

II Curso de Infecciones de Transmisión Sexual *ITS*

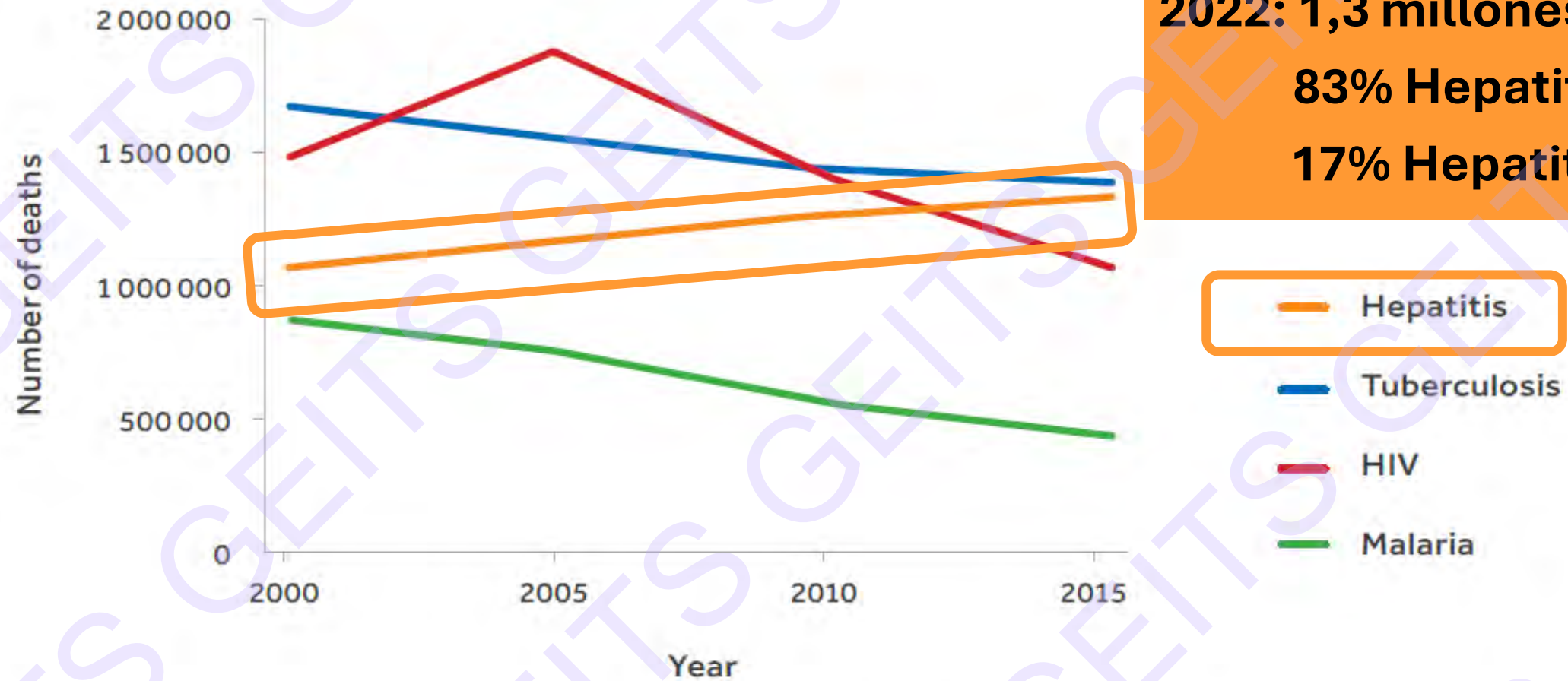


Resistencia a Antivirales: VHB/VHD y VHC

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Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing



2022: 1,3 millones muertes
83% Hepatitis B
17% Hepatitis C

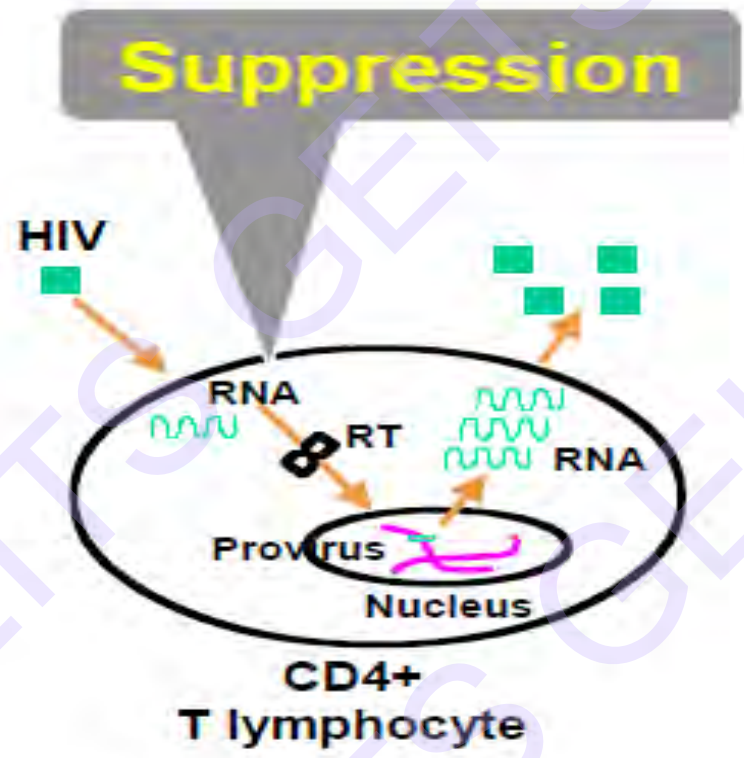
Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.)

Elimination of viral hepatitis as a public health threat by 2030
 (reducing new infections by 90% and mortality by 65%) based on **5 core interventions**

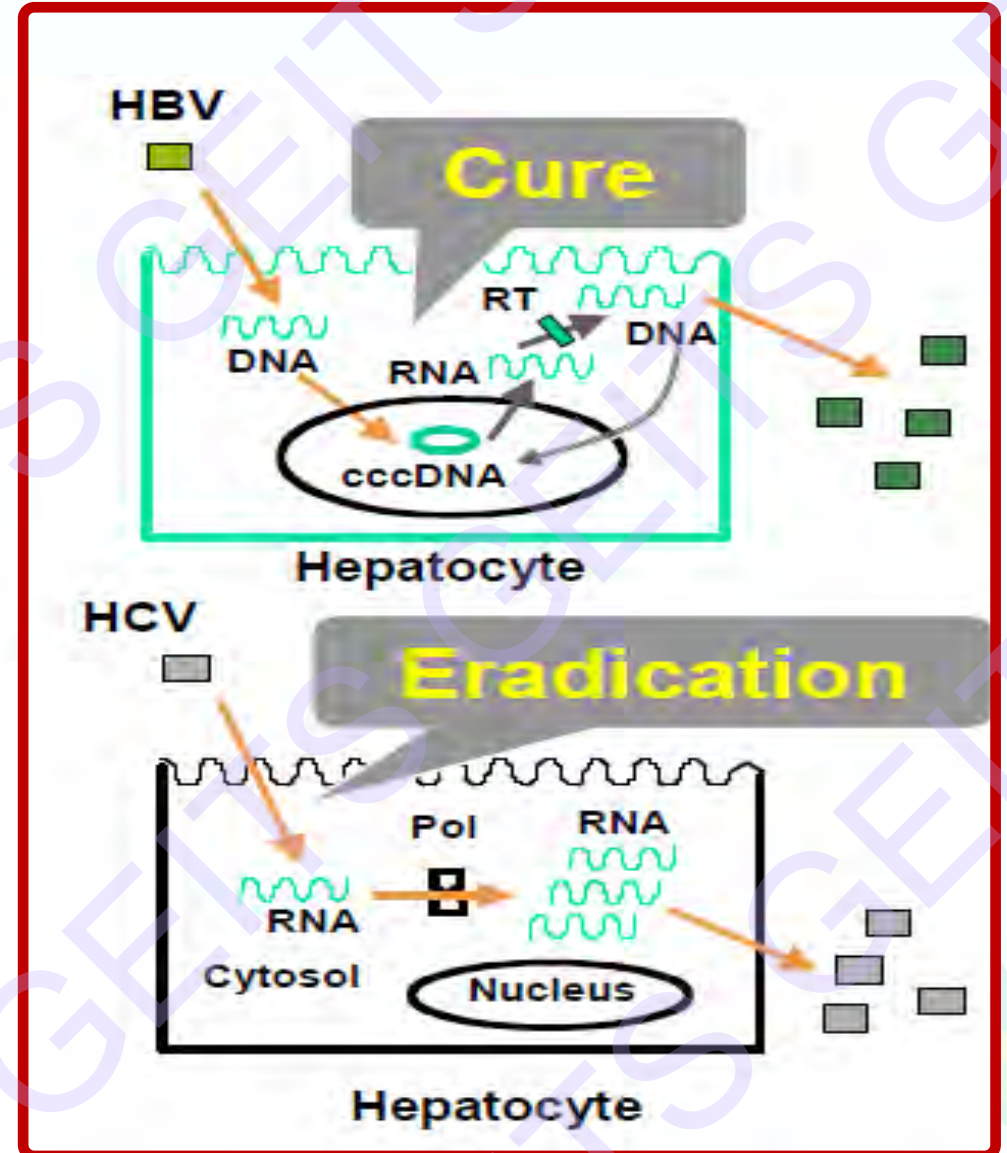
Interventions	Indicator	2015 baseline	2020	2030
1 Hepatitis B vaccination	HEPB3 coverage	84%	90%	90%
2 HBV PMTCT ^a	HEP vaccine birth dose coverage	39%	50%	90%
3 Blood safety	Donations screened with quality assurance	97%	95%	100%
	Injection safety	Proportion of unsafe injections	5%	0%
4 Harm reduction	Syringes & needles distributed/PWID/year	27	200	300
5 Testing services	% HBV-infected diagnosed	9%	30%	90%
	% HCV-infected diagnosed	20%	30%	90%
Treatment	% diagnosed with HBV on treatment	8% ^b	— ^c	80% ^d
	% diagnosed with HCV started on treatment	7% ^b	— ^c	80% ^d

HCV ≠ HIV

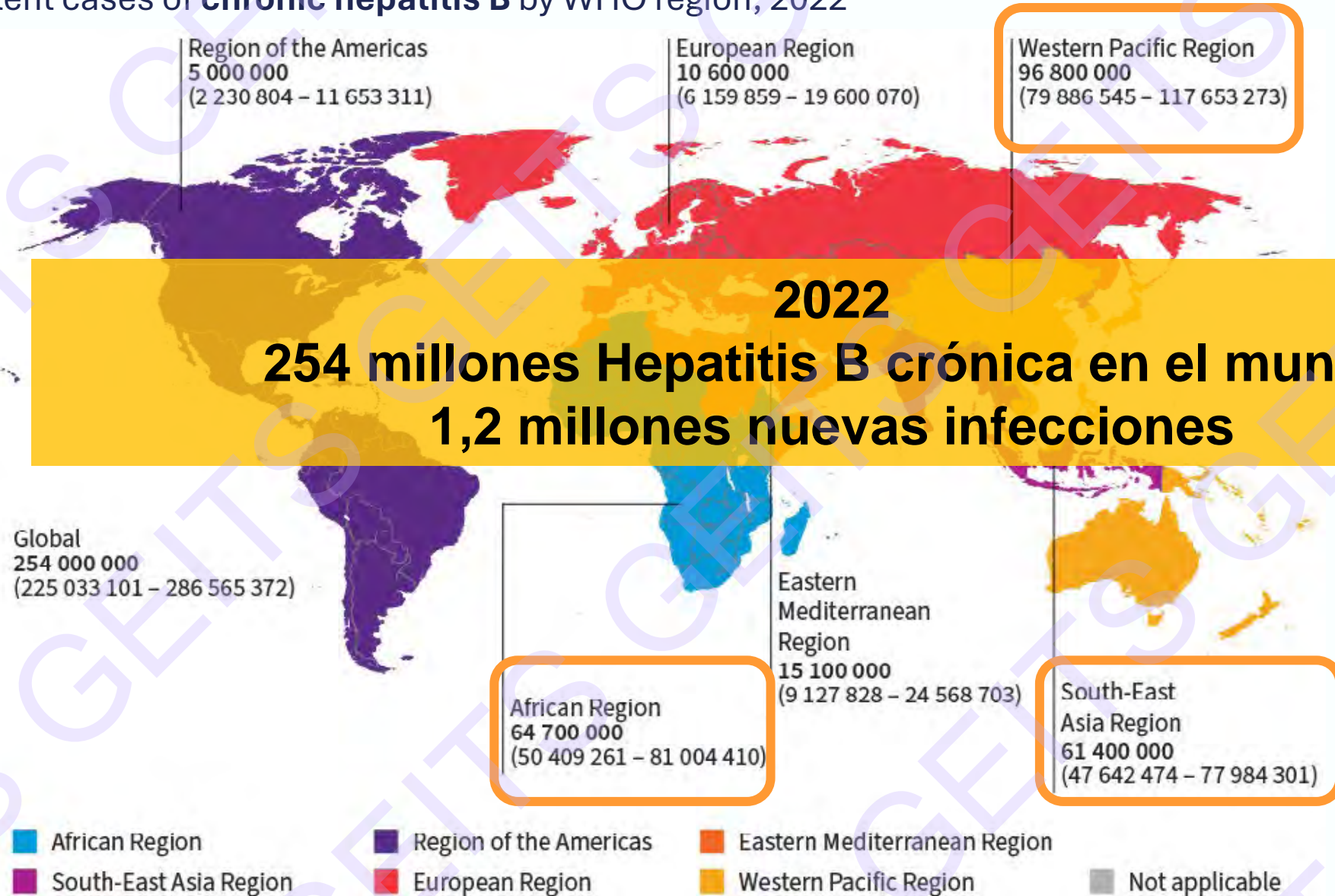
HCV ≠ HBV



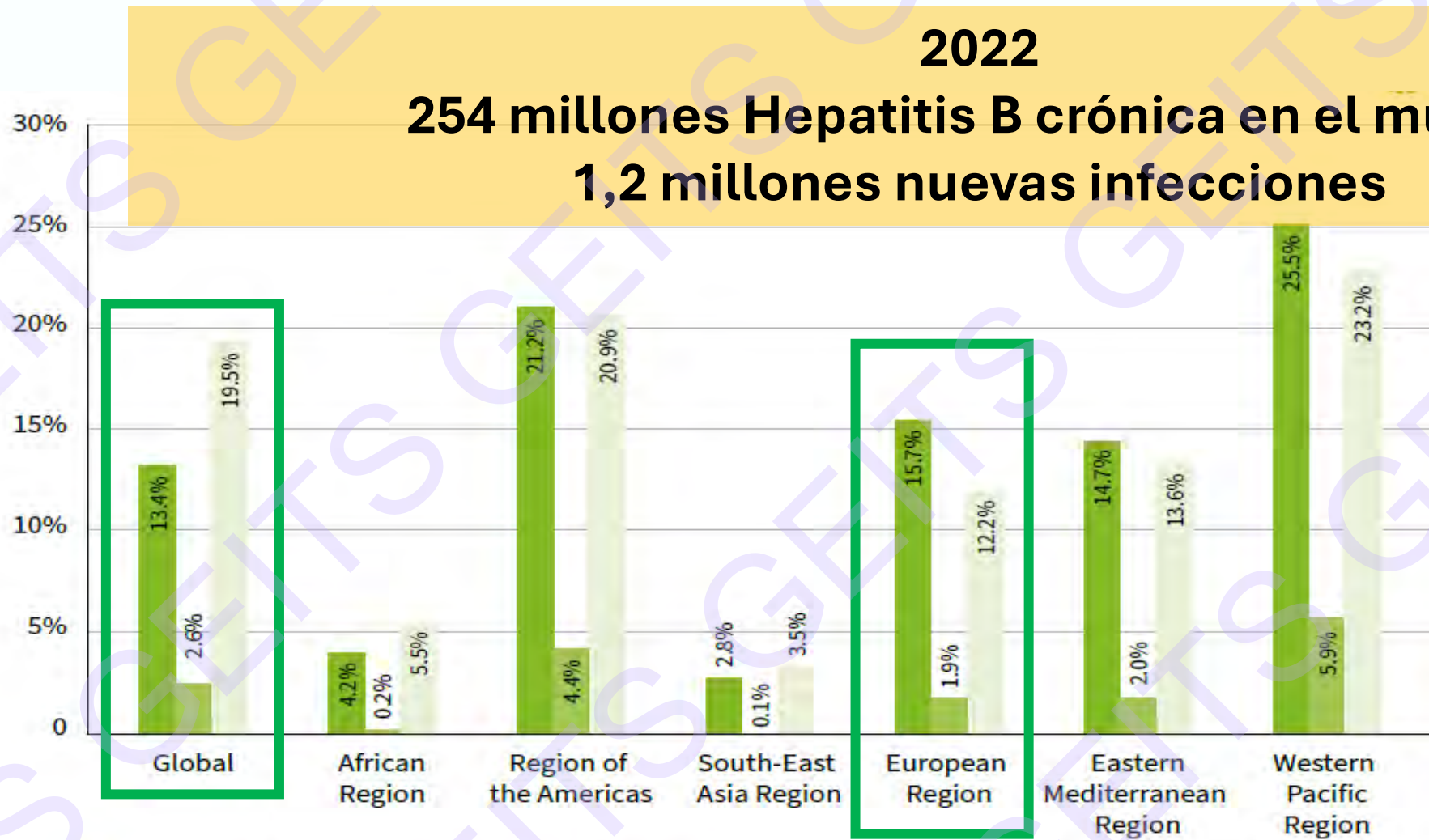
Soriano et al. JAC 2008



Prevalent cases of **chronic hepatitis B** by WHO region, 2022

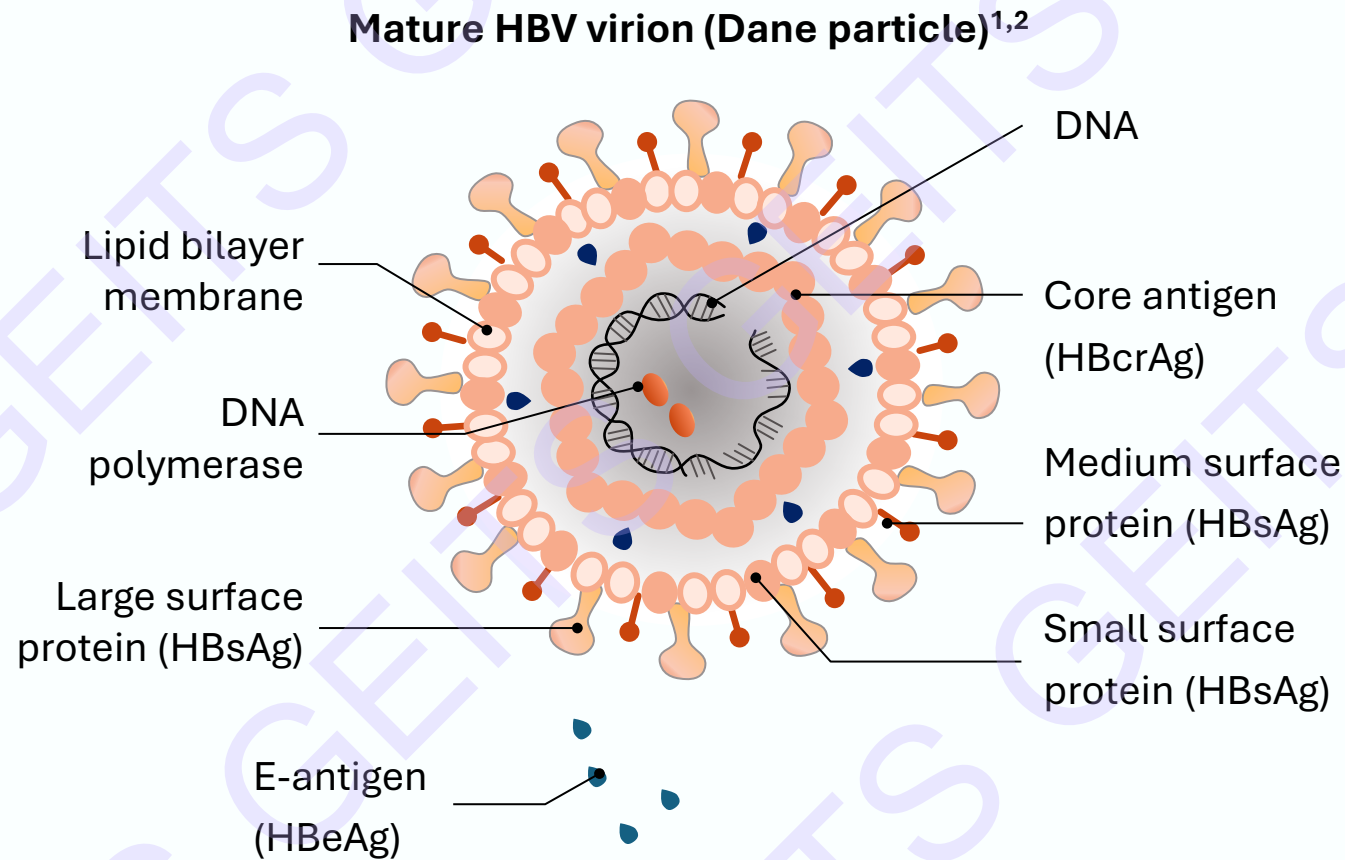


Coverage of hepatitis B testing and treatment by WHO region, 2022



- Hepatitis B diagnosis coverage to end of 2022
- Hepatitis B treatment coverage to end of 2022 (of all people with hepatitis B)
- Hepatitis B treatment coverage to end of 2022 (of all people diagnosed with hepatitis B)

HBV standard markers



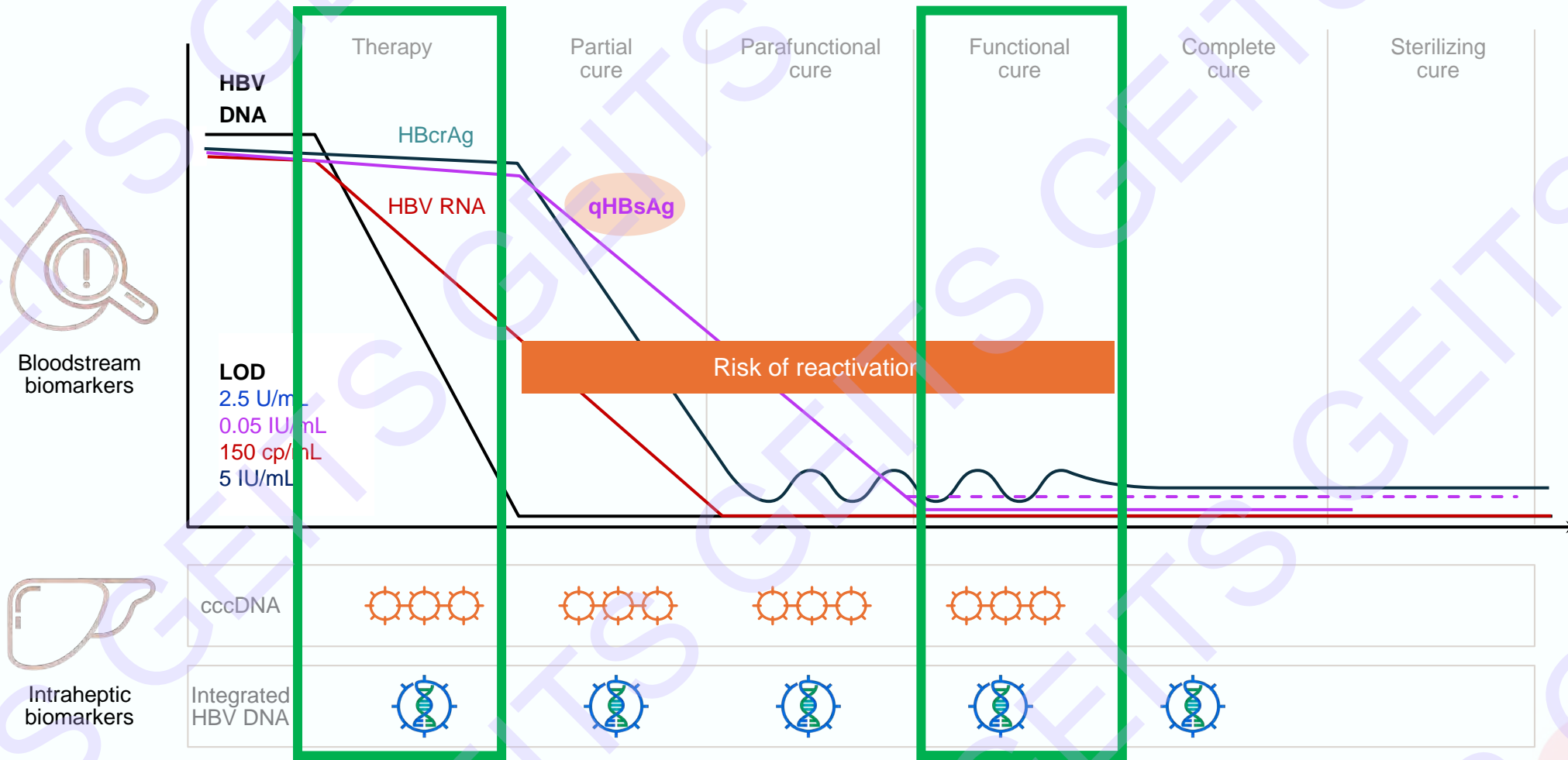
Standard markers³⁻⁵

- HBsAg
- Anti-HBs
- HBeAg/anti-HBe
- HBV DNA
- Anti-HBc

1. Lamontagne RJ, et al. Hepatoma Res 2016;2:163–86; 2. Prifti G-M, et al. Pharmaceuticals 2021;14:417;
3. EASL. J Hepatol 2017;67:370–98; 4. Höner Zu Siederdisen C, et al. Best Pract Res Clin Gastroenterol 2017;31:281–
9; 5. Lampertico P, personal opinion.

DNA, deoxyribonucleic acid;
HBeAg, hepatitis B virus E antigen.

New biomarkers could be useful in defining HBV cure¹



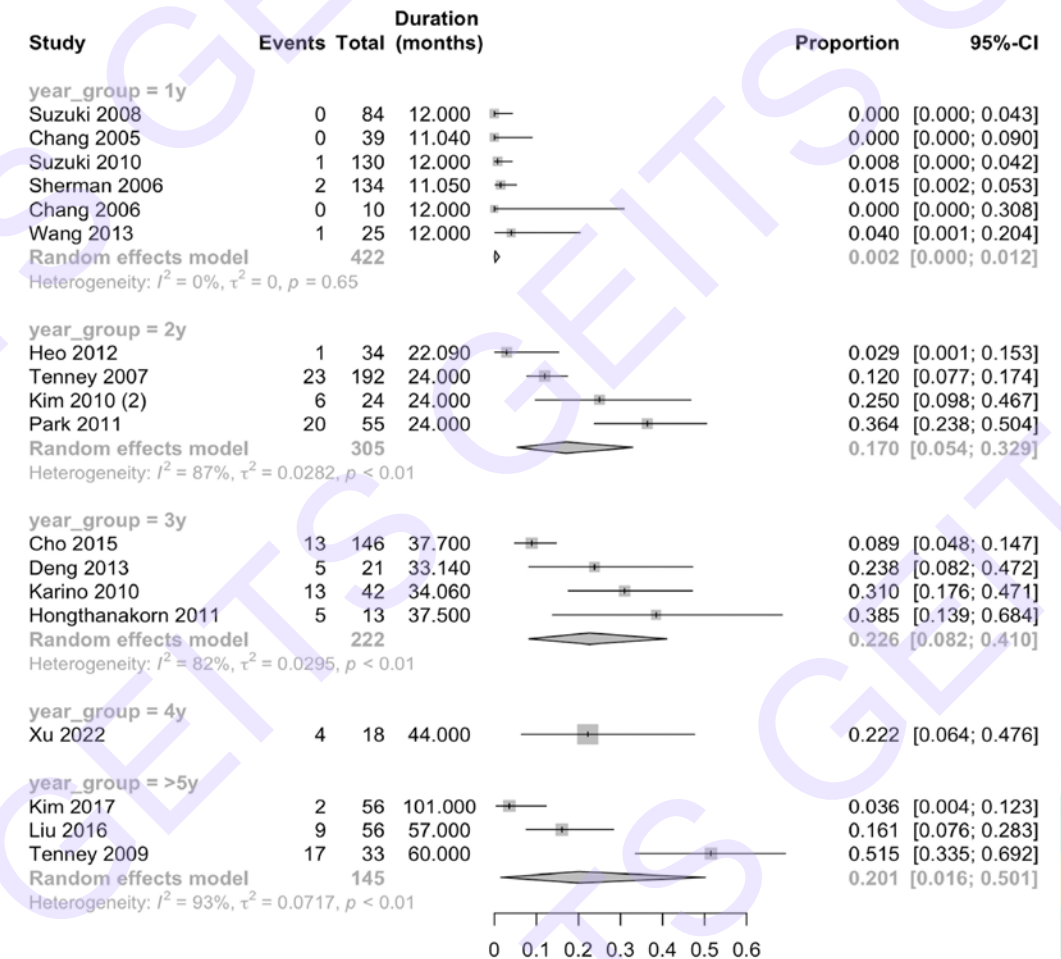
1. Charre C, et al. Antiviral Res 2019;169:104553.

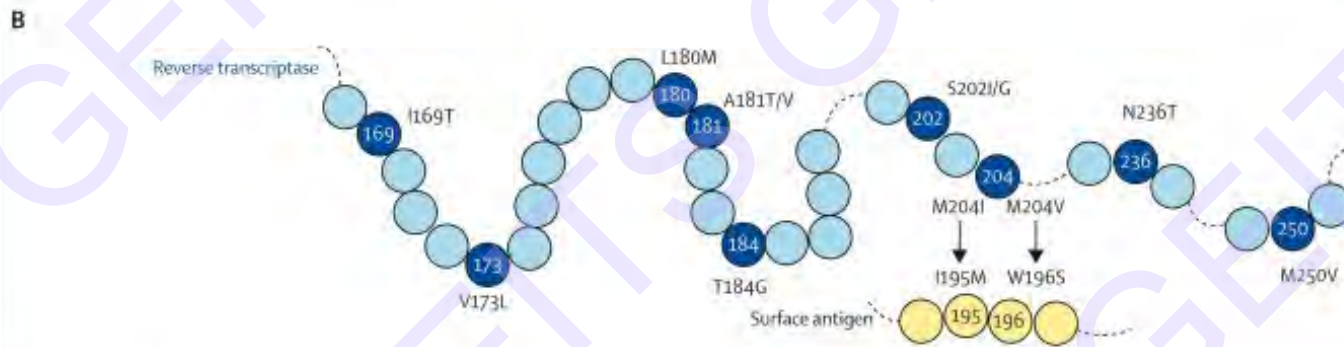
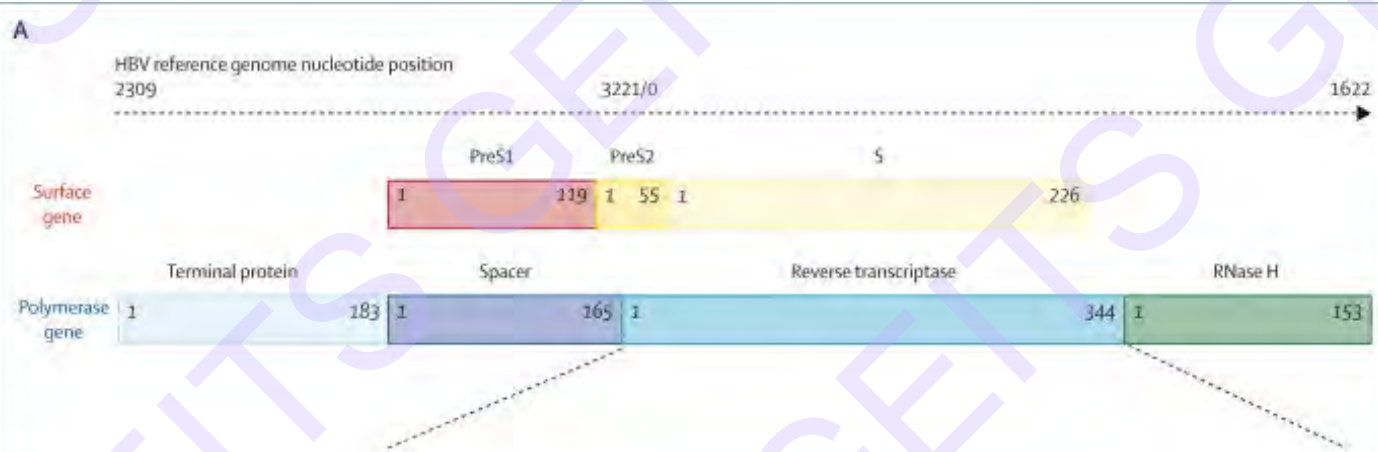
*Sterilizing cure is not currently considered to be possible, and there are currently no biomarkers to define it.
LOD, level of detection.

A systematic review and meta-analysis of the **risk of hepatitis B virus (HBV) resistance** in people treated with **entecavir or tenofovir**

- N=12358 HBV patients
- **Entecavir/Tenofovir alta barrera genética**
- **Entecavir** (Resistance at ≥ 5 years)
 - Naïve: 0,9%
 - **NA-experienced: 20,1%**
- **Tenofovir**
 - Naïve: 0%
 - NA-experienced: 0%

B. Experienced/Entecavir





C

HBV variant	Nucleos(t)ide analogue drug agent				
	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild-type	S	S	S	S	S
M204V	R	S	I	I	S
M204I	R	R	I	I	S
L180M + M204V	R	R	I	I	S
A181T/V	I	I	S	R	I
N236T	S	S	S	R	I
L180M + M204V/I +/- I169T +/- V173L +/- M250V	R	R	R	S	S
L180M + M204V/I +/- T184G +/- S202I/G	R	R	R	S	S

• Risk Factors for HBVDR :

• Prior NA exposure

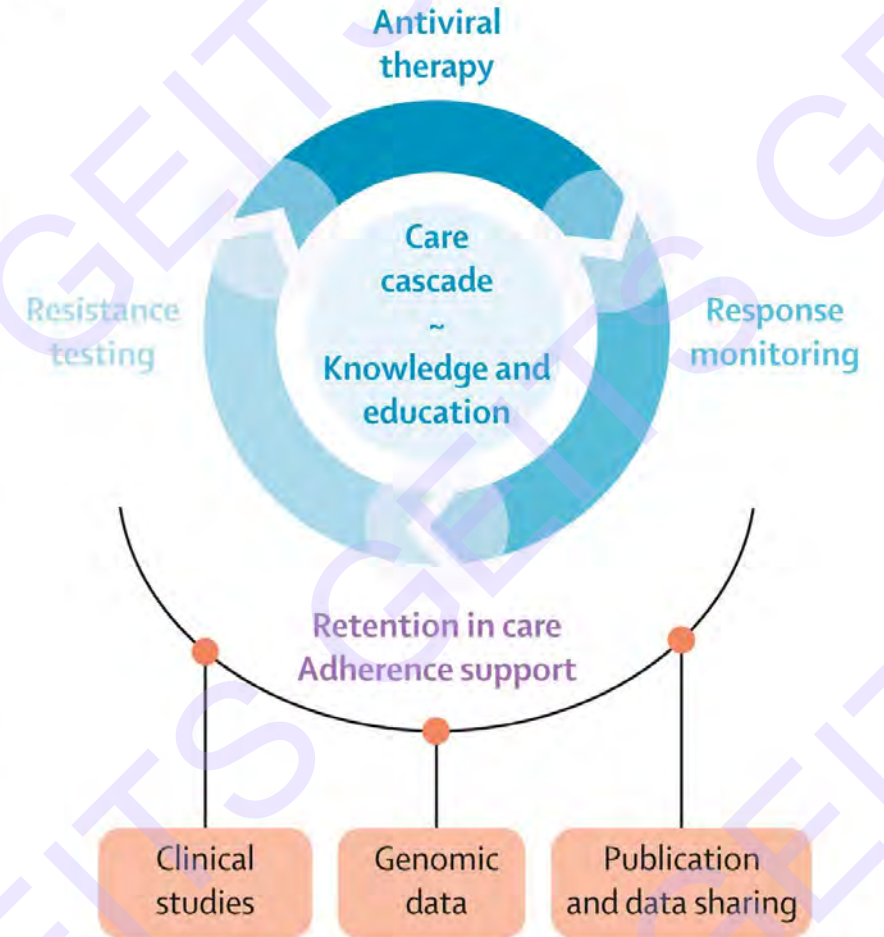
- Viral load
- HBV genotype
- Elevated ALT
- Older age
- Long Duration
- Cirrhosis
- Elevated BMI

A

SeqHepB/ DeepChek	Geno2pheno [HBV]	HIV-GRADE HBV tool	HBVdb	Stanford HBVseq
				

INPUT		SeqHepB/ DeepChek	Geno2pheno [HBV]	HIV-GRADE HBV tool	HBVdb	Stanford HBVseq
Plain text or FASTA		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
FASTQ, BAM or SAM		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
OUTPUT		SeqHepB/ DeepChek	Geno2pheno [HBV]	HIV-GRADE HBV tool	HBVdb	Stanford HBVseq
Genotype (A-J)		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Resistance mutations		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Escape mutations		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
ACCESS		SeqHepB/ DeepChek	Geno2pheno [HBV]	HIV-GRADE HBV tool	HBVdb	Stanford HBVseq
Rules available		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Regular updates		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Free of charge		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

B



Nuevas dianas terapéuticas para la cura funcional del VHB

Papel de la terapia combinada

Inhibición de la replicación

- NAs
- Moduladores de ensamblaje de la cápside (CAM)

±

Reducción del antígeno

- siRNA
- Oligonucleótidos antisentido (ASOs)
- Inhibidores de la entrada
- Polímeros de ácidos nucleicos (NAPs)

±

Estimulación respuesta inmune

- peg-IFN α
- TLR7/8 agonist
- Inhibidores de checkpoint (e.g., anti-PD1 therapies)
- Vacunas terapéuticas
- Anticuerpos monoclonales (anti-HBs)

*Some treatment classes have more than one mechanism of action.

Anti-HBs, antibody against hepatitis B surface antigen; ASO, antisense oligonucleotide; FXR, Farnesoid X receptor; HBV, hepatitis B virus; LNA, locked nucleic acid; NA, nucleos(t)ide analogue; NAP, nucleic acid polymer; PD1, programmed cell death protein 1; peg-IFN α , pegylated interferon α ; siRNA, small interfering RNA; TLR, toll-like receptor.

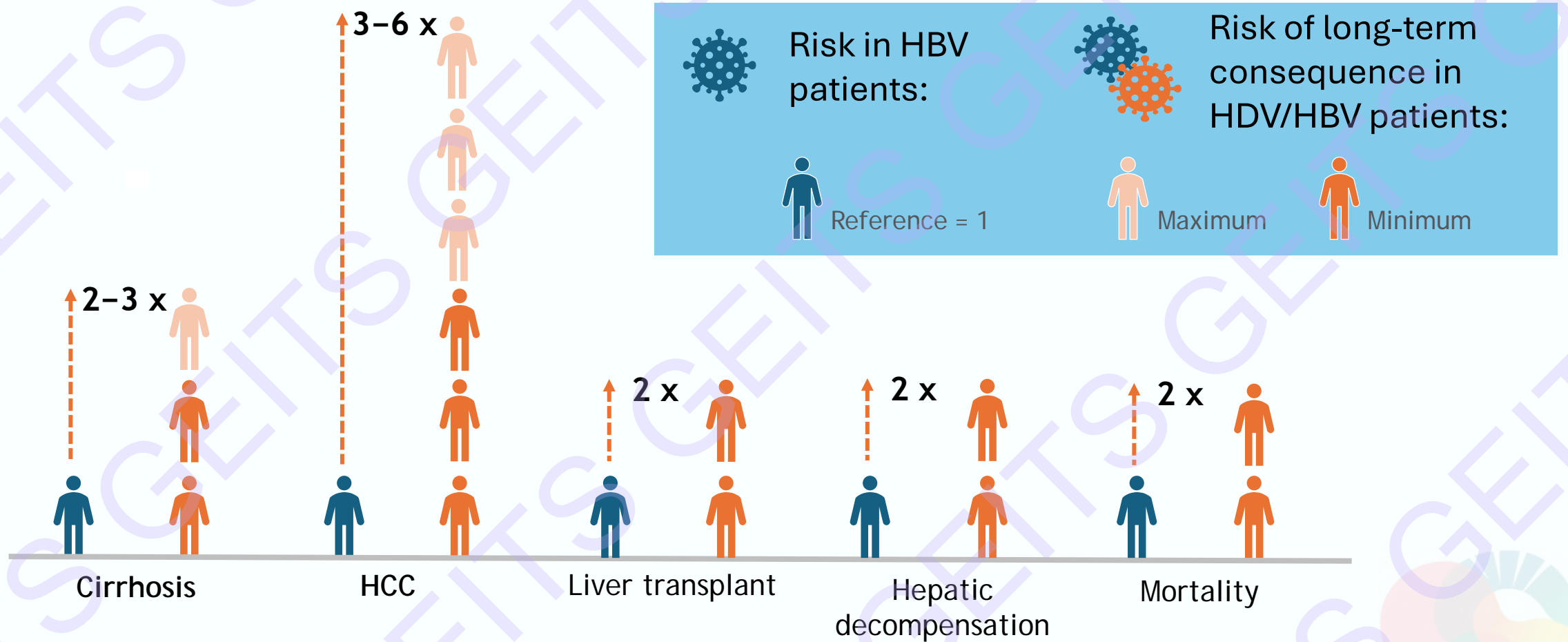
1. Gopalakrishna H, et al. *Curr Hepatol Rep.* 2024;23(2):241–252; 2. Lim SG, et al. *Nat Rev Gastroenterol Hepatol.* 2023;20(4):238–253; 3. Watanabe T, et al. *J Gastroenterol.* 2024;59(4):315–328.

Cura Funcional Hepatitis B: PÉRDIDA SOSTENIDA HBsAg (>6meses)

**ADN VHB <10UI/mL (blips)
Anti-HBs +/-**

**1-5% tratamientos actuales (NA)
10-25% nuevos tratamientos (siRNA/ASO)**

Increased risk of long-term consequences of viral hepatitis in HBV/HDV patients versus HBV monoinfection

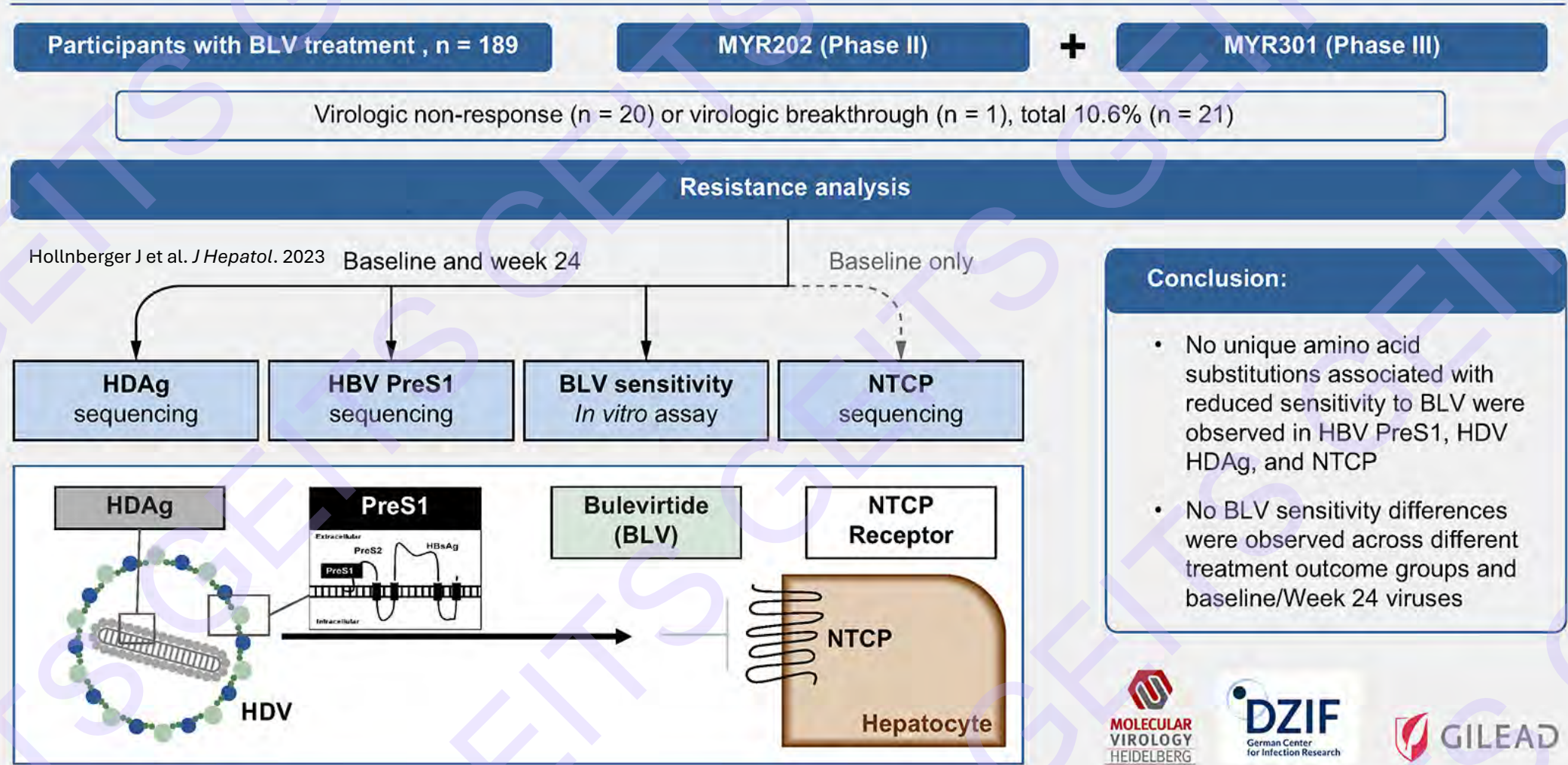


Disease progression in chronic hepatitis B is not linear and HCC can develop in the absence of cirrhosis.

HBV: hepatitis B virus;

HCC: hepatocellular carcinoma; HDV: hepatitis delta virus

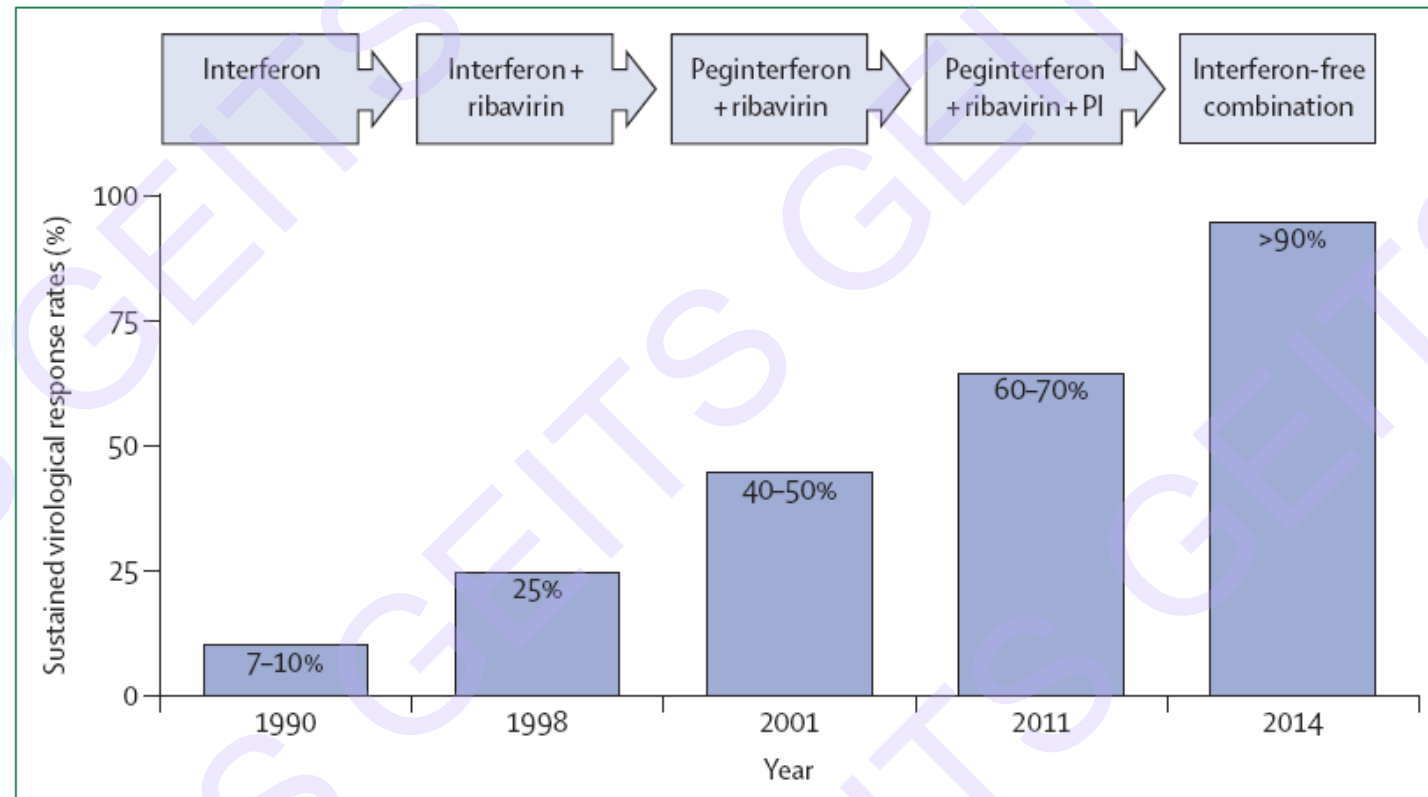
No virologic resistance to bulevirtide monotherapy detected in patients through 24 weeks treatment in phase II and III clinical trials for chronic hepatitis delta



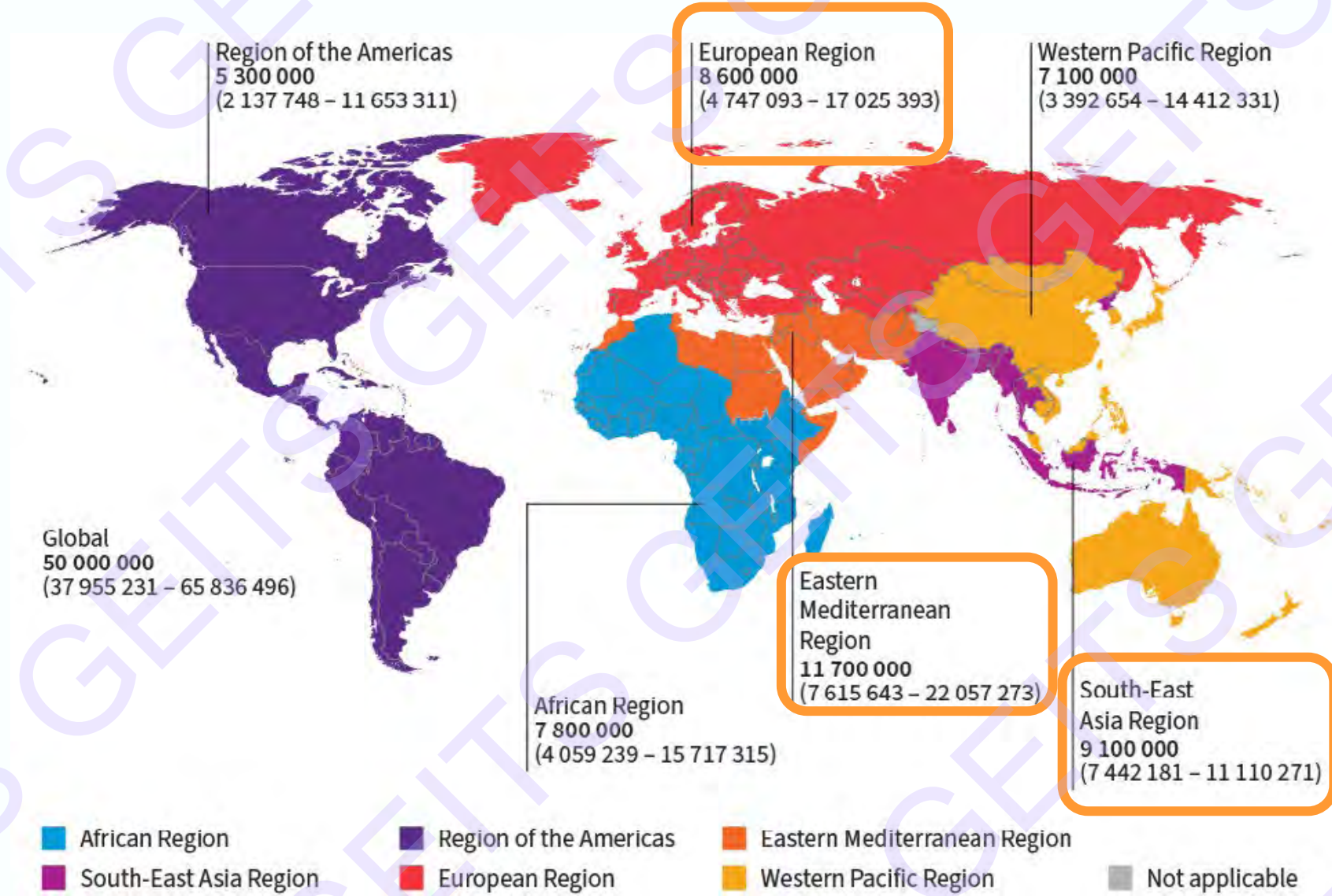
There were no cases of confirmed viral resistance emerging during treatment (Lampertico et al, *J Viral Hepat.* 2025)

INTRODUCCIÓN Hepatitis C

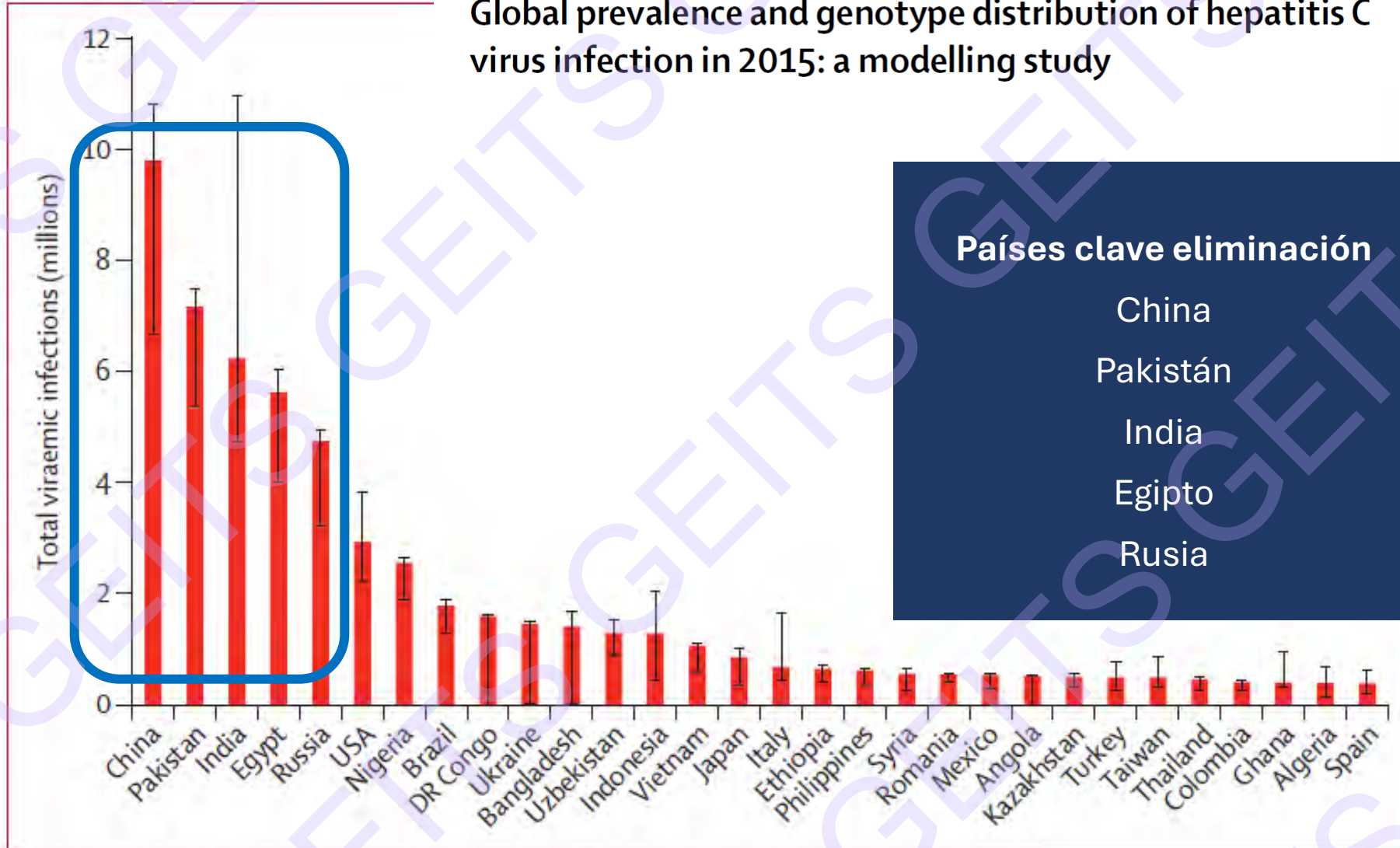
- 2022: **50 millones VHC crónica en el mundo**
 - **36% diagnosticados**
 - **10 millones tratados AAD (2015-2019)**
- Tratamiento hasta 2011:
 - Telaprevir /Boceprevir + PegIFN y RBV (RRAA)
 - 65-75% RVS GT1
- Después 2014:
 - Terapias libres de IFN
 - **Sofosbuvir/Velpatasvir**, Daclatasvir, **Glecaprevir/Pibrentasvir**, **Voxilaprevir**.
 - **Pangenotípicas**
 - **90-95% RVS12**



Prevalent cases of **chronic hepatitis C** by WHO region, 2022



Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study



Países clave eliminación

- China
- Pakistán
- India
- Egipto
- Rusia

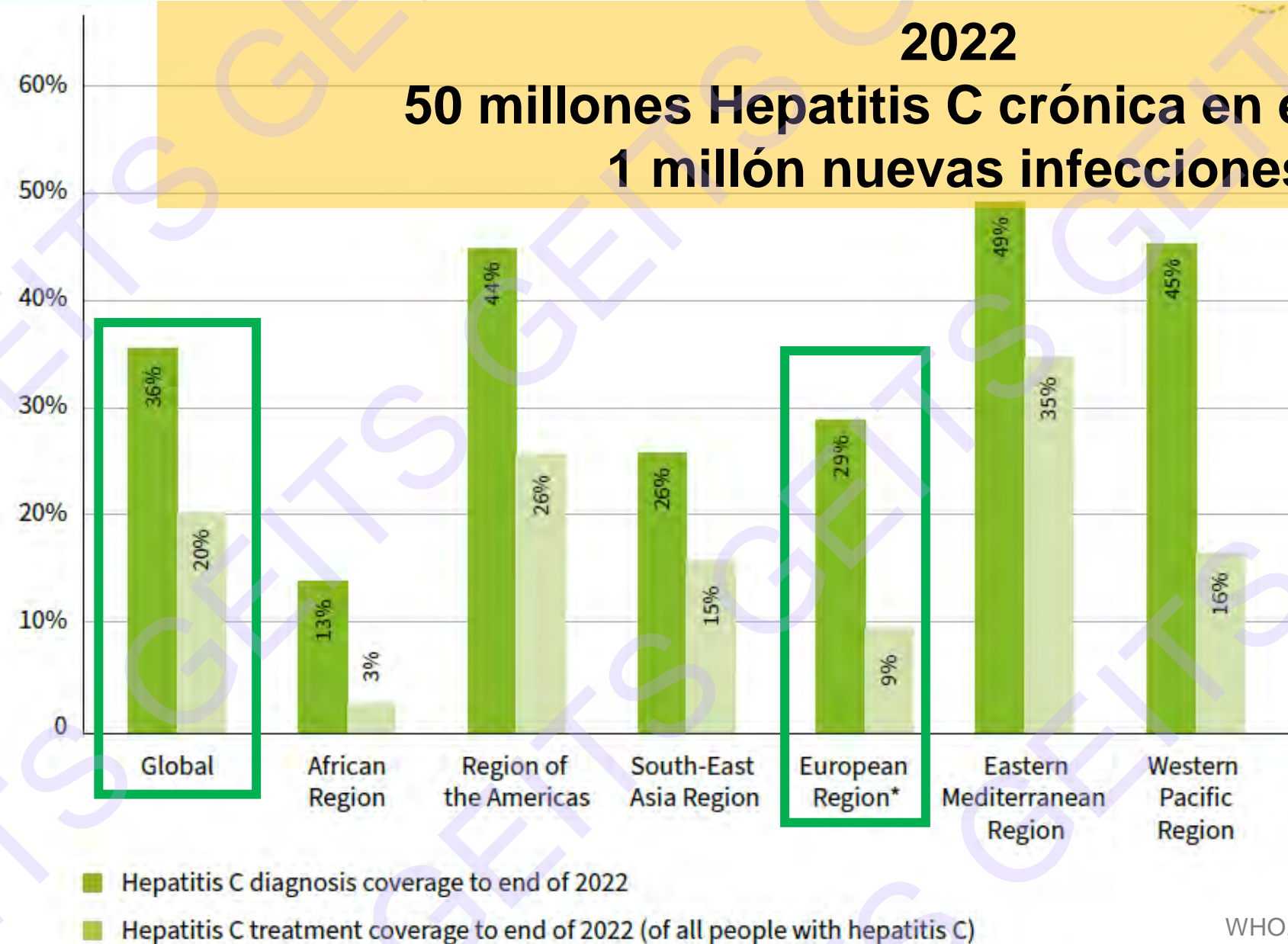
Figure 2: Countries accounting for 80% of the total viraemic HCV infections

HCV=hepatitis C virus.

Estudios globales prevalencia VHC – Data Quality



Coverage of hepatitis C testing and treatment by WHO region, 2022



Impacto del genotipo/subtipo en el tratamiento

- **8 genotipos (>100 subtipos)**
 - Genotipo: 31-33% diferencias nt
 - Subtipo: 20-25% diferencias nt
- Alta tasa de replicación y alta tasa de mutación
- Mutaciones virales espontáneas:
 - Presión Sistema Inmune
 - Presión DAA
 - **Cuasiespecies**



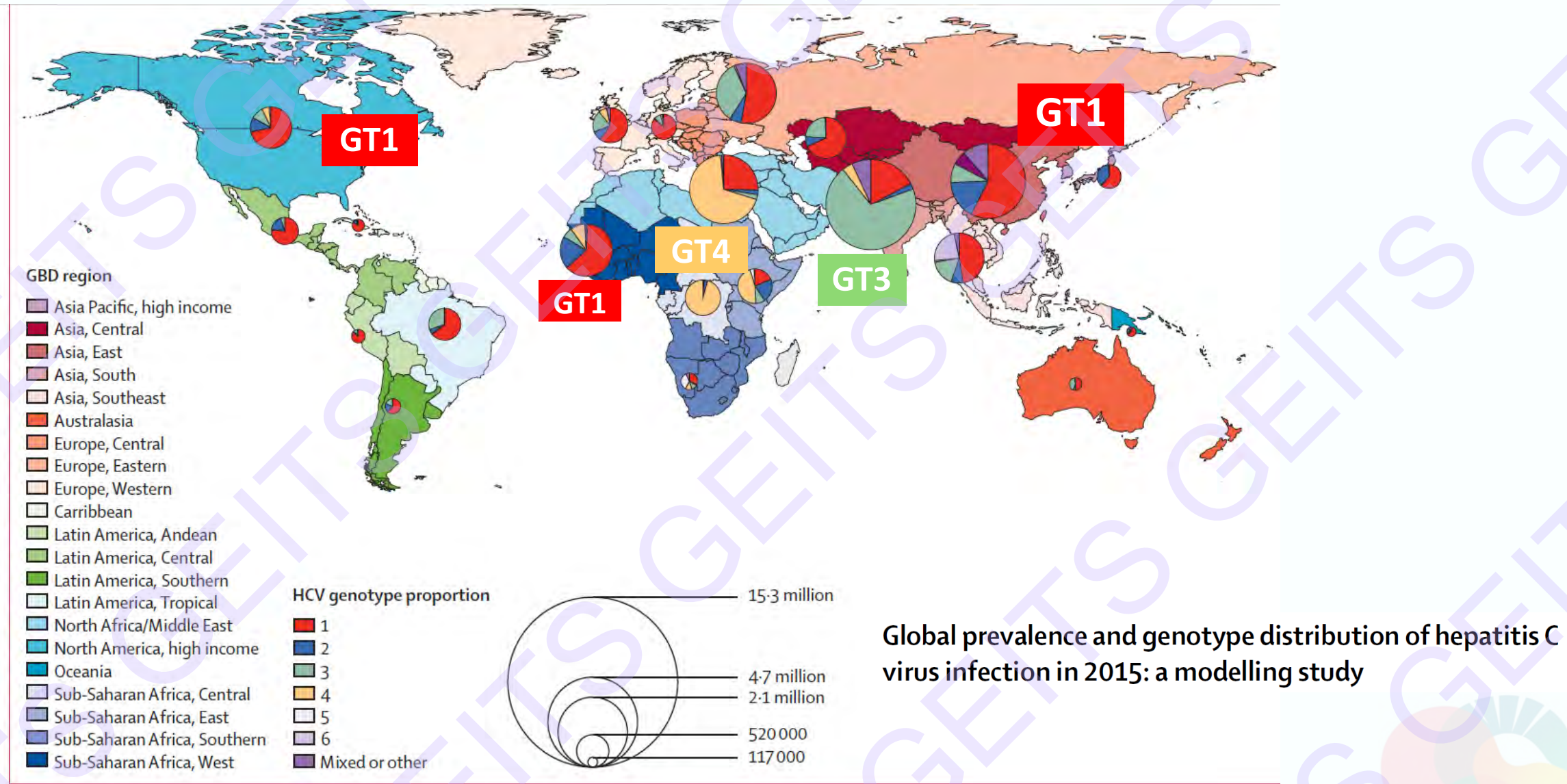
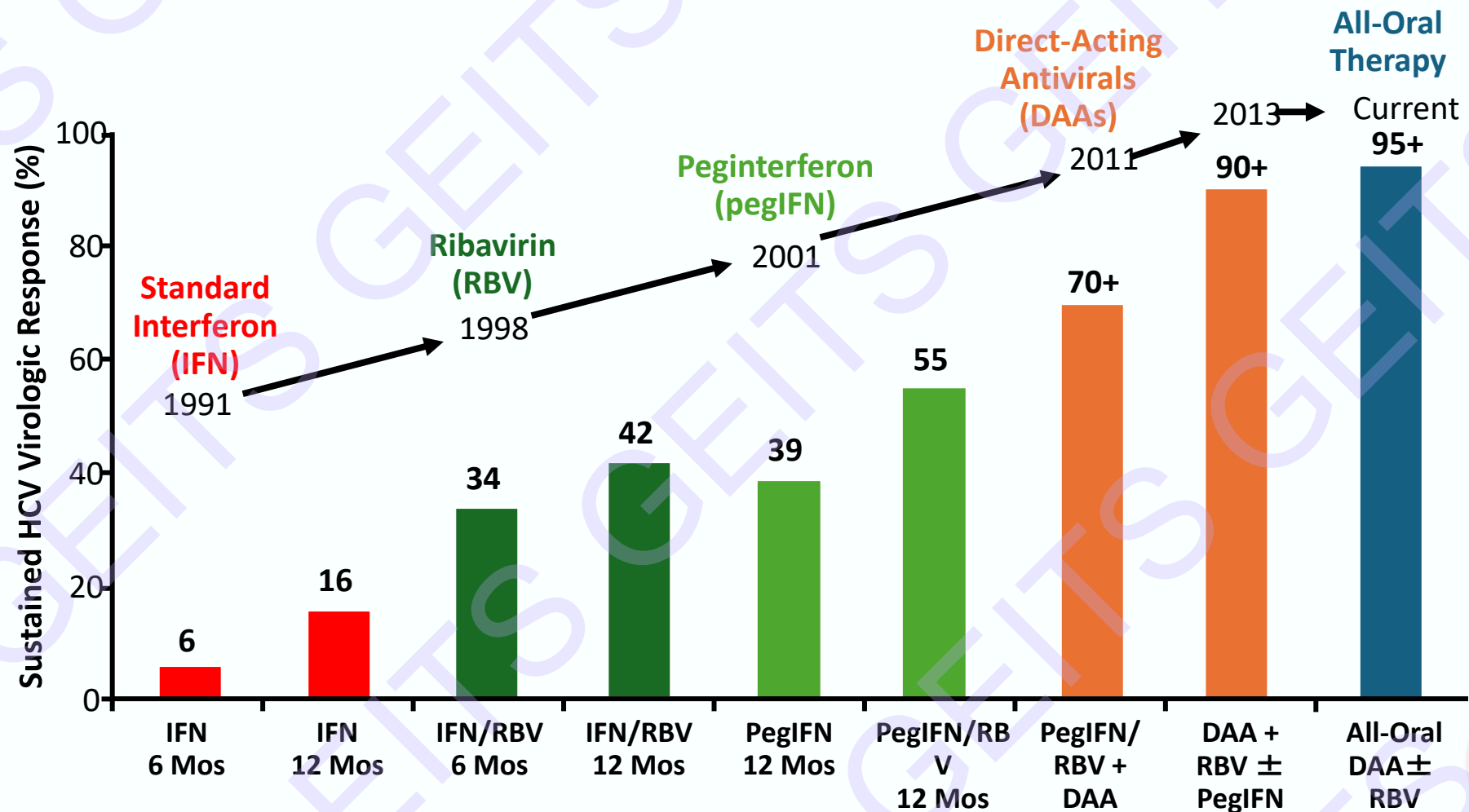


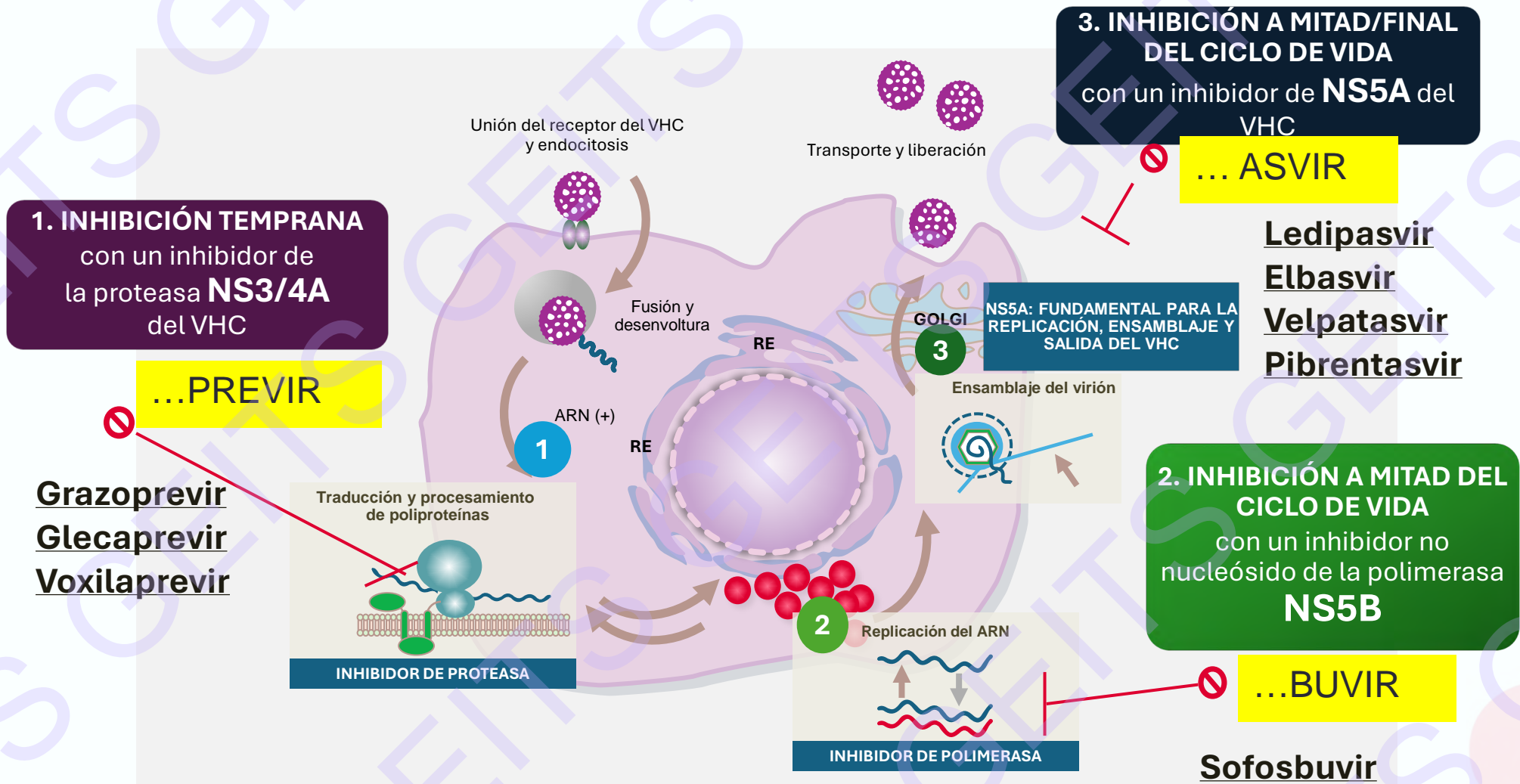
Figure 4: Genotype distribution

By GBD region (A) and HCV genotype and total infected by GBD region (B). GBD=Global Burden of Disease.

Eficacia creciente de los tratamientos frente al VHC



Dianas terapéuticas del ciclo de replicación del VHC



Are all RAS the same? Are all DRUGS the same?

Fold-change	1a				1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
LDV	20x	>100x	>100x/ >100x	>1,000x/ >10,000		>100x/--
Ombitasvir	>1000x	>100x	<3x	>10,000x/ >10,000x	<10x	20x/50x
			>100x			
DCV	>100x	>1000x	>100x/ >1000x	>1,000x/ >10,000x	<10x	20x/50x
Elbasvir	20x	>100x	>10x	>1,000x/ >1,000x	<10x	>100x/--
			>100x			
Velpatasvir	<10x	<3x	20x/50x	>100x/ >1000x		<3x/--
ACH-3102	30x	20x	<10x	>100x/>100x		<3x/<3x
Pibrentasvir	<3x	<3x	<3x	<10x/<10x	<3x	<3x/<3x
MK-8408	<10x	<10x	<10x	<10x	<10x	<10x

Characteristics of HCV resistance in an international cohort after a decade of direct-acting antivirals



Patients and Methods

3355 HCV patients from 22 countries

- 40% >F3 fibrosis
- GT1a (34%), GT1b (25%), GT2 (3%), GT3 (30%), GT4 (7%), GT5/6 (<1%)

Most patients were treated with the first generation DAAs

- NS5AI+NI (59%), NS5AI+PI (22%), PI+NI (4%), NS5AI+PI+NI/NNI (11%)

37% sustained viral response, 63% virologic failure

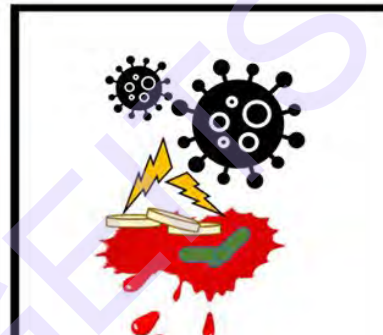
6994 HCV NS3, NS5A, NS5B sequences linked with metadata

- 41% baseline, 59% follow-up

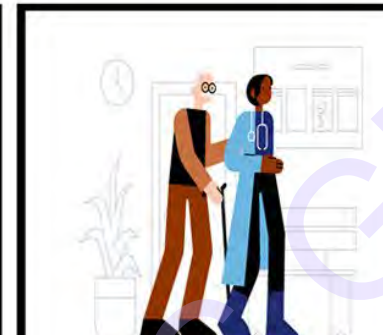
Characteristics of Resistance-associated Substitutions (RAS) After Treatment Failure



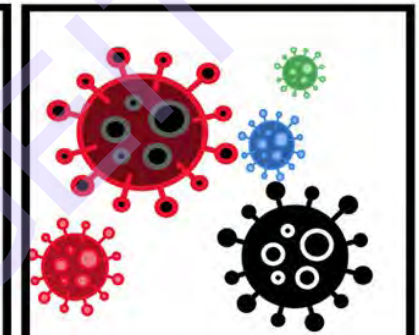
The prevalences of RAS in drug-target genes increase compared to their natural frequencies



Multi-drug resistance is common
94% harbor drug resistance; 63% against ≥2 drug classes



Resistance selection is more frequent in older patients with cirrhosis and those infected with GT1b/4



New variants with complex RASs continue to emerge

Drug resistance in HCV is frequent after failing DAAs. A collaborative effort is required to safeguard HCV global elimination

SHARED

Surveillance of Hepatitis C Antiviral Resistance, Epidemiology and methoDologies

SHARED: <https://hcvdb.med.ubc.ca>

@HCVShared

Characteristics of HCV resistance in an international cohort after a decade of direct-acting antivirals

- 22 countries
- N=3355 HCV patients
- N=730 DAA failures
- Most treated with 1st-gen DAA
- RAS Frequency increased after DAA exposure
 - NS3: 37% to 60%
 - **NS5A: 29% to 80%**
 - NS5B: 15% to 22%

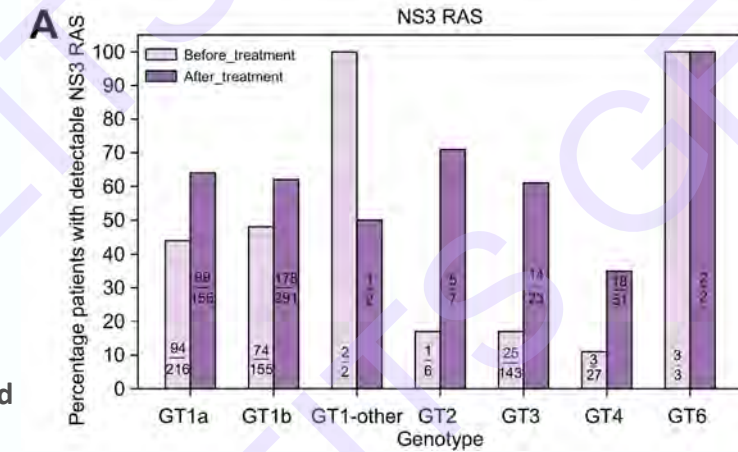
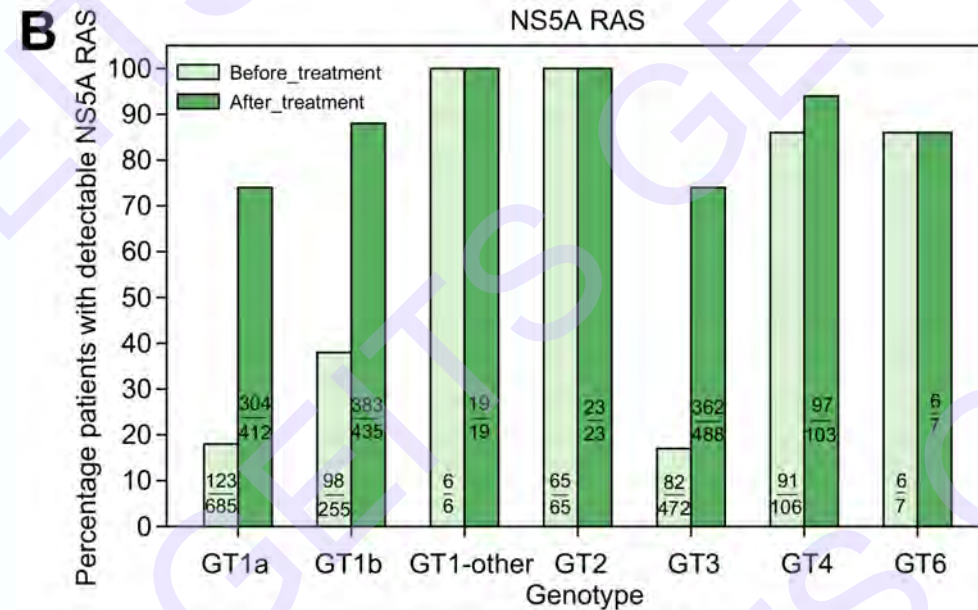
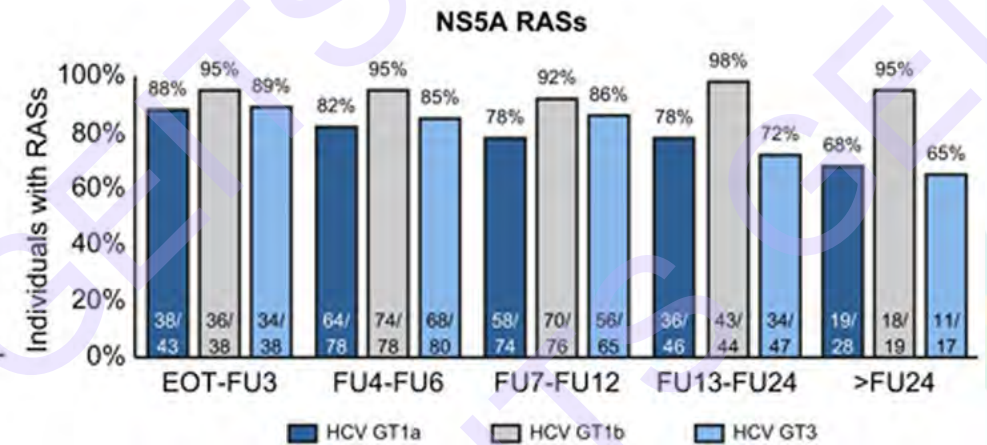
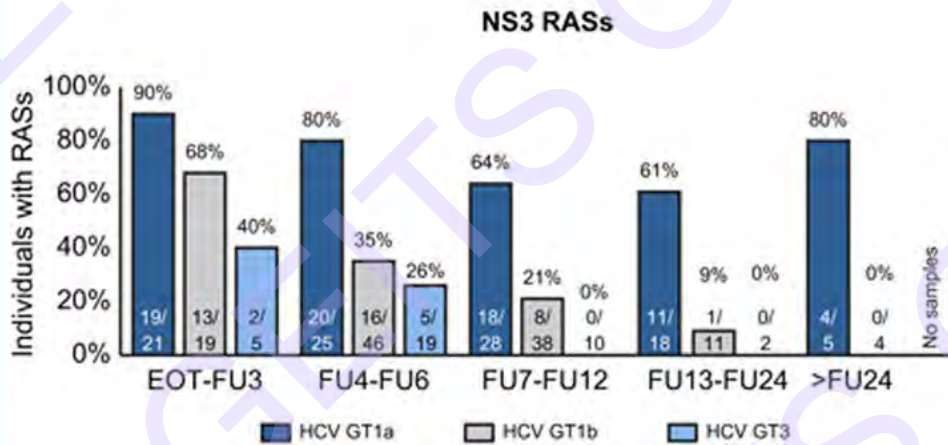
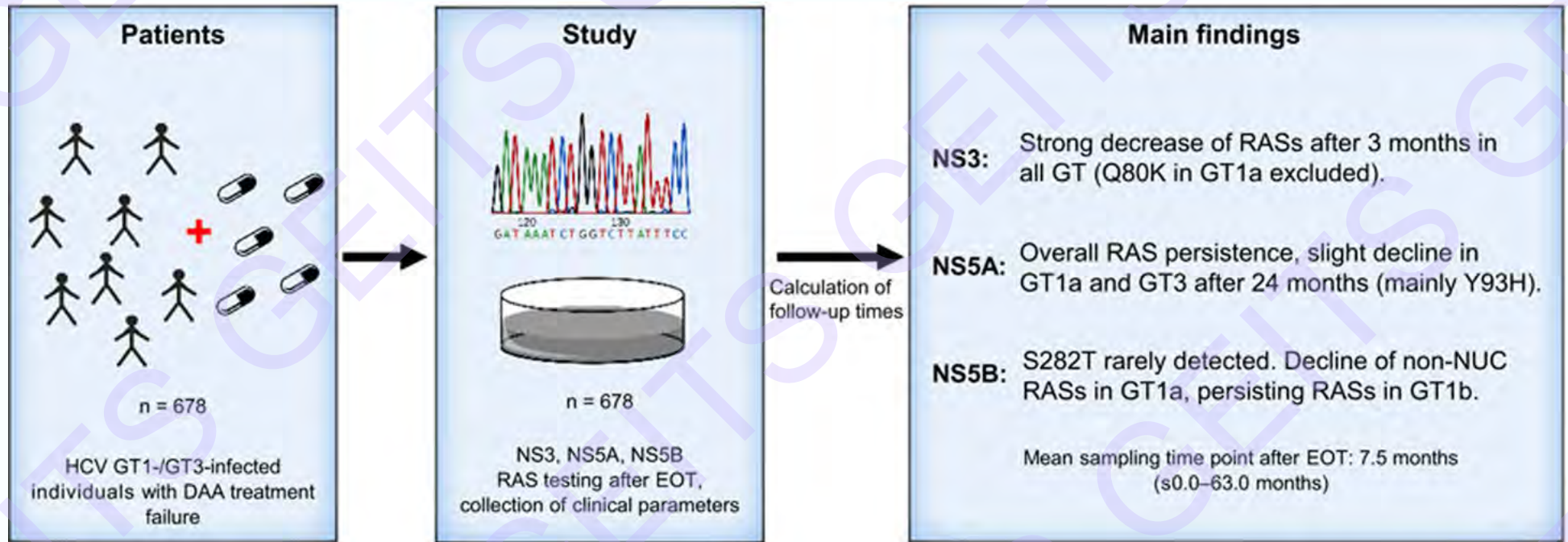


Fig. 1 Prevalence of resistance-associated substitutions in DAA-naïve and -experienced patients with HCV.



Long-term persistence of HCV resistance-associated substitutions after DAA treatment failure



Characteristics of hepatitis C virus resistance in an international cohort after a decade of direct-acting antivirals

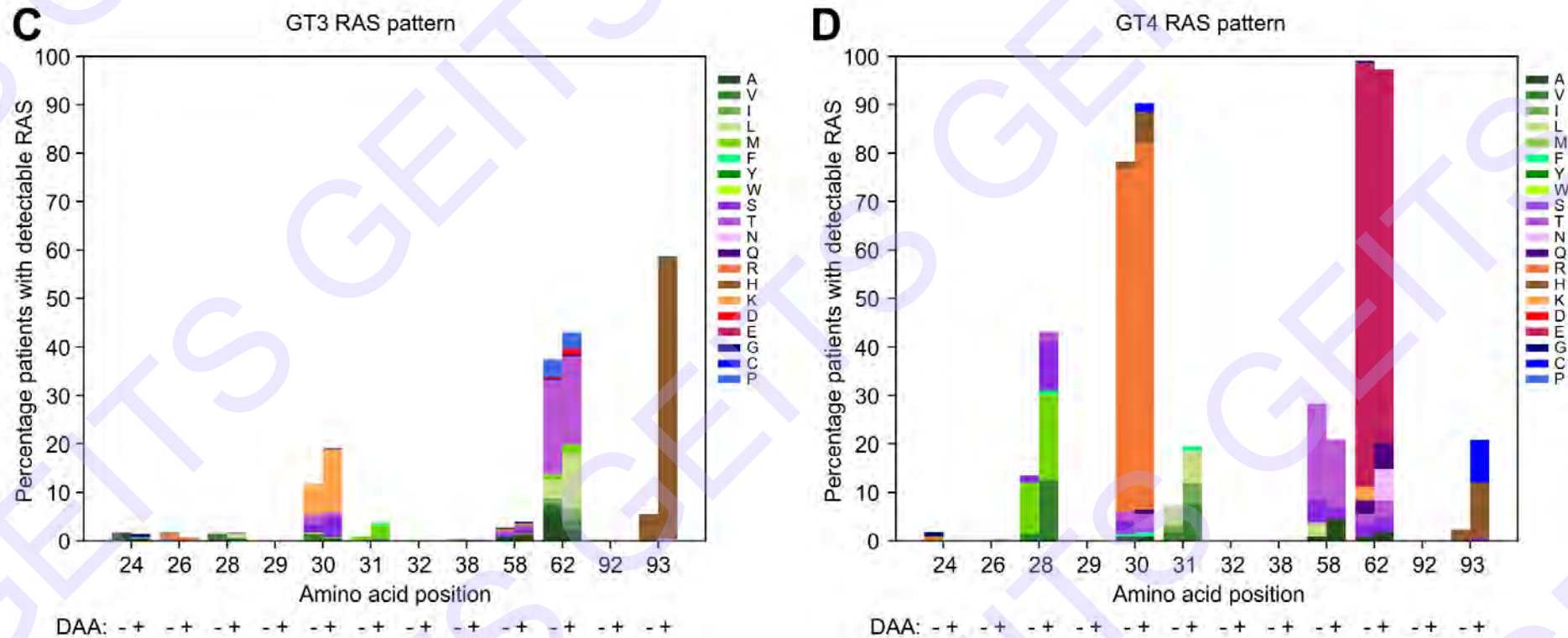
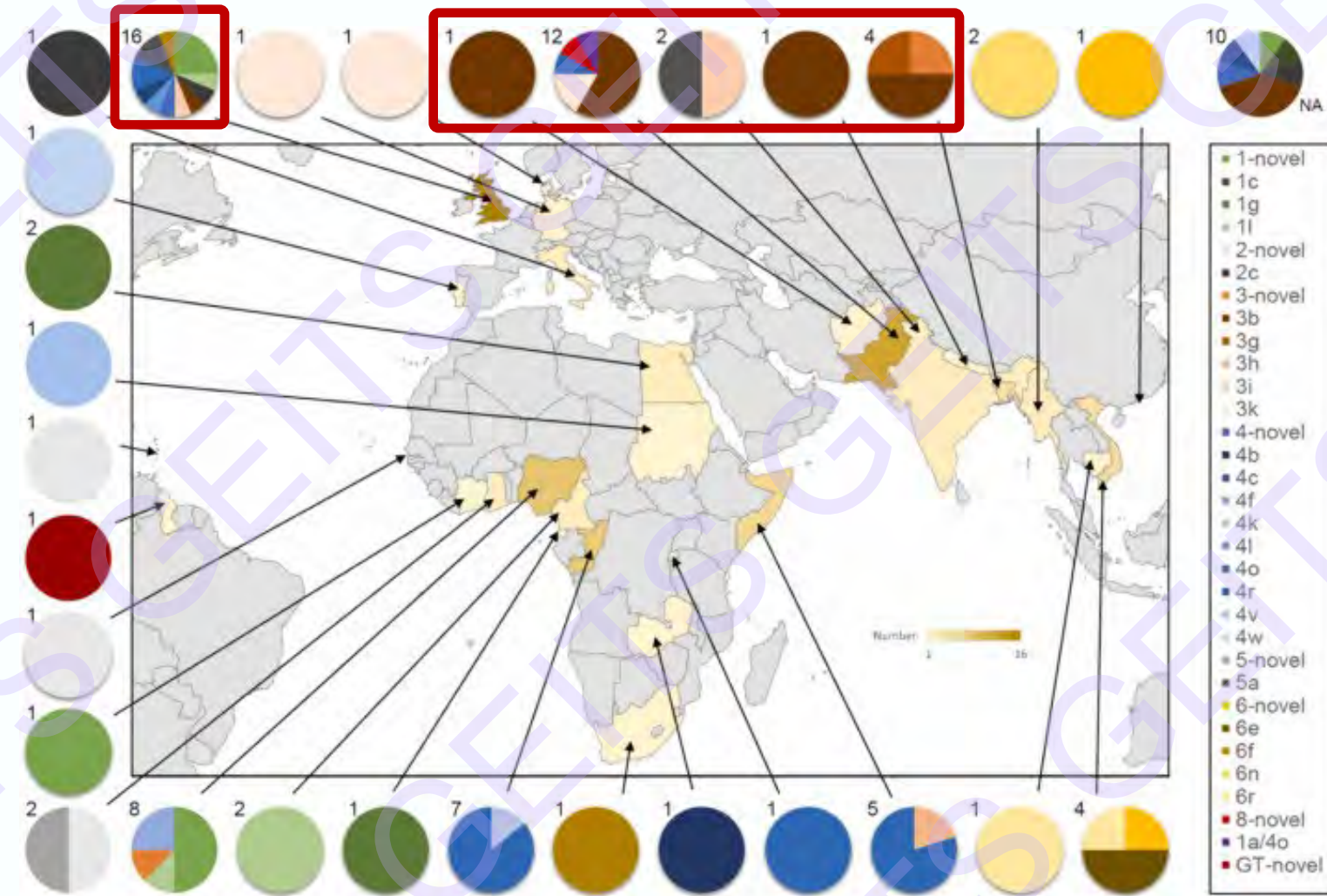


Fig. 3 NS5A resistance patterns in different genotypes.

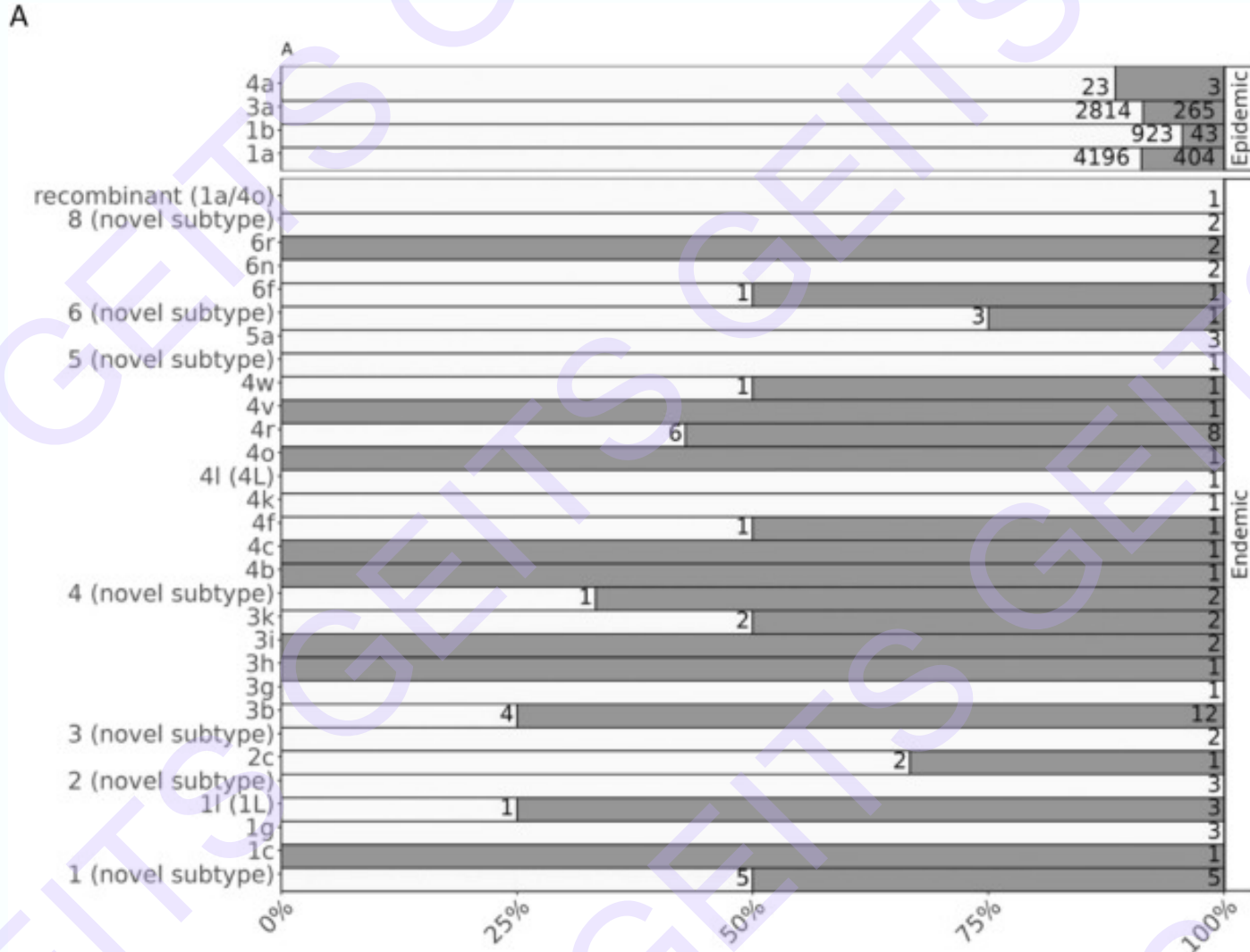
- **Older age** (>64) (aOR 1.95, 95% CI 1.21–3.19; $p = 0.01$), **cirrhosis** (aOR 1.80, 95% CI 1.18–2.76; $p = 0.01$), **GT1b** (aOR 1.77, 95% CI 1.15–2.75; $p = 0.01$) and **GT4** (aOR 10.20, 95% CI 3.52–29.56; $p < 0.001$) infections (compared to GT1a infections) were positively and independently associated with the presence of NS5A RASs post-treatment

Direct-acting antiviral treatment outcomes in people infected with endemic compared to epidemic HCV subtypes in England

- 2019-2023 (n=11024) (non-SVR12: 762)
- SVR12:
 - 92% Epidemic subtypes (1a/1b/3a/4a)
 - **49% Endemic subtypes (GT1/3b/4r/6f)**
 - **aOR 0.07 (95%CI 0.04–0.12)**
- Birth region (endemic)
 - 40% Africa
 - 32% Asia
 - **25% Europe (20% UK)**



Direct-acting antiviral treatment outcomes in people infected with endemic compared to epidemic HCV subtypes in England

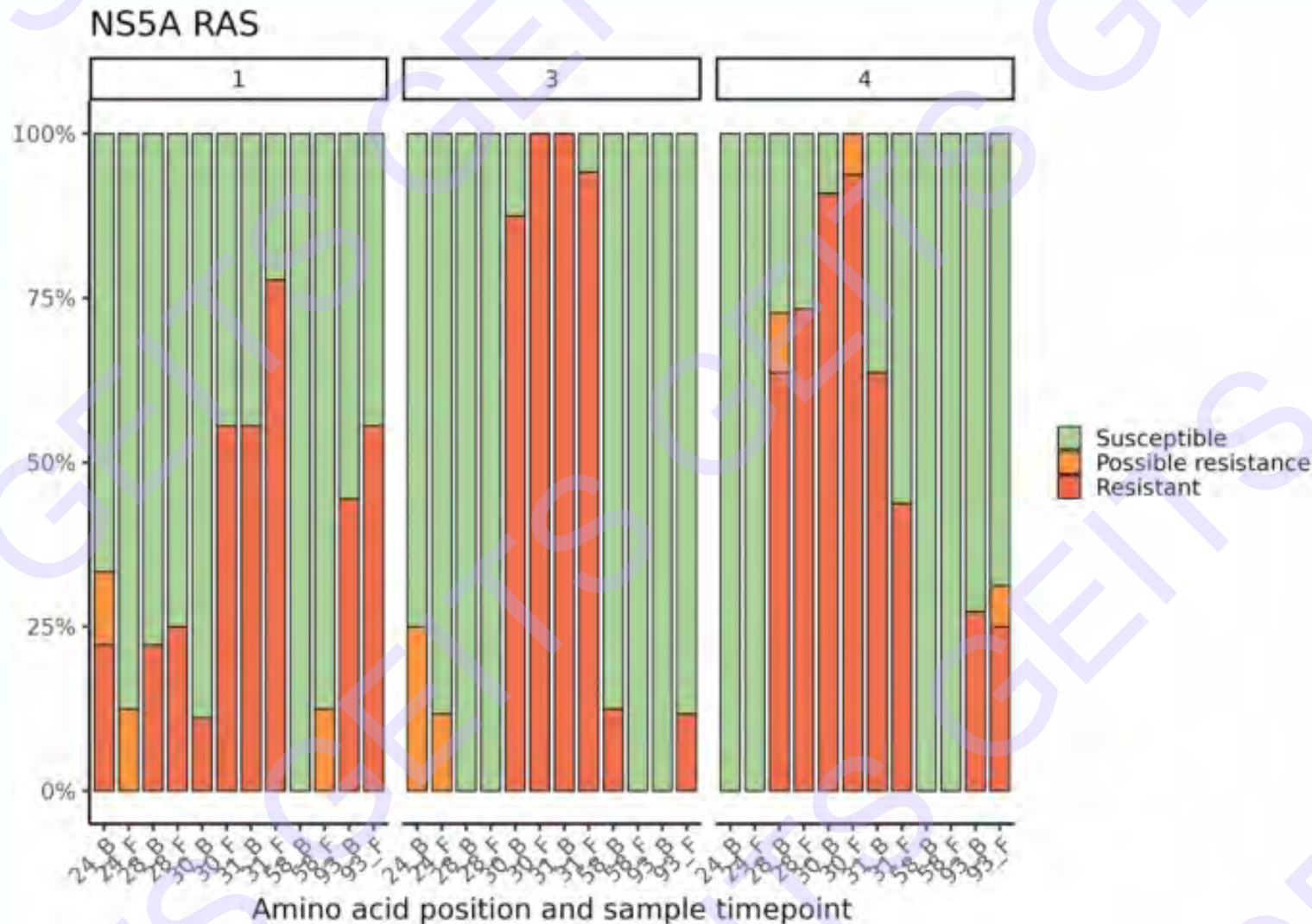


2nd gen DAA (**SOF/VEL** or **GLE/PIB**):

- 99%: GT1,2,4,5
- **27%: GT3 (25% 3b)**

Baseline: 2-3 NS5A RAS

SOF/VEL/VOX cured **89%** individuals with **subtype 3b** (Pakistan, Bangladesh, Nepal or Afghanistan)



- **Subtype 4r: 43-67% SVR**
- NS5A: 28V+30R+31V+93C
- Failure SOF/VEL/VOX
- **GT1 (non-1a/1b): 47-100% SVR**
- NS5A RAS increased after failure at positions 30, 31 and 93.

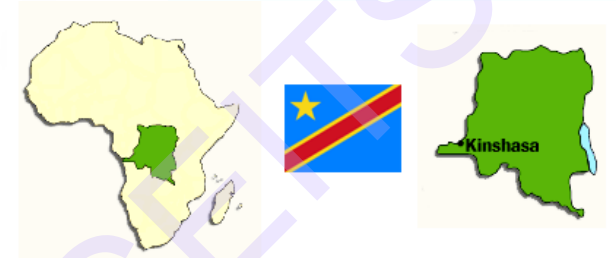
Case-finding of people with endemic subtypes and linkage to treatment services should be prioritised to avoid the possibility for treatment-resistant subtypes bridging into high-risk transmission networks



Article

HCV Diagnosis and Sequencing Using Dried Blood Spots from Patients in Kinshasa (DRC): A Tool to Achieve WHO 2030 Targets

Teresa Carrasco ¹, David Barquín ¹, Adolphe Ndarabu ², Mirian Fernández-Alonso ^{1,3,4}, Marina Rubio-Garrido ⁵, Silvia Carlos ^{3,4,6}, Benit Makonda ², África Holguín ⁵ and Gabriel Reina ^{1,3,4,*}



¹ Microbiology Department, Clínica Universidad de Navarra, 31008 Pamplona, Spain; mcarrasco.4@alumni.unav.es (T.C.); dbarquin@alumni.unav.es (D.B.); mferalon@unav.es (M.F.-A.)
² Department of Internal Medicine, Centre Hospitalier Monkole, Ngafani, Kinshasa 4484,

Table 4. Baseline amino acids found at the main RAS positions in NS5A region.

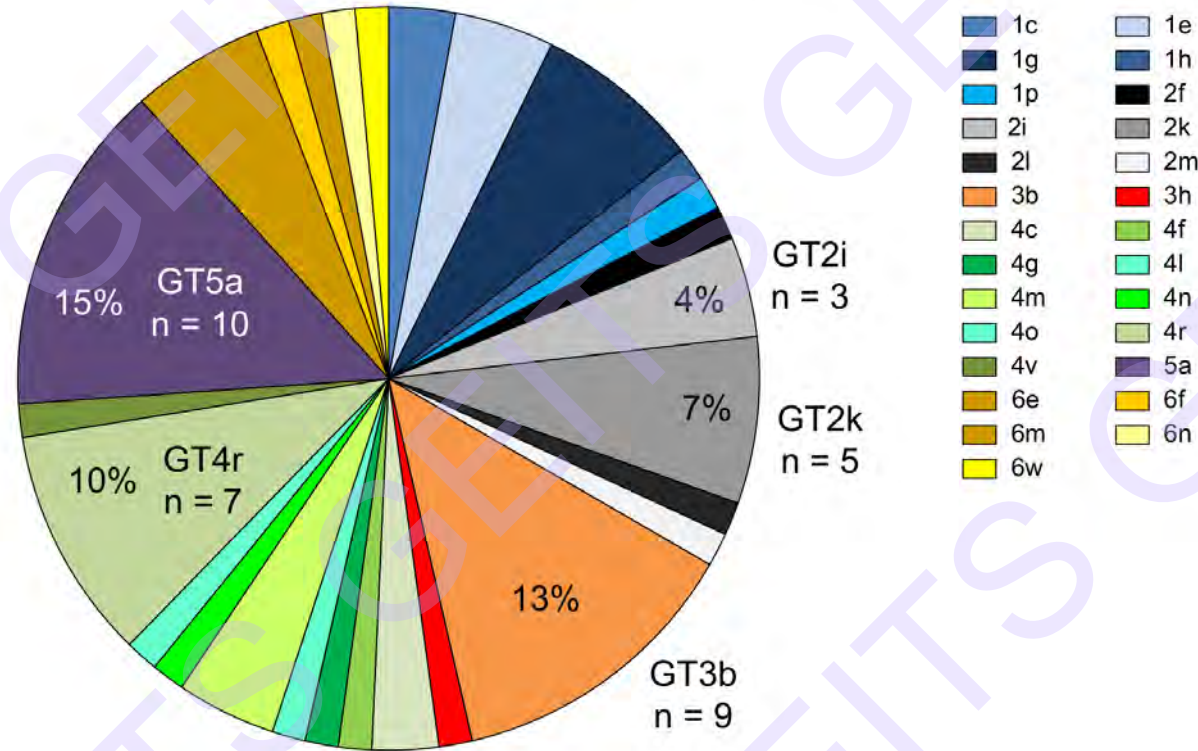
Subtype	Sample ID	NS5A RAS Codons				
		28	29	30	31	32
4r	CUN-8	V	P	R	L	P
4r	CUN-112	I	P	R	L	P
4r	CUN-319	I	P	R	L	P
4r	CUN-369	F	P	S	L	P
4c	CUN-26	L	P	R	M	P
4c	CUN-66	L	P	R	M	P
4c	CUN-285	L	P	R	M	P
4k	CUN-71	L	P	R	L	P

Note: Substitutions associated with reduced susceptibility to NS5A inhibitors are highlighted in bold.

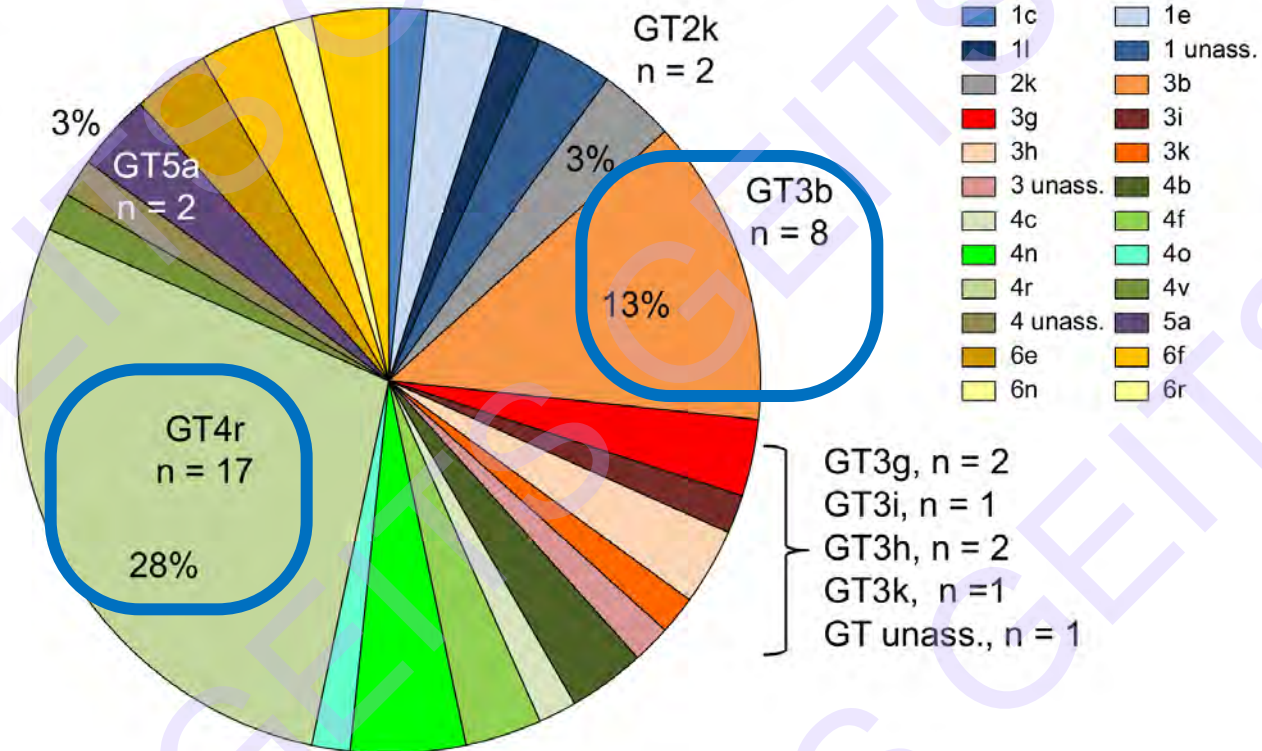
Citation: Carrasco, T.; Barquín, D.; Ndarabu, A.; Fernández-Alonso, M.; Rubio-Garrido, M.; Carlos, S.; Makonda, B.; Holguín, Á.; Reina, G. HCV Diagnosis and Sequencing Using Dried Blood Spots from Patients in Kinshasa (DRC): A Tool to Achieve WHO 2030 Targets. *Diagnostics* **2021**, *11*, 522. <https://>

Rare HCV subtypes and retreatment outcomes in a cohort of European DAA-experienced patients

A DAA-naïve patients (n = 69)

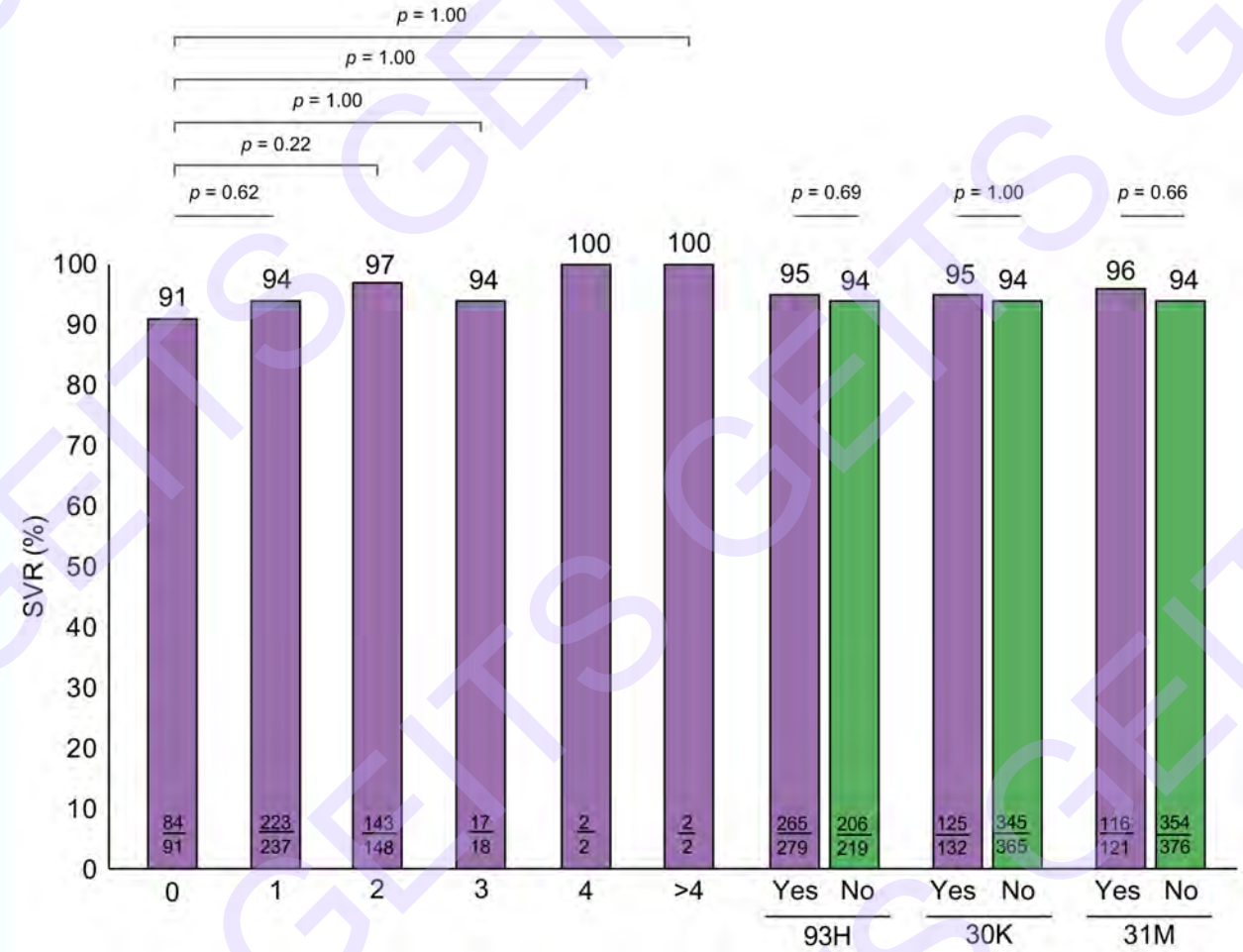


B DAA-failure patients (n = 60)

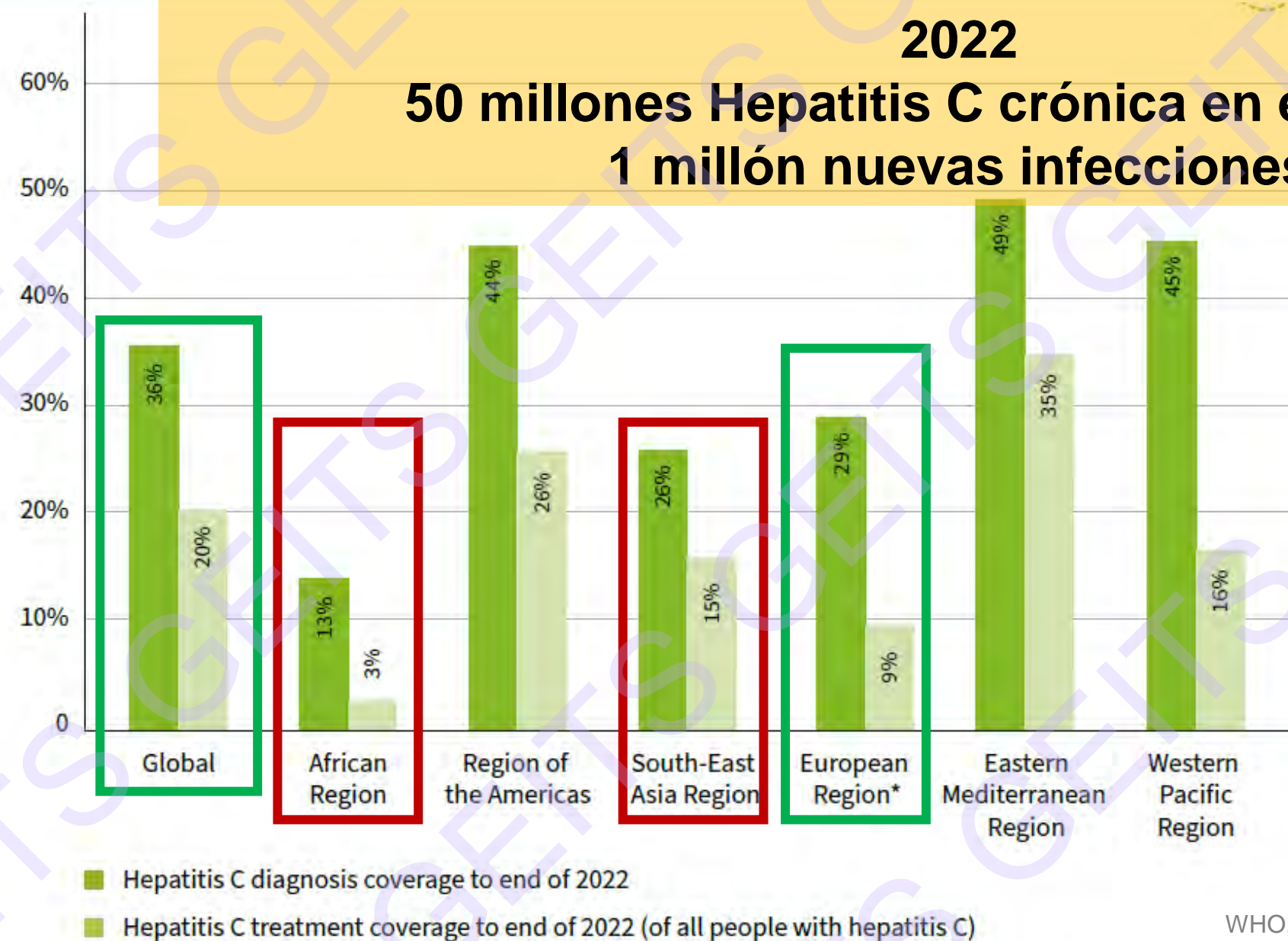


Real-world effectiveness of VOX/VEL/SOF in patients following DAA failure

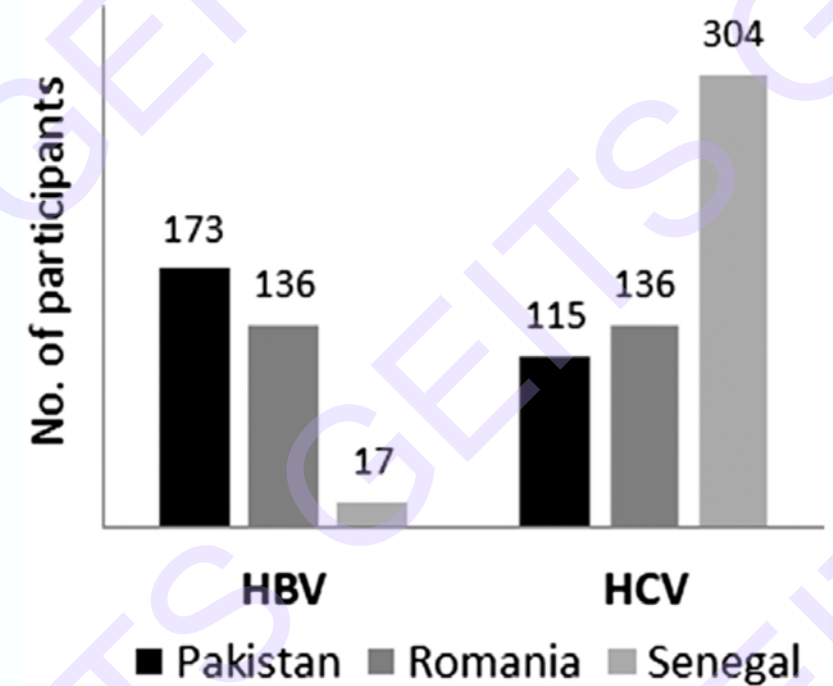
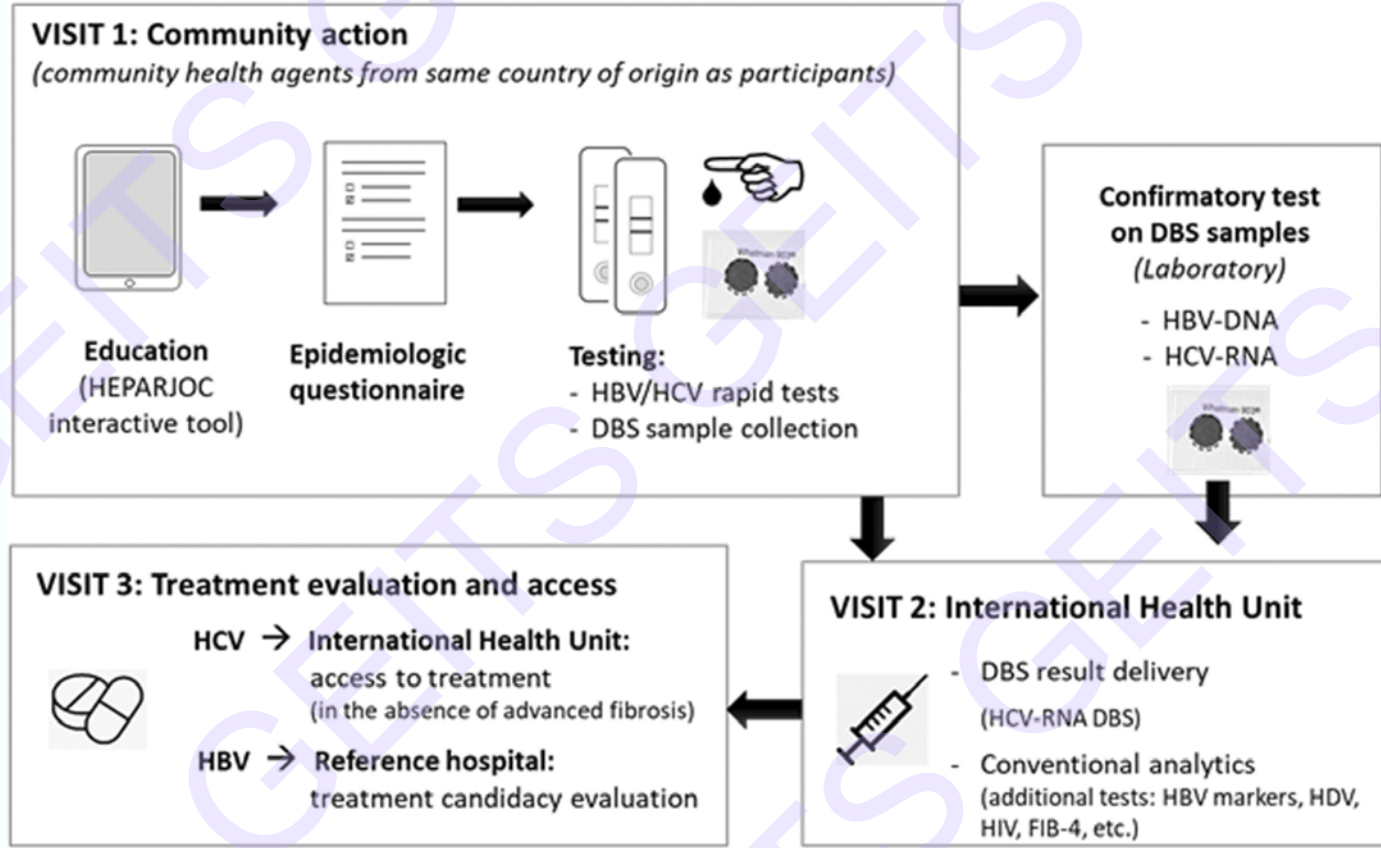
- **High effectiveness** of VOX/VEL/SOF
- **RASs** as well as **rare genotypes** and chimera **did not impact SVR** rates following VOX/VEL/SOF re-treatment
- **Cirrhosis, GT3 and HCC** onset were identified as independent **negative predictors** of treatment response to **VOX/VEL/SOF**



Coverage of hepatitis C testing and treatment by WHO region, 2022



Hepatitis B and C Screening and Linkage to Care in Migrants From Endemic Countries in Barcelona Through a Community Action



Novel **community action** successfully reached **migrants** in a situation of vulnerability and provided them **access to testing and care**

Resistencia a Antivirales: Hepatitis B/D

Take home messages

- **Entecavir** y, especialmente, **tenofovir** tienen una **alta barrera genética**, lo que hace que la aparición de resistencias sea excepcional en pacientes sin tratamientos previos.
- La **exposición previa** a análogos de nucleósidos de **baja barrera genética** (especialmente **lamivudina**) es el **principal factor de riesgo** para seleccionar mutaciones de resistencia en el VHB.
- **Nuevas terapias** frente al VHB (ASO/siRNA), como **bepirovirsen**, en combinación con los tratamientos actuales, muestran potencial para **incrementar significativamente la tasa de cura funcional**.
- **Hasta la fecha no se han documentado resistencias** clínicamente relevantes a **bulevirtide** en el tratamiento de la hepatitis delta (VHD).

Resistencia a Antivirales: Hepatitis C

Take home messages

- Los AAD pangenotípicos de segunda generación (**SOF/VEL, GLE/PIB**) ofrecen **eficacia** muy **elevada** en los **subtipos epidémicos** más comunes (**1a, 1b, 3a, 4a**).
- Existen **subtipos endémicos** (**no 1a/1b, 3b, 4r**) que presentan **mutaciones naturales de resistencia en NS5A**, por lo que se deben utilizar combinaciones de AAD frente a las tres dianas (NS3, NS5A y NS5B) para garantizar una respuesta óptima.
- Las **RAS** en **NS5A** pueden **persistir** durante **años**, condicionando la elección de regímenes en retratamientos.
- Es clave **diagnosticar y subtipar VHC** en pacientes procedentes de regiones con **subtipos “raros”** (**África subsahariana y el Sudeste asiático**), ya que puede influir en la selección del tratamiento.
- Ante **fallos terapéuticos**, es fundamental **monitorizar, caracterizar** el virus, y planificar un **rescate adecuado**, minimizando el riesgo de transmisión de variantes resistentes.

II Curso de Infecciones de Transmisión Sexual *ITS*



Muchas gracias

Resistencia a Antivirales: VHB/VHD y VHC

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