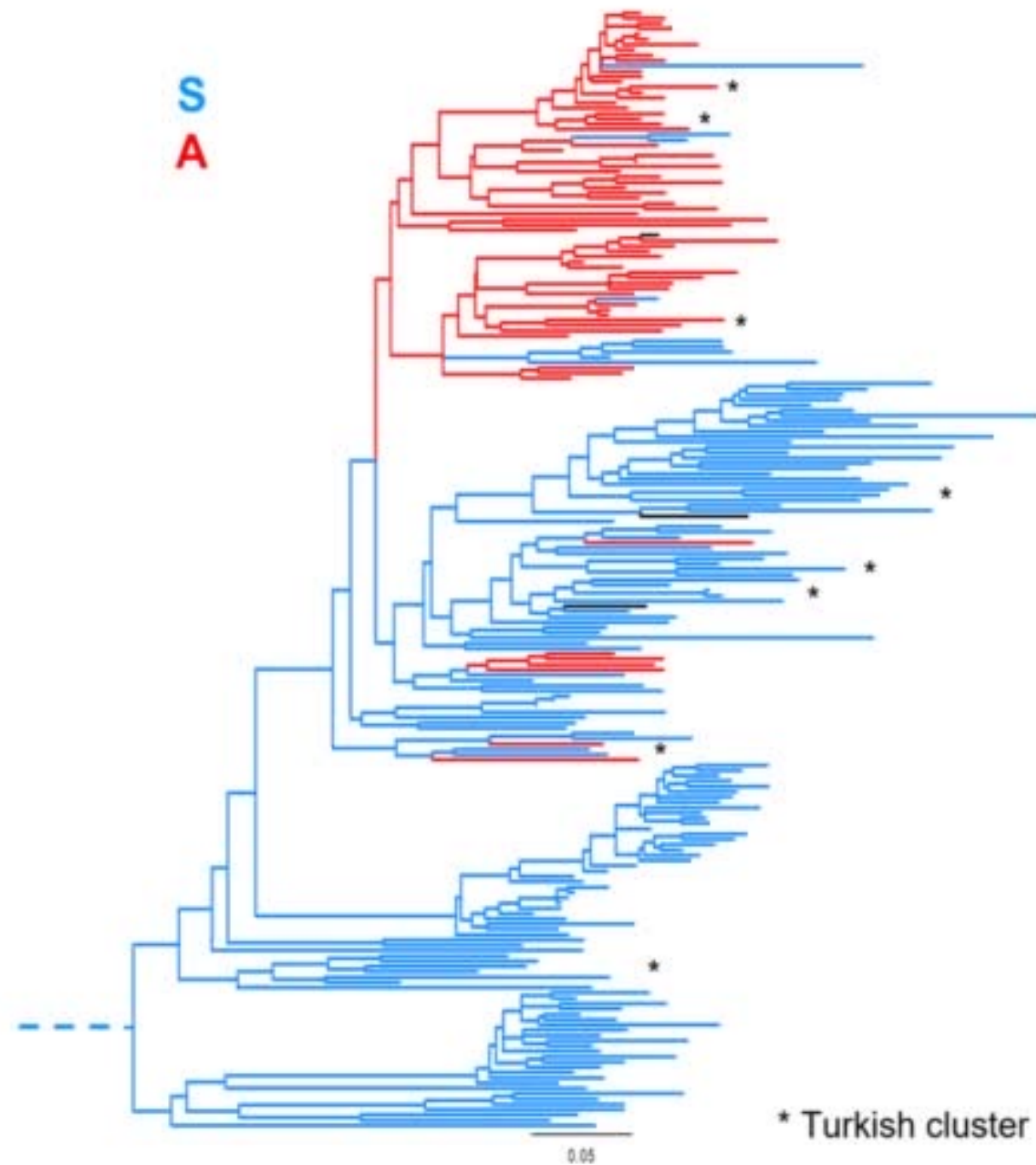
First diversification into HDV-3 and the ancestor of all other genotypes
5,691 yrs BCE

tMRCA of all HDV sub-Saharan strains
4,496 yrs BCE

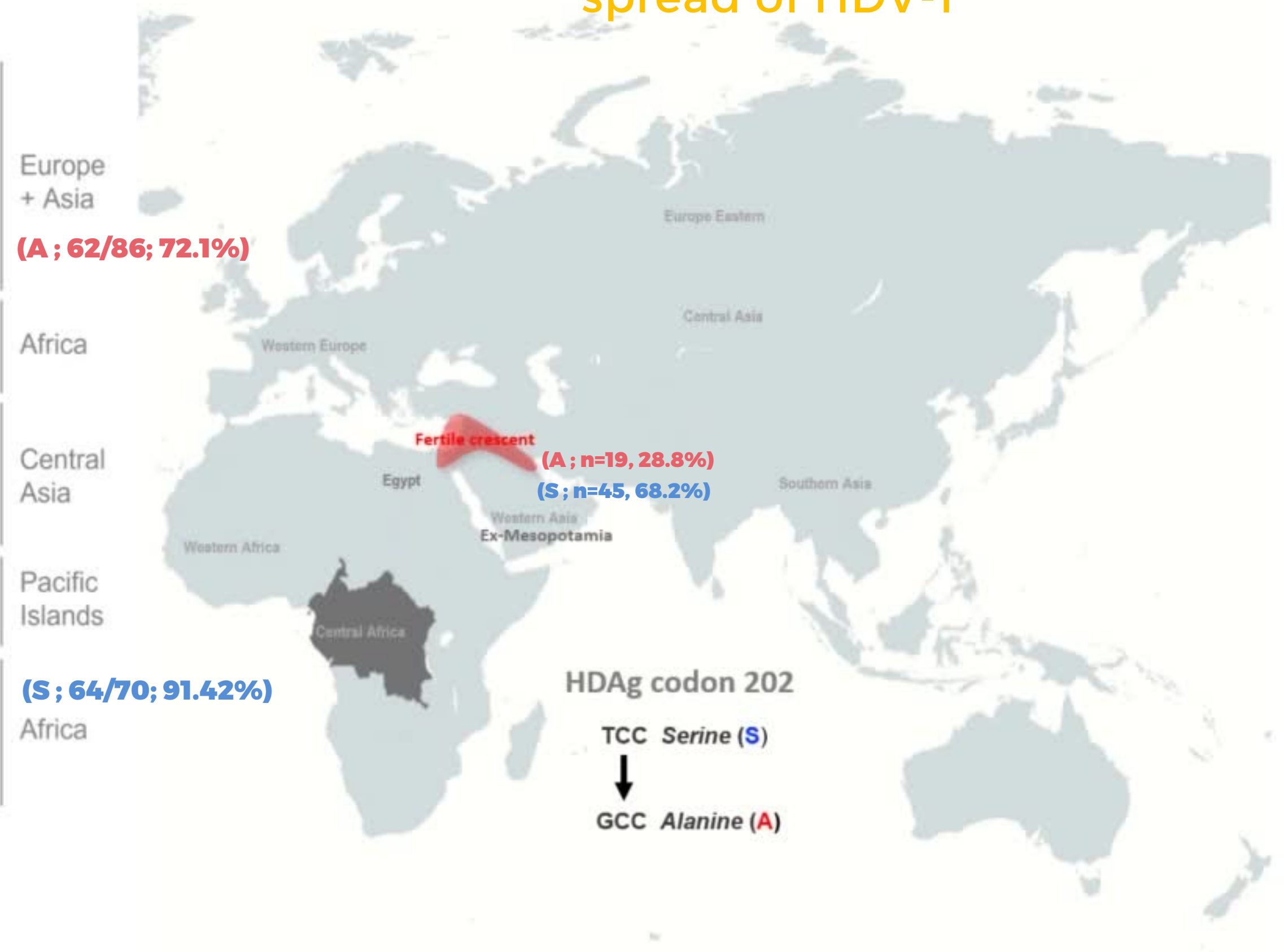


L-HDAg codon 202 : Geographical marker of HDV-1 dissemination

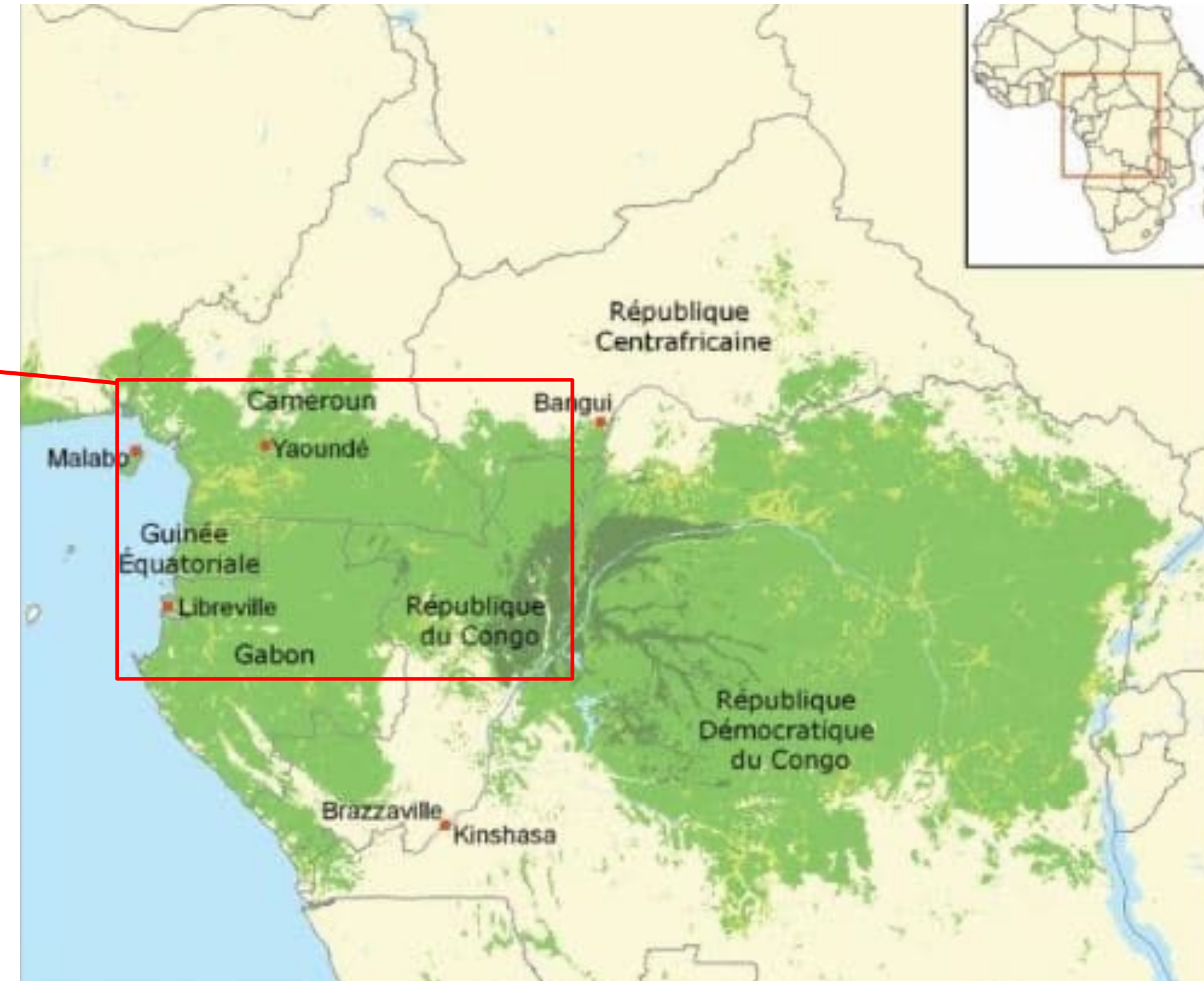
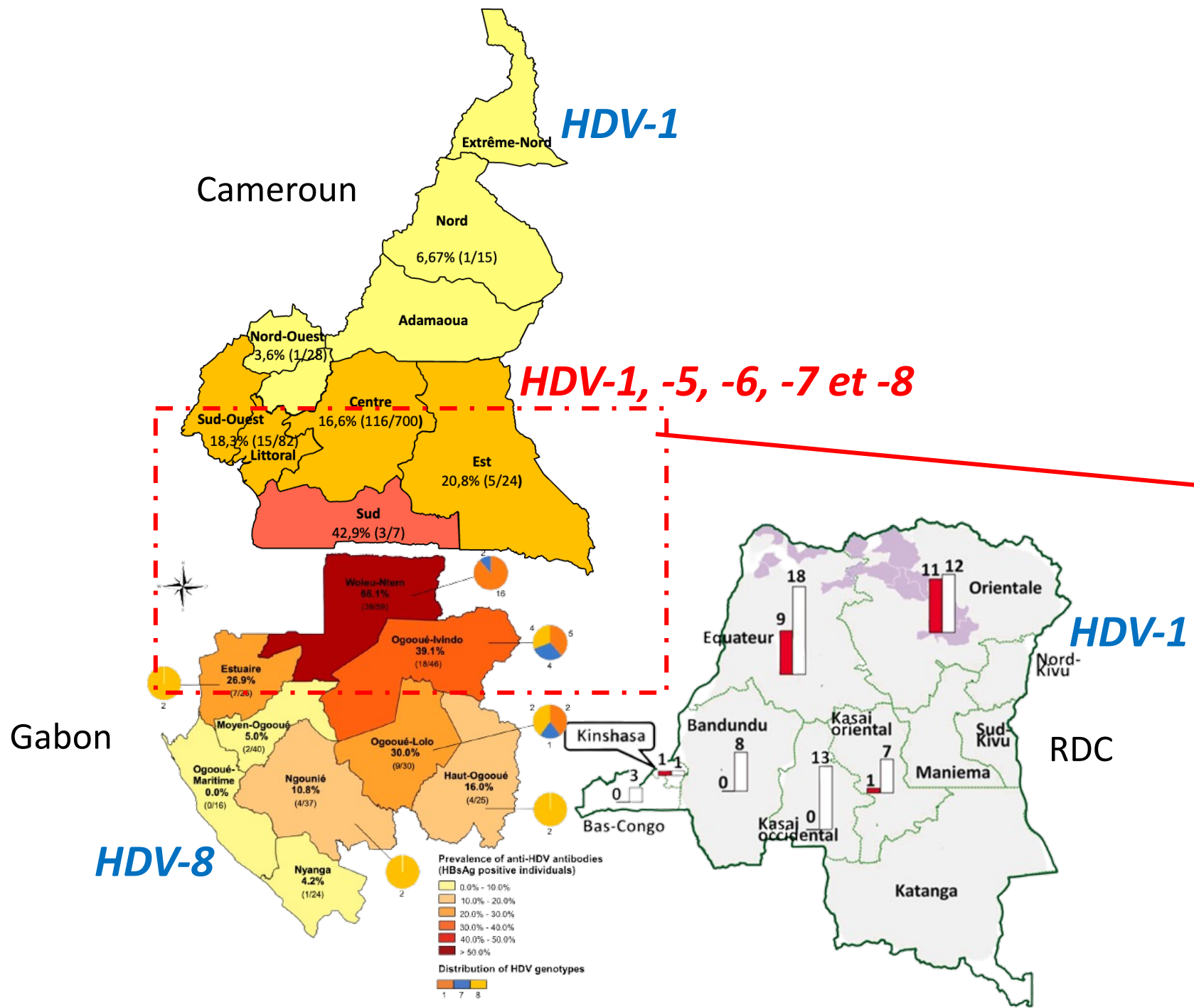
Phylogenetic distribution of HDV-1 L-HDAg codon 202



L-HDAg codon 202 reflects global spread of HDV-1



Central Africa as a “hot spot” for HDV infection



ORIGINAL ARTICLE

WILEY **JVH**

AMERICAN SOCIETY FOR MICROBIOLOGY **Journal of Clinical Microbiology**

VIROLOGY



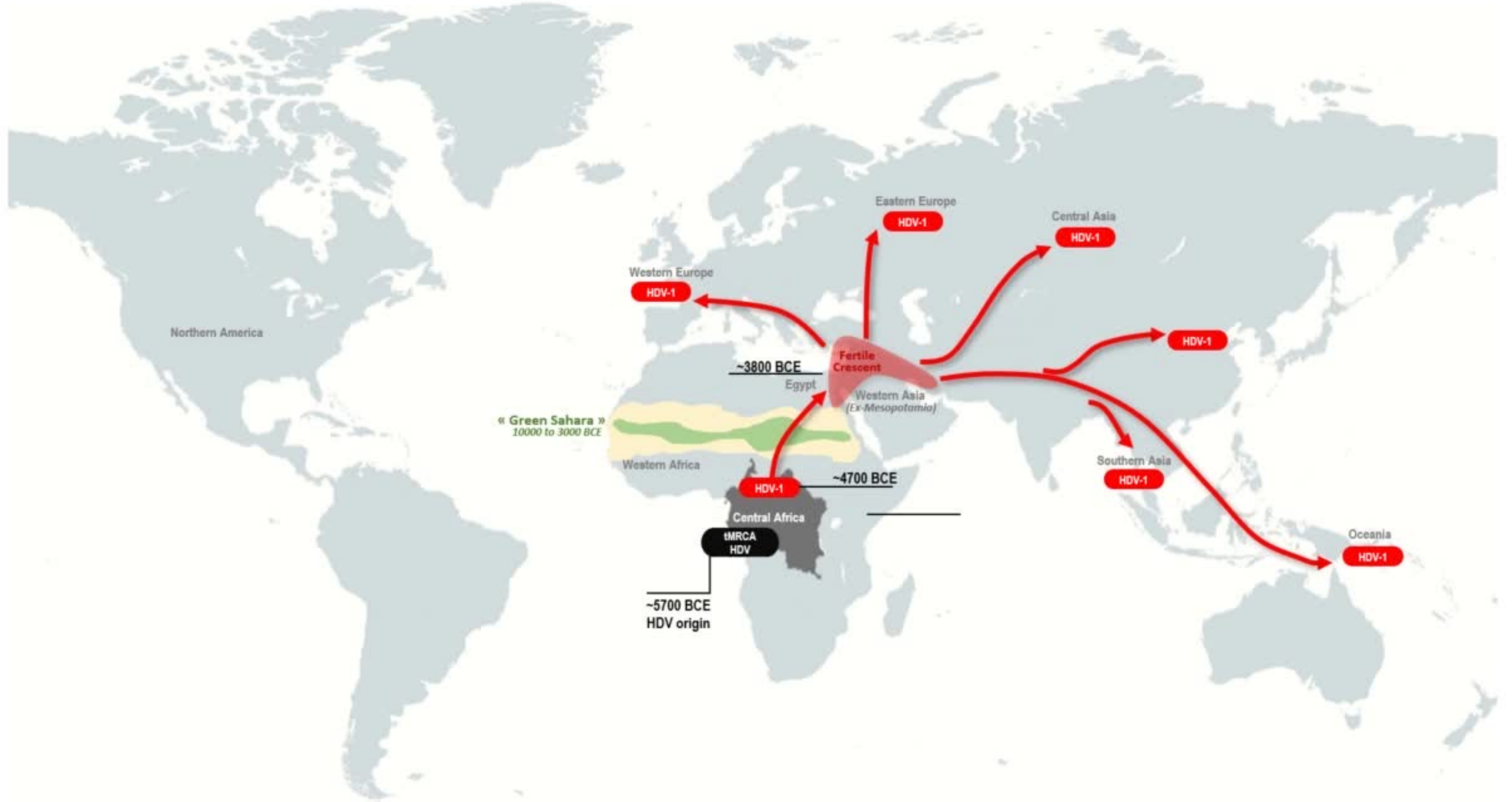
High prevalence and diversity of hepatitis B and hepatitis delta virus in Gabon

Soraya Groc¹ | Jessica Lee Abbate^{1,2} | Frédéric Le Gal^{3,4} | Athenaïs Gerber³ | Edouard Tuailon^{5,6} | Jean-Louis Albert⁷ | Dieudonné Nkoghé⁷ | Eric M. Leroy^{1,7} | Benjamin Roche^{1,2} | Pierre Becquart¹

High Prevalence and Diversity of Hepatitis Viruses in Suspected Cases of Yellow Fever in the Democratic Republic of Congo

Sheila Makiala-Mandanda,^{a,b} Frédéric Le Gal,^c Nadine Ngwaka-Matsung,^b Steve Ahuka-Mundeke,^{b,d} Richard Onanga,^a Berthold Bivigou-Mboumba,^a Elisabeth Pukuta-Simbu,^a Athenaïs Gerber,^c Jessica L. Abbate,^{a,b} Dieudonné Mwamba,^a Nicolas Berthet,^{a,b} Eric Maurice Leroy,^{a,b} Jean-Jacques Muyembe-Tamfum,^{a,d} Pierre Becquart^a

Proposed scenario of HDV spread



Summary



When: Neolithic period (~5,500 BCE) and rapid diversification and radiation (~4,500 BCE) into 8 genotypes;

HDV-1: most ancient genotype in humans.



Where: Origin of HDV in the human population (Central Africa);

HDV-1: key role played by Eurasia in worldwide dissemination;



How: Unresolved points

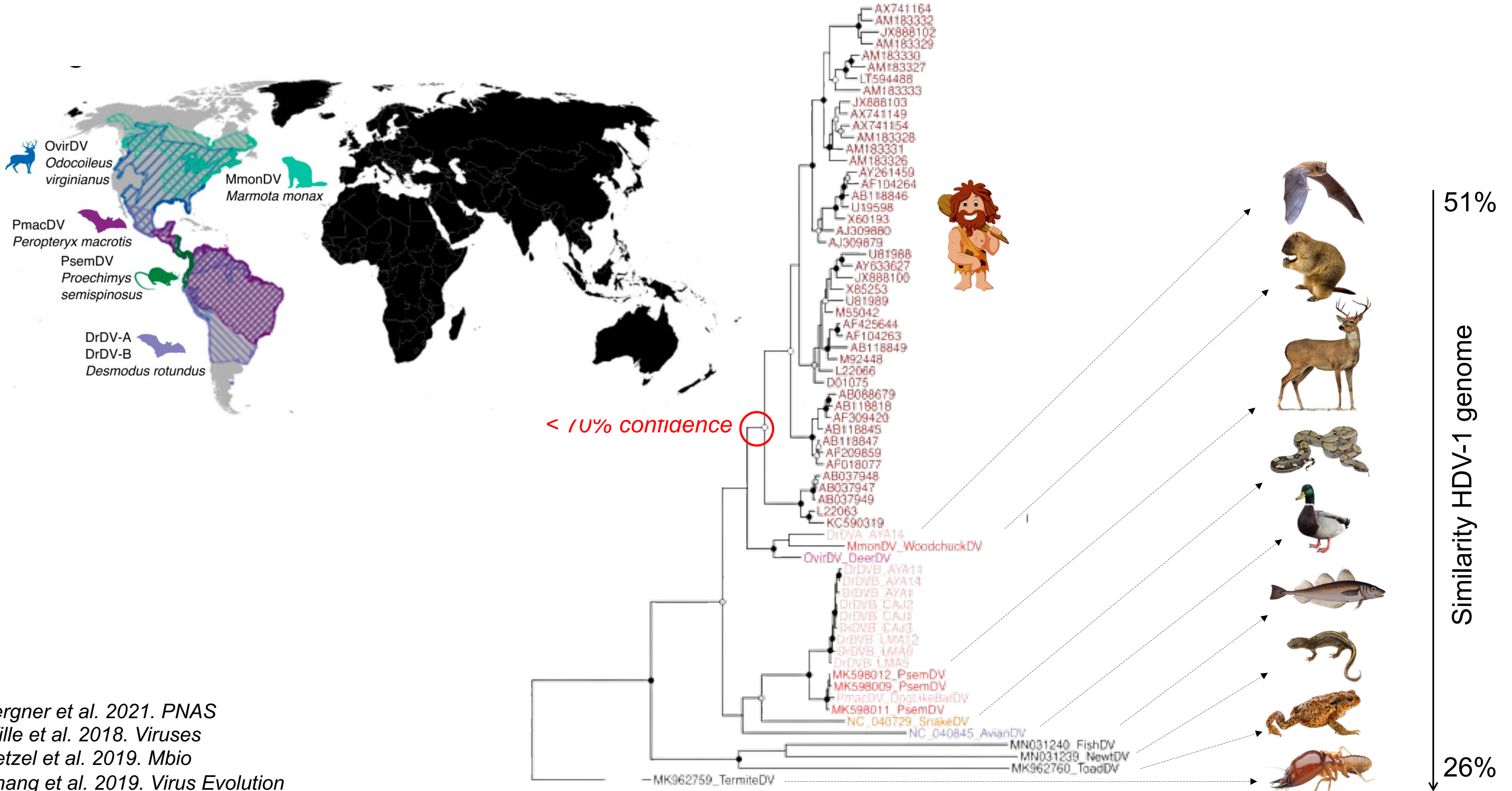
- HDV-3 in South America: one or two introduction(s)?
- HDV-2 in Southeast Asia – HDV-4 in Japan/Taiwan: one or multiples exportation(s) – local divergence?



Who: Plant ? HDV-likes – zoonotic?

Who?

HDV-like genomes



Bergner et al. 2021. PNAS
 Wille et al. 2018. Viruses
 Hetzel et al. 2019. Mbio
 Chang et al. 2019. Virus Evolution

Next project



(1) Study of Genebank transcriptomes



(1) Study of Genebank transcriptomes

*(2) HDV & HBV by PCR on **10 000 samples** from Central Africa :*

Bats, Primates, Rodents, Antelopes



Thank You for Your Attention

Virological part

Stéphanie Tomba
Emmanuel Gordien
Ségolène Brichler
Athenais Gerber



Jean Michel Pawlotsky
Christophe Rodriguez
Slim Fourati

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Stéphane Hué



Historical part (Neolithic period)

Frédéric Gerber



Jean Paul Demoule

