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IRD 198

Hépatite E et infection VIH

JNI 06/2011 – Toulouse

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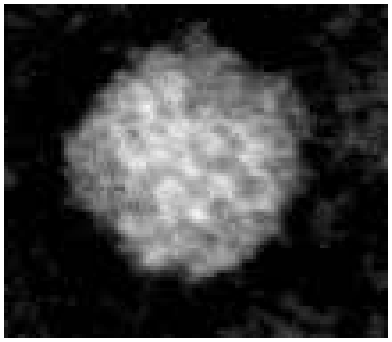

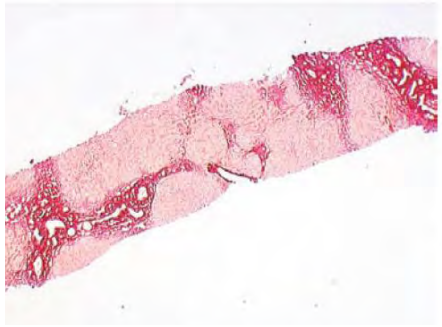

Plan

- Intérêt accru pour l'hépatite E chez les patients VIH+
- Anciennes études de séroprévalence (<2000)
- Cas rapportés d'hépatite E
- Etudes récentes de prévalence (>2008)
- Discussion/Conclusion

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- **Intérêt accru pour l'hépatite E chez les patients VIH+**
- Anciennes études de séroprévalence (<2000)
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Hepatitis E virus: An important pathogen in tropical and subtropical regions

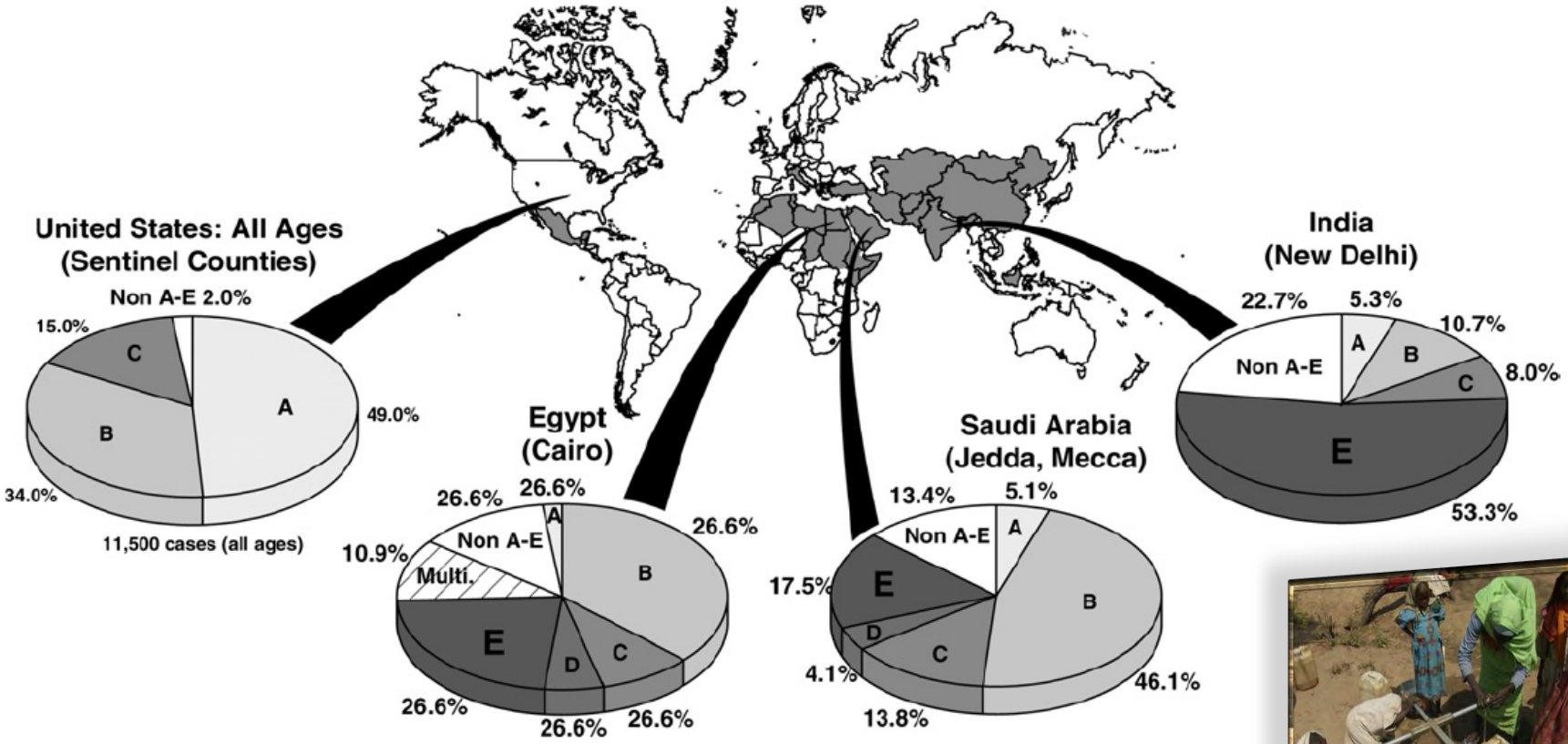
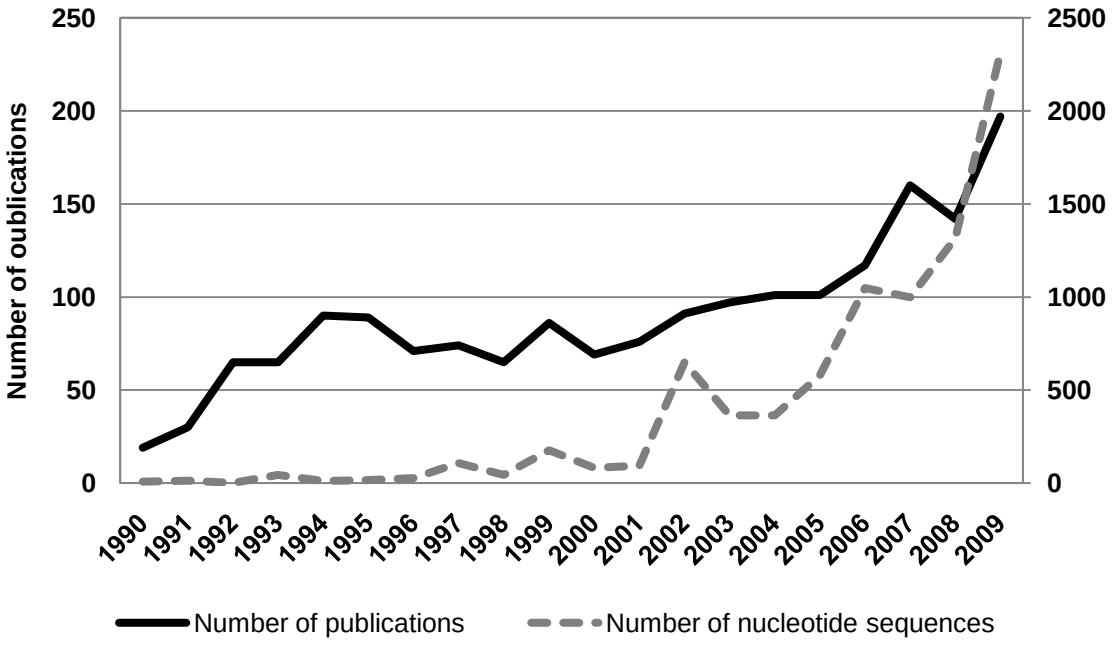
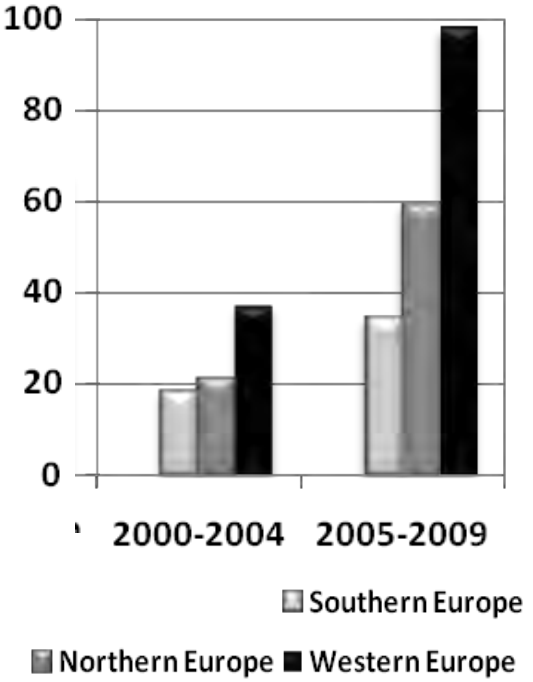


Fig. 1. Geographic distribution of clinically significant hepatitis E and relative importance of hepatitis E virus (HEV) in the etiology of clinical hepatitis among adults in selected regions [25–27].

Purcell RH, Emerson SU. J Hepatol 2008

HEV publications and published sequences





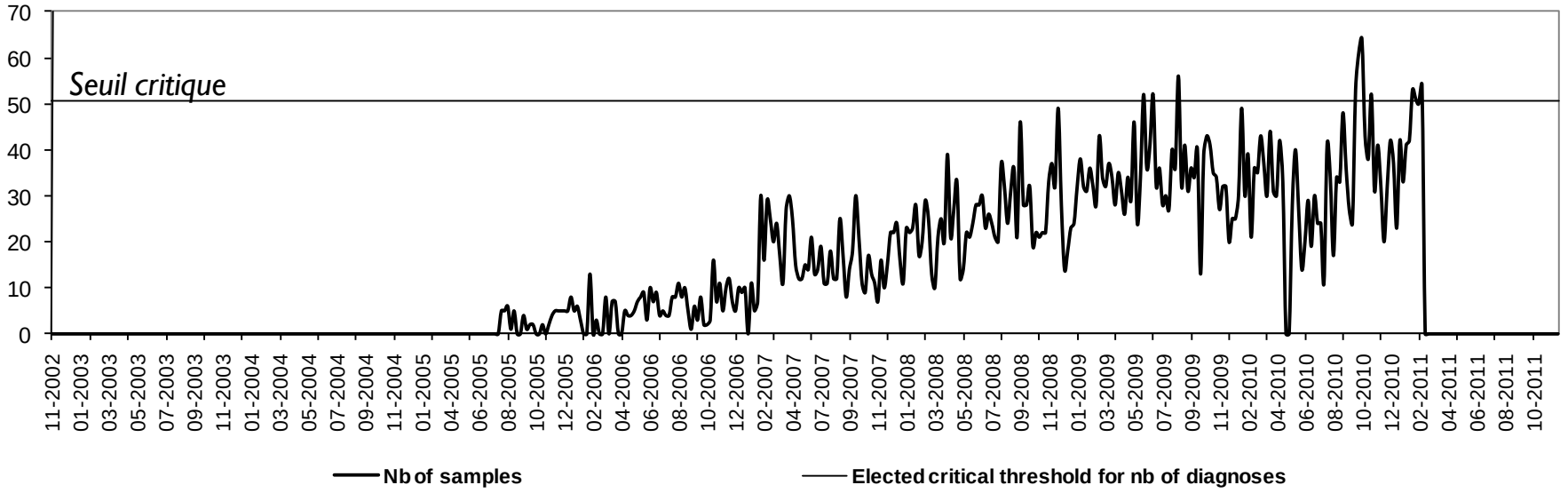
Hepatitis E is an emerging disease in developed industrialized countries

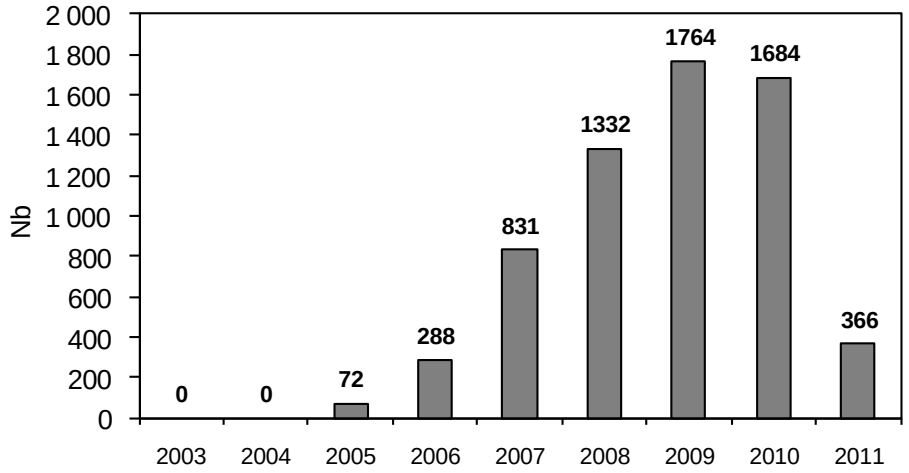
According to ISI web of science

Surveillance de l'hépatite E - EPIMIC

Pôle des Maladies Infectieuses et Tropicales Clinique et Biologique, Fédération de Bactériologie-Hygiène-Virologie, CHU Timone, AP-HM, Marseille

Demandes de sérologies VHE





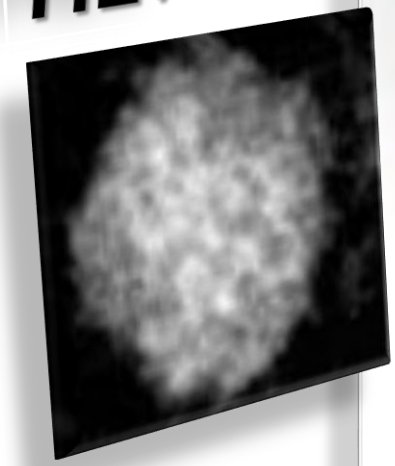
HEV has emerged as the leading identified cause of autochthonous acute hepatitis among adults in our clinical setting (public hospitals)

	Incidence		Cases with fatal outcome		Seroprevalence	
	Marseilles Timone Microbiology laboratory	France	Marseilles Timone Microbiology laboratory	France	Marseilles Timone Microbiology laboratory	France
HAV	**9** [a]	**6000**[c]	0 [a]	Unknown	56	~ 50
HBV	**4**	**600 (150)** [d]	2	1-2 [d]	1.9[e]	0.68 [f]
HDV	**1**	**Unknown**	0	Unknown	5-10 of HBsAg prev.	5-10 of HBsAg prev.
HCV	**3**	**~ 5000-10 000**	0	0 ?	5	0.89 [f]
HEV	**18** [b]	**Unknown (110 reported)**	1 [b]	<5 ?	~ 10 (8)	3-16

[a] Motte A, Borentain P, Minodier P, *et al.* Hepatology 2008;48(4):1185A
[b] Colson P, Moal V, Motte A, *et al.* Hepatology 2008;48(4):1185A
[c] Couturier E, Letort MJ, Roque AM, *et al.* BEH 29-30 / 17 juillet 2007 253
[d] Antona et al., BEH 51-52 / 25 décembre 2007:425
[e] Colson P, Richet H, Tamalet C. 44th annual meeting of the European Association for the Study of the Liver, 2009; abstr. A-158-0019-01580
[f] Meffre C, Le Strat Y, E Delarocque-Astagneau E, *et al.* 41st annual meeting of the European Association for the Study of the Liver, 2006, abstract 46.
http://www.invs.sante.fr/publications/2005/analyse_descriptive_140205

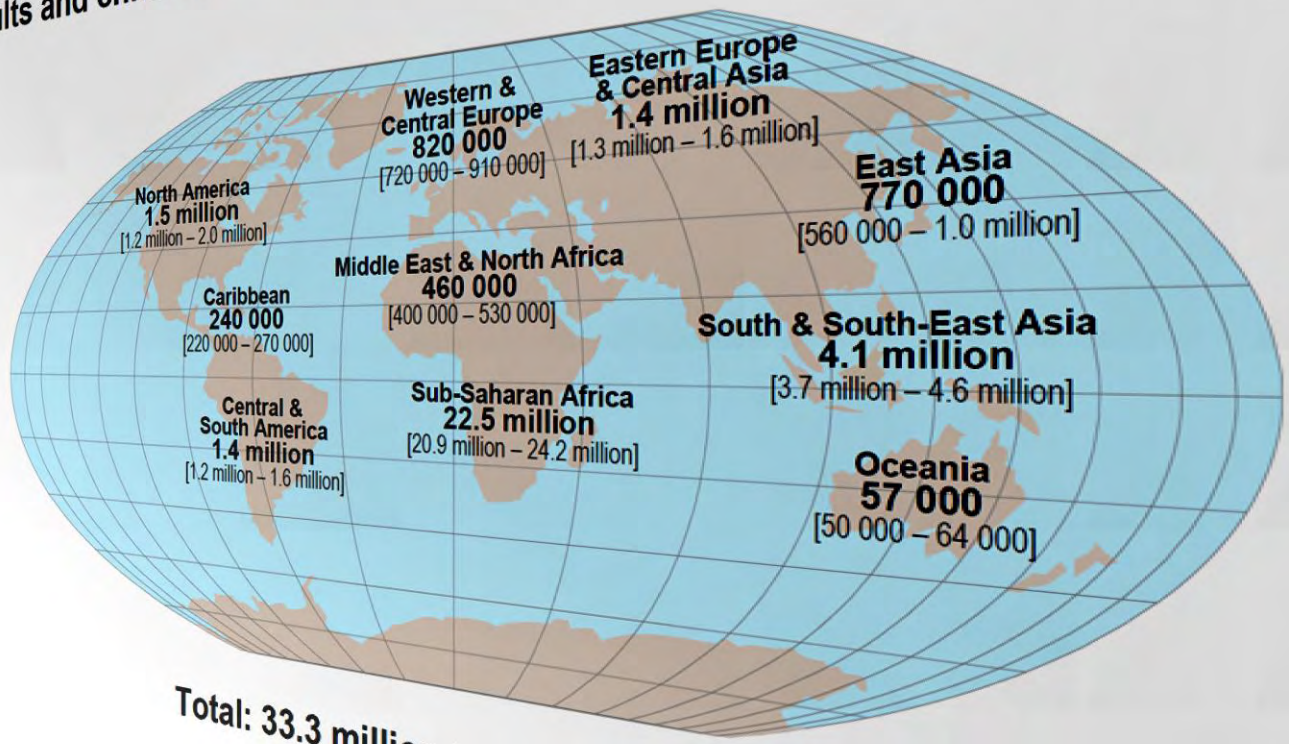
Colson P, Moal V, Motte A, *et al.,* EASL 2011; abstract A-343

HEV



GLOBAL REPORT

Adults and children estimated to be living with HIV | 2009



Total: 33.3 million [31.4 million – 35.3 million]

World Health Organization

UNAIDS

Fulminant liver failure from acute autochthonous hepatitis E in France: description of seven patients with acute hepatitis E and encephalopathy

Table 2 Characteristics of patients with acute sporadic hepatitis E: comparison of patients with (severe form) and without (mild form) encephalopathy

Variables	Severe form (encephalopathy) ($n = 7$)	Mild form (no encephalopathy) ($n = 33$)	Univariate analysis
Age (years)	65 ± 11	56 ± 18	NS
Sex (M/F)	5/2	25/8	NS
Active alcohol abuse >40 g/day (yes/no)	5/2	6/27	$P = 0.04$
Chronic liver disease (yes/no)	6/1	4/29	$P < 00005$
Length of hospitalization (days)	21 ± 18	6 ± 6	$P < 0.0005$
Death (yes/no)	5/2	0/33	$P < 0.0005$
Aspartate transaminase*	3181 ± 1512	1833 ± 1498	$P = 0.037$
Alanine transaminase*	3239 ± 2003	2498 ± 1855	NS
Alkaline phosphatase	430 ± 217	650 ± 410	NS
γGT	207 ± 118	408 ± 258	$P = 0.053$
Bilirubin	350 ± 218	134 ± 107	$P < 0.0005$
Prothrombin index (%)†	37 ± 16	78 ± 24	$P < 0.0005$
Accelerin (%)†	56 ± 24	112 ± 41	$P = 0.002$

Peron JM, Bureau C, Poirson H, *et al.*, J Viral Hepatitis, 2007

Locally acquired hepatitis E in chronic liver disease

Age and sex	Clinical details	Bilirubin (µmol/L)	ALT (U/L)	AP (U/L)	Albumin (g/L)	INR	HEV IgM	Rising HEV IgG	HEV PCR	Liver biopsy	Outcome
70M	Jaundice, malaise, anorexia	314	1761	173	33	1·6	+	+	–	Idiopathic fibrosis	Encephalopathy: recovered
59M	Jaundice, fever, malaise	160	1381	188	32	1·3	+	+	+*	Alcoholic cirrhosis	Liver failure: died week 18
76M	Jaundice, abdominal pain	86	2286	128	34	1·7	–	+	–	Alcoholic cirrhosis	Liver failure: died week 24

ALT=alanine aminotransferase, AP=alkaline phosphatase, INR=international normalised ratio. Laboratory values are those at presentation. Hepatitis E case definition: ALT >500 U/L and HEV IgM positive, or a rising HEV IgG or HEV PCR positive.[3] *Viral sequencing showed this to be HEV genotype 3.

Table: **Clinical details and laboratory findings in three patients with locally acquired hepatitis E and underlying cirrhosis**

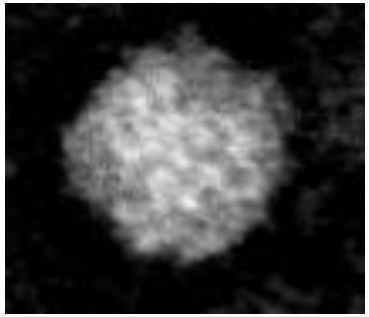
Dalton HR, Hazeldine S, Banks M, *et al.* Lancet 2007;369:1260

Prevalence of liver disease in persons infected with HIV [Sulkowski, J Hepatol 2008]

- **HCV co-infection:** varies depending on the route of HIV transmission:
  - 10% to 14% among persons reporting high-risk sexual exposure
  - ~85–90% among those reporting IDU [Sulkowski, Ann Intern Med 2003]. In the United States and Europe, 33% of all HIV-infected persons are HCV infected [Sulkowski, JAMA 2002; Sherman et al., 2002; Rockstroh et al., 2003]
- **HBV co-infection:**
  - Prior HBV infection in approximately 90% of HIV-infected persons
  - Chronic HBV infection in ~5–15% of HIV-infected persons globally [Thio et al., 20003].
- **Antiretroviral Therapy:**
  - has been associated with hepatic injury (e.g., hepatocellular necrosis and steatosis) [Sulkowski, JAMA 2000].
  - In a cohort of 23,441 HIVinfected patients, Weber et al. observed an increased risk of liver-related mortality with longer ART exposure [2006].

Sulkowski, J Hepatol 2008; Sulkowski, JAMA 2000, 2002; Weber et al., Archiv Intern Med 2006; Sulkowski, Ann Intern Med 2003; Sulkowski, AIDS 2005; Maid et al., J AIDS 2006; Thi et al., Semin Liv Dis 2003; Sherman et al., Clin Infect Dis 2002; Rockstroh et al., J Infect Dis 2003;

Specific risks for HEV infection in persons infected with HEV ?



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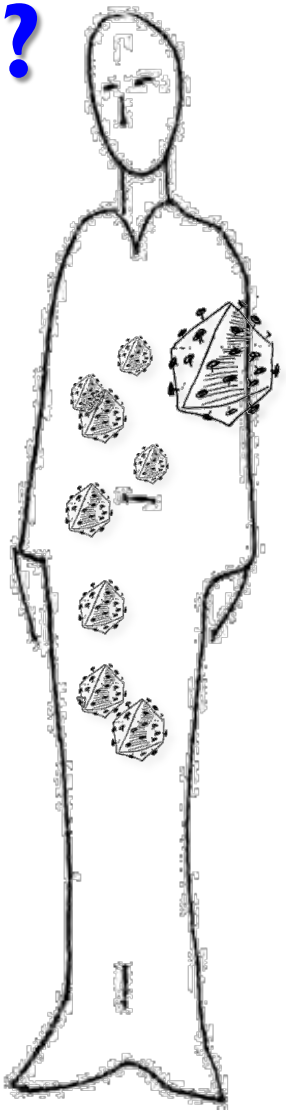


HIV-infected persons

Hepatitis E virus as a newly identified cause of acute viral hepatitis during HIV infection

Table 1. Evolution of biochemical, haematological and virological markers

Marker	Date				
	6 June 2007	18 June 2007	6 July 2007	17 September 2007	22 January 2008
Alanine aminotransferase (IU/L)	29	15	10	813	10
Aspartate aminotransferase (IU/L)	22	19	17	714	22
γ- Glutamyl transferase (IU/L)	73	43	34	778	26
Bilirubinaemia (μmol/L)	11	6	11	31	60
Alkaline phosphatase (IU/L)	90	82	51	204	71
Prothrombin index (%)	100	100	100	100	–
Platelet count (per mm^3)	181	304	258	212	–
Lymphocyte T-CD4 cell count (per mm^3)	462	248	231	246	–
HEV RNA in serum[a]	Negative	–	–	Positive	Negative
Anti-HEV IgG antibodies[a]	Negative	–	Negative	Negative	Positive
Optical density ratio[b]	<0.9	–	<0.9	<0.9	3.6
Anti-HEV IgM antibodies[a]	Negative	–	Negative	Positive	Positive
Optical density ratio[b]	<0.9	–	<0.9	10.0	7.7
HBV serology	–	–	–	Negative	–
HBV DNA in serum (IU/mL)	–	–	–	Negative	–
Anti-HCV antibodies	–	–	–	Negative	–
HCV RNA in serum (IU/mL)	–	–	–	Negative	–
HIV-1 RNA in serum (copies/mL)	<40	87 366	489 543	829	<40
Antiretroviral therapy	Interruption of treatment that included ABC, TDF, fosAPV, and RTV[c]	None	Re-introduction of treatment that included ABC, TDF, ATV, and RTV	ABC, TDF, ATV, RTV	ABC, TDF, ATV, RTV

–, Not available; HEV, hepatitis E virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ABC, abacavir; TDF, tenofovir; fosAPV, fosamprenavir; RTV, ritonavir; ATV, atazanavir.

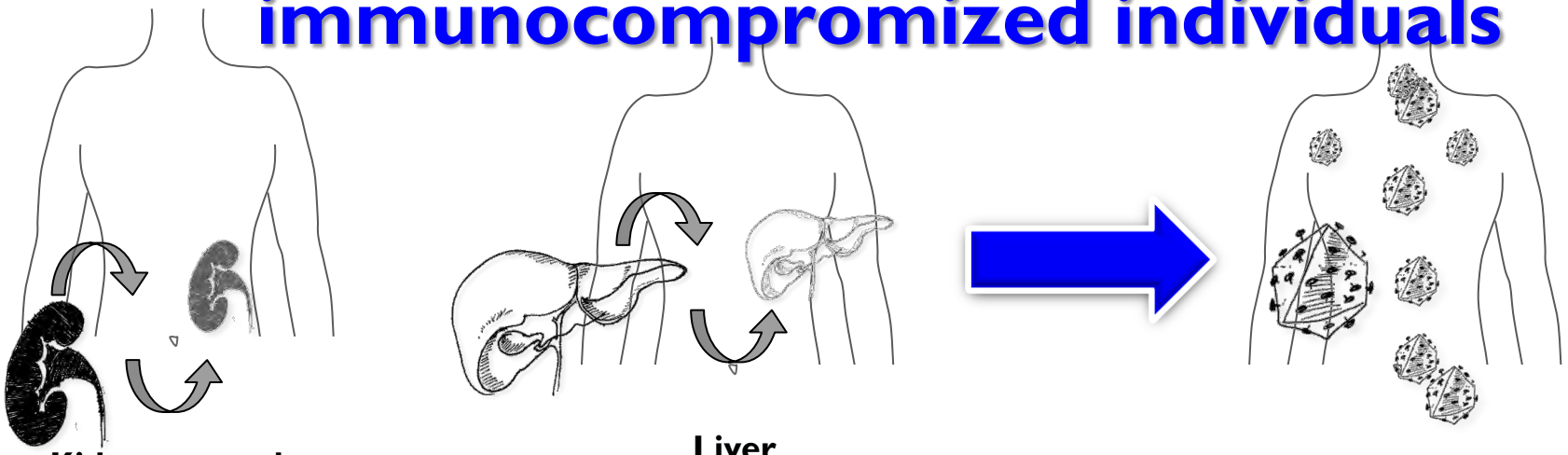
[a]Retrospective analysis of serum samples could be performed due to their availability for routine laboratory examinations in the context of HIV infection.

[b]Positivity corresponds to an optical density ratio >1.

[c]Interruption of antiviral therapy was motivated by severe lipodystrophia.

Colson P, Dhiver C, Gérolami R. Clin Microbiol Infect 2008;14(12):1176-80

HEV infection in severely immunocompromized individuals



Kidney transplant recipients

Liver transplant recipients

HIV-infected persons

Solid organ transplantation:

- The **incidence of HEV infection was found to be ≥1% after liver transplantation** in the Netherlands and in France [Haagsma et al., 2009; Kamar et al., 2008] and **4.5% over a 36 month-period in kidney transplant recipients in France** [Kamar et al., 2008].
- The **prevalence was 0.4-3.4% in liver transplant recipients** in the Netherlands, Germany and Spain [Haagsma et al., 2009; Pischke et al., 2010; Buti et al., 2010].
- During a 32 month-period, HEV infection was diagnosed in **~1% of the 1,500 kidney-transplant recipients** in our institution in Marseille, and we found a HEV RNA prevalence of 1.9% in 109 of them [Colson et al., Hepatology 2009].
- Furthermore, in these previous studies, **progression toward chronicity occurred in about 60% of kidney-transplant recipients** infected with HEV.

A new causative agent of chronic hepatitis in HIV-infected persons?

Plan

- Intérêt accru pour l'hépatite E chez les patients VIH+
- **Anciennes études de séroprévalence (<2000)**
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Hepatitis E virus and HIV infection in homosexual men

SIR—Montella and colleagues (Nov 19, p 1433) describe an increased seroprevalence of hepatitis E virus (HEV) antibodies
HIV-negati
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A more lik

SIR—HEV accounts for most enterically transmitted non-A non-B hepatitis in developing countries, and occurs in both epidemic and sporadic forms.[1] There is less information on the importance of HEV in western countries, where a low prevalence of anti-HEV has been shown in volunteer blood donors.[2-4] Th
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Hepatitis E antibodies and HIV status

SIR—The prevalence of hepatitis E virus (HEV) antib
European countries is estimated to be about 2%, ac
to studies in blood donors.[1] An Italian study suggeste
prevalence of HEV antibodies in HIV-infected hom
men.[2] We carried out a systematic search for HEV an
in inpatients in our department of infectious dise
assess the prevalence of HEV antibodies according
status, markers of hepatitis A, B, and C viruses (HAV

Montella et al., Lancet 1994; Medrano et al., Lancet1995; Nandwani, Lancet 1995; Bissuel et al., Lancet 1996

Journal of Viral Hepatitis, 1997, 4, 279–283

Antibody to hepatitis E virus in HIV-infected individuals and AIDS patients

M. S. Balayan,[1] O. E. Fedorova,[1] M. I. Mikhailov,[2] P. G. Rytick,[3] V. F. Eremin,[3] T. I. Danilova,[4] B. I. Shevelev,[4] E. C. Gorbacheva[4] and G. Y. Pankova[4] [1]*Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russia,* [2]*Gamaleya Institute of Epidemiology and Microbiology, Moscow, Russia,* [3]*Institute of Epidemiology and Microbiology, Minsk, Belarus and* [4]*Second Hospital for Infectious Diseases, Moscow, Russia*

Received 13 January 1997; accepted for publication 13 March 1997

SUMMARY. Antibody to hepatitis E virus of IgG class (anti-HEV IgG) is regularly detected in industrialized countries, where HEV is non-endemic, at levels not exceeding 2–3%; seropositive individuals are often found in certain groups of patients and professionals exposed to an increased risk of blood-borne infections. The present study was aimed at the identification of anti-HEV IgG in patients with human immunodeficiency virus (HIV) infection, including acquired immune deficiency syndrome (AIDS), living in Russia and Belarus, an area of low anti-HEV prevalence with a moderate spread of HIV infection and AIDS. In Russia, 13 out of 117 HIV-infected patients (11.1%) were found to be anti-HEV seropositive. This differed significantly from the frequency observed in the normal population (1.7%) but not from the frequency in a matching control, high-risk group consisting of male prisoners (8.0%). No difference in the frequency of anti-HEV IgG seropositivity was found between groups of HIV-infected men subdivided by sexual orientation. The rate of anti-HEV seropositivity increased with the progression of HIV infection, reaching 43.3% in AIDS patients and 38.1% in those who died from AIDS. In Belarus, anti-HEV IgG seropositivity was not found among 20 HIV-infected subjects nor among individuals from the control risk group, which consisted of 25 intravenous drug users. In conclusion, HEV infection may have common transmission mechanisms (risk factors) with HIV infection rather than represent an additional opportunistic infection in AIDS.

Keywords: AIDS, antibody to hepatitis E virus, hepatitis E, HIV infection, seroprevalence.

Table 1 Prevalence of anti-HEV IgG in the study groups

Group	Number tested	Anti-HEV seropositives	
		n	%
Russia			
HIV-infected	117	13	11.1*
Control (prisoners)	50	4	8.0
Normal population	180	3	1.7*
Belarus			
HIV-infected	20	0	0.0
Control (intravenous drug users)	25	0	0.0

*Difference is statistically significant at $P < 0.001$ for HIV infected *vs* normal population.

Table 2 Anti-HEV IgG in HIV-infected men by sexual orientation (Russia)

Sexual orientation	Anti-HEV seropositives	
	Number positive/number tested	%
Homosexuals and bisexuals	9/47	19.1
Heterosexuals and unknown	5/33	15.1

Difference is not statistically significant.

Table 3 Anti-HEV IgG in HIV-infected individuals and AIDS patients

	HIV infected	HIV infected + AIDS symptomology
Number tested	87	30
Number seropositive (%)	13 (14.9)	13 (43.3)

Difference is statistically significant at $P < 0.001$.

Journal of Viral Hepatitis, 1999, 6, 53–57

Prevalence of hepatitis viruses in an anti-human immunodeficiency virus-positive population from Argentina. A multicentre study

H. Fainboim,[1] J. González,[2] E. Fassio,[3] A. Martínez,[4] L. Otegui,[2] M. Eposto,[3] P. Cahn,[4] R. Marino,[1] G. Landeira,[3] G. Suaya,[4] E. Gancedo,[1] R. Castro,[2] L. Brajterman[2] and H. Laplumé[3] [1]*Dr Francisco Muñiz Hospital,* [2]*National Institute of Microbiology Dr Carlos Malbrán,* [3]*Professor Alejandro Posadas Hospital and* [4]*Dr Juan Fernández Hospital, Buenos Aires, Argentina*

Received 4 August 1998; accepted for publication 1 September 1998

SUMMARY. The objectives of this study were to investigate the prevalence of infections with hepatotrophic viruses in an anti-human immunodeficiency virus (HIV)-positive population from Buenos Aires and to compare it among the main risk groups for HIV infection. Four hundred and eighty-four consecutive patients attending the HIV outpatients clinic were studied: 359 men and 125 women, median age 29 years (range 16–67 years); 35.5% had presented acquired immune deficiency syndrome (AIDS)-defining conditions. Two hundred and thirty-four patients were intravenous drug users (IVDU), 99 had homosexual and 142 heterosexual preference, seven had received blood transfusions and two had no risk factors. Hepatitis B surface antigen (HBsAg), and antibodies to hepatitis B core antigen (HBcAb) and to hepatitis C virus (anti-HCV) were investigated in all patients; antibodies to HBsAg (HBsAb) and IgG antibodies to hepatitis D virus (anti-HDV) in all HBcAb-positive patients; hepatitis B e antigen and antibodies to HBeAg (HBeAg) in all HBsAg-positive patients; IgG antibodies to hepatitis A virus (anti-HAV) in the first 307 patients; and IgG antibodies to hepatitis E virus (anti-HEV) in the first 91 patients. As control groups, contemporary voluntary blood donors were studied for prevalence of HAV, HBV, HCV and HEV. The percentages of HBcAb, HBsAg, anti-HCV and anti-HEV (58.5, 14.5, 58.5 and 6.6%, respectively) were significantly higher in anti-HIV-positive patients than in control groups (3.2, 0.5, 1.0 and 1.8%, respectively) ($P = 0.000$). The prevalence of HBcAb was significantly higher in IVDU (72.6%) than in heterosexuals (33.8%) ($P = 0.0001$) and in homosexuals (59.6%) ($P = 0.0189$). The percentage of HBsAg was significantly higher in IVDU (19.2%) than in heterosexuals (6.3%) ($P = 0.0004$). Anti-HCV was significantly higher in IVDU (92.3%) than in homosexuals (14.1%) and in heterosexuals (33.1%) ($P = 0.000$ in both cases). The prevalence of anti-HDV was relatively low (1.9%). There was no difference in the percentage of anti-HAV between HIV-positive and negative subjects. In conclusion, there is a high prevalence of HBV and HCV infections in HIV-positive patients from our area. Drug use is the main route of transmission, but prevalence of HCV in patients with, probably, sexually acquired HIV infection is also higher than in the control group. The increased prevalence of HEV infection in HIV-positive individuals is another provocative finding that warrants further study.

Keywords: HIV infection, prevalence, viral hepatitis.

	Anti-HAV	HBcAb	HBsAg	Anti-HCV	Anti-HDV	Anti-HEV
HIV positive						
Overall	84.0	58.5†	14.5†	58.5†	1.9	6.6†
IVDU	85.7	72.6‡	19.2§	92.3¶	3.4	6.6
HOMO	83.3	59.6	15.2	14.1	1.0	3.8
HETERO	86.3	33.8	6.3	33.1	0	10.0
Blood donors	82.4	3.2	0.5	1.0	NA	1.8

*Four hundred and eighty-four non-selected anti-HIV-positive patients; 1500 voluntary blood donors. Anti-HAV, -HCV, -HDV, -HEV: IgG antibodies present to HAV, HCV, HDV and HEV, respectively; HBcAb, antibodies to hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HETERO, heterosexuals; HOMO, homosexuals; IVDU, intravenous drug users; NA, not available.
†$P = 0.0000$ *vs* blood donors; ‡$P = 0.0000$ *vs* HETERO and $P = 0.0189$ *vs* HOMO; §$P = 0.0004$ *vs* HETERO; ¶$P = 0.0000$ *vs* HOMO and HETERO.

Table 1 Overall, and according to risk groups, per cent prevalence of viral markers in a human immunodeficiency virus (HIV)-positive population and in a control group (blood donors) from the same area*

Plan

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- Anciennes études de séroprévalence (<2000)
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- Discussion/Conclusion

Hepatitis E and jaundice in an HIV-positive pregnant woman

Hepatitis E (HEV), which causes water-borne epidemics and sporadic acute often self-limiting hepatitis, is a major public health disease in developing countries [1]. HEV spreads mainly by faeco-oral transmission. Secondary cases among household members of patients occur in approximately 1–2% of cases [2]. Although nonendemic in the industrialized world, anti-HEV antibodies are detected in the general population [3]. HEV represents a rare but important differential diagnosis of hepatitis in pregnancy [4]. Infection in the last trimester results in high rates of preterm labour and maternal mortality of 15–26.9% [3,5,6] compared with a case fatality of between 0.2 and 4% during epidemics [7]. In the case of HIV coinfection, complications and mortality rates are unknown.

toxicity even though uncommon for the current regimen. On days 4 and 5 after admission, betamethasone was given intramuscularly (2×12 mg) to induce foetal lung maturation and stop haemolysis. Transaminases and bilirubin improved during the course and the patient was discharged on day 10 (ALT 372 IU/l; bilirubin 19.5 mg/dl). Due to an HIV load of 10^6 copies/ml, therapy was restarted on day 17, but after a rise in transaminases (ALT 691 IU/l) on day 23, NFV was exchanged for tenofovir (TDF). With this regimen and possibly betamethasone, liver enzymes and haemolysis normalized by day 56, it was virologically effective. Repeated HIV resistance testing showed no new or TDF-related mutations. HEV-IgG was repeated during follow-up on day 17 and was now positive. The patient delivered a healthy child at week 36 by Caesarean section.

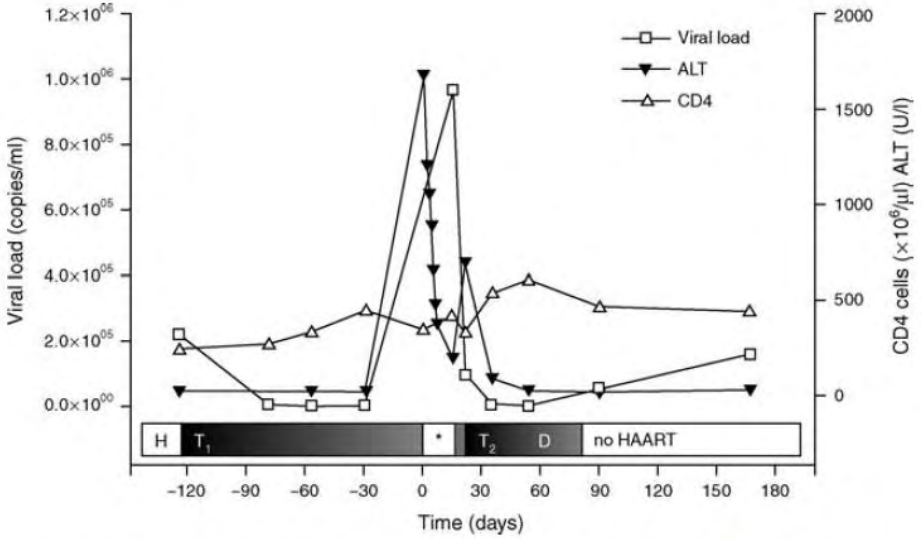

Fig. 1. Course of HIV infection and acute hepatitis. Alanine aminotransferase (ALT), HIV load and CD4+ cell count between HIV diagnosis and follow-up after delivery are shown. ALT (normal range 10–35 IU/L), CD4+ cell count (normal range 300–1400×10^6 per μl), viral load (normal range <40 copies/ml). D, delivery at week 36; T_1, highly active antiretroviral therapy (HAART) consisting of zidovudine (AZT), lamivudine (3TC), nelfinavir; T_2, HAART consisting of AZT, 3TC, tenofovir; *, phase of acute hepatitis with interruption of T_1 and consecutive rise in HIV load.

Thoden et al., AIDS 2008

Acute Hepatitis E Virus Infection in an HIV-Infected Person in the United States

Background: Hepatitis E virus (HEV) is an enterically transmitted cause of viral hepatitis that is rarely noted without international travel.

Objective: To report the first case of an HIV-infected man with acute hepatitis due to HEV infection who had not traveled outside the United States.

Case Report: A 45-year-old HIV-positive man had mildly elevated aminotransferase levels that were asymptomatic. He had a CD4 cell count of 0.36×10^9 cells/L (31%) with undetectable HIV RNA (<50 copies/mL) while receiving abacavir–lamivudine, atazanavir, and ritonavir. He had visited Maine and Illinois 4 weeks previously but reported no exposure to sick persons, nonmunicipal water, or farm animals; international travel; or medication changes. He reported having had anonymous sexual partners but did not report alcohol or illicit drug use.

Over the next week, the patient developed low-grade fever, abdominal tenderness, fatigue, and diffuse myalgias. Examination revealed right upper-quadrant tenderness with a palpable liver edge. Repeated laboratory testing revealed levels of alanine aminotransferase at 1396 U/L (normal range, 0 to 45 U/L), aspartate aminotransferase at 810 U/L (normal range, 0 to 40 U/L), total bilirubin at 5.7

Curry et al., Ann Intern Med 2008

Concurrent autochthonous acute hepatitis E and hepatitis B reverse seroconversion in an HIV-1-infected patient

- A 54-year-old HIV-1-infected homosexual male presented in June 2007 with jaundice and asthenia. His alanine aminotransferase (ALT) level was 373 IU/l, bilirubinemia was 52 mmol/l, and prothrombin index (PI) was 56%.
- The CD4 count was 77 cells/mm3 and plasma HIV-1 RNA was 2.5 log10copies/ml. Tenofovir and emtricitabine, two anti-HIV/HBV drugs, had been interrupted six months earlier.
- **HBV reactivation was diagnosed** based on serum HBV DNA-positivity (52 900 000 IU/ml; Cobas TaqMan Roche) and hepatitis B surface antigen (HBsAg) seroreversion (Axsym Abbott assay).
- **Unexpectedly, concurrent hepatitis E was diagnosed** based on positive results on IgM anti-hepatitis E virus (HEV) antibody testing (optical density ratios for IgG and IgM anti-HEV antibodies were 0.20 and 10.4, respectively; EIAGen Adaltis kits) and HEV RNA detection and sequencing from serum. The HEV was genotype 3.

One virus may hide another

Colson et al., Int J Infect Dis 2009

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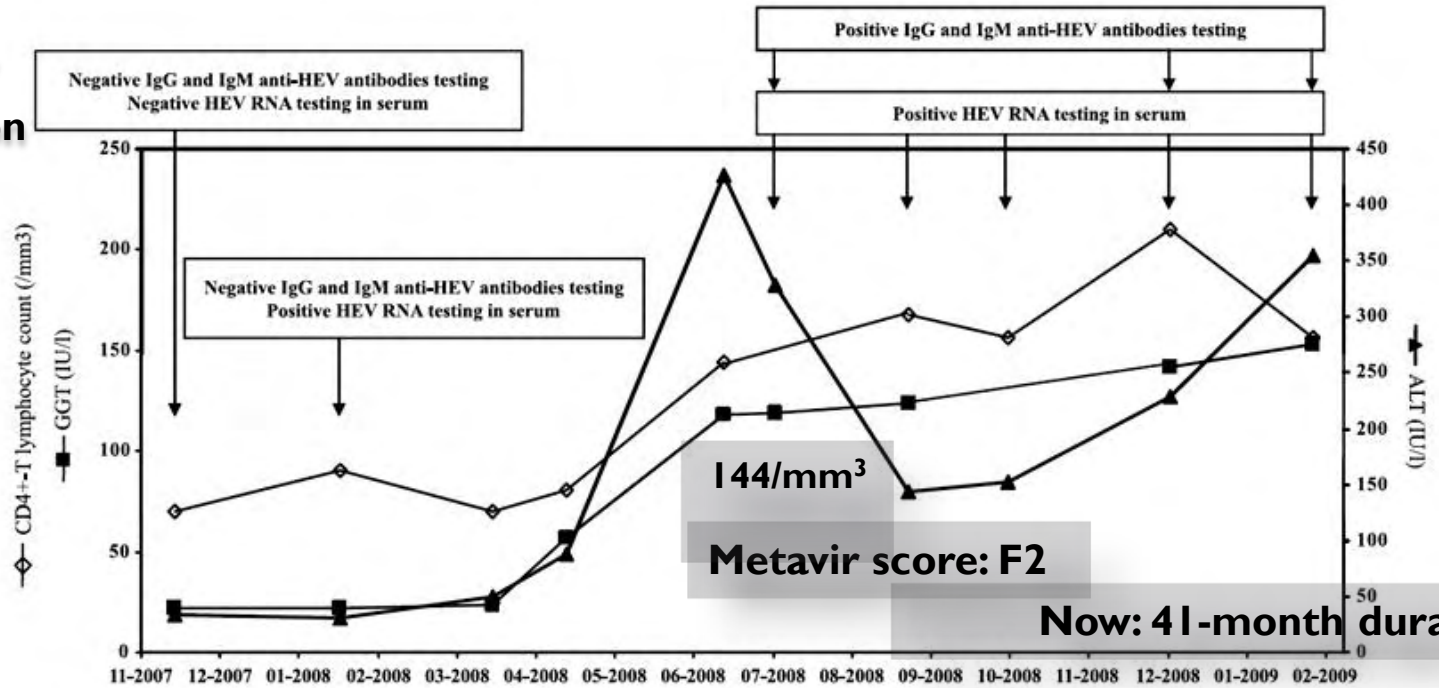
Virology Question and Answer Scheme (VIROQAS)

Hepatitis E in an HIV-infected patient

Philippe Colson[a,b,*], Mamadou Kaba[a,b], Jacques Moreau[c], Philippe Brouqui[b,c]

Genotype 3

M/50
Sexual HIV transmission



144/mm³

Metavir score: F2

Now: 41-month duration

Fig. 1. Changes in alanine aminotransferases (ALT) levels, gamma-glutamyltransferases (GGT) levels, CD4+ T lymphocyte counts, and virologic testing of HEV RNA and IgG and IgM anti-HEV antibody in serum.

Colson P, Dhiver C, Gérolami R *et al.*, J Clin Virol 2009

Persistent Carriage of Hepatitis E Virus in Patients with HIV Infection

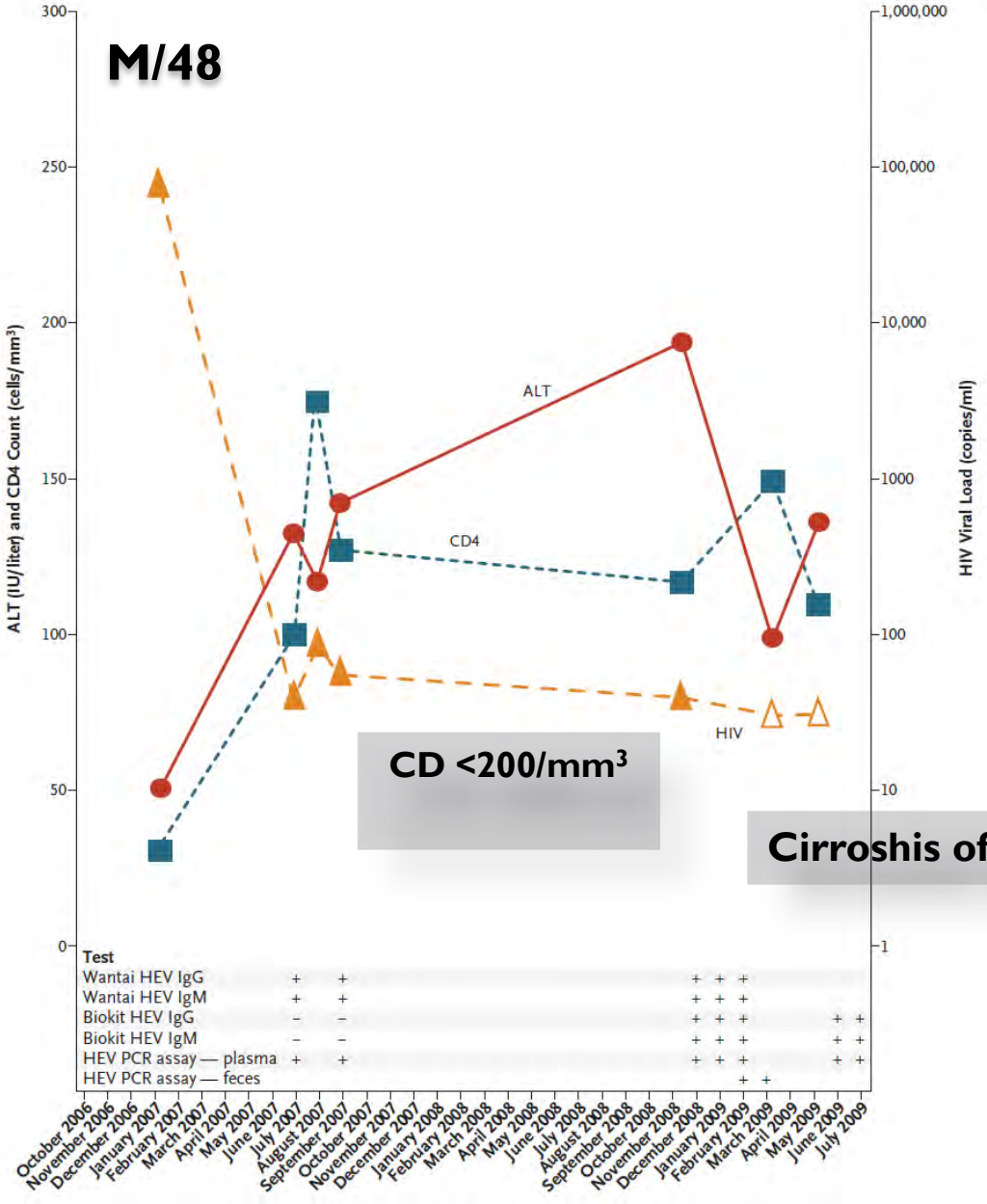


Figure 1. Laboratory Data for a Patient with Coinfection with Human Immunodeficiency Virus (HIV) and Hepatitis E Virus (HEV). For the HIV viral load, the final two data points (shown as open triangles) represent plasma samples with undetectable levels (<40 copies per milliliter). For the serologic and polymerase-chain-reaction (PCR) tests, the plus signs indicate positive results, and the minus signs negative results. ALT denotes alanine aminotransferase.

Dalton *et al.*, N Engl J Med 2009; 361(10):1025

Acute and chronic hepatitis E in patients infected with human immunodeficiency virus

References	Age and sex	ALT (IU/L)	CD4 T-cell count (/mm^3)	HIV-1 RNA [Log(copies/mL)]	Antiretroviral therapy	HCV/ HBsAg	HEV IgG (ratio*)	HEV IgM (ratio*)	HEV RNA (in serum)	HEV genotype (GenBank accession no.)	Outcome
Cited in ref. [2]	49 H	813	246	2.9	Yes	−/−	−	+ (>10)	+	3f (GQ426994)	Resolved in <6 months
[3]	45 H	1396	360	<1.6	Yes	−/−	+	+	+	3	Resolved in <6 months
[4]	54 H	373	77	2.5	No†	−/+	−	+ (>10)	+	3f (EU116332)	Unresolved, death at month-4 attributed to lymphoma
[2]	50 H	427	144‡	<1.6	Yes	−/−	+ (>10)	+ (>10)	+	3f (GQ228083)	Chronic hepatitis, significant fibrosis
[5]	48 H	51	30‡	4.9	Yes	−/−	+	+	+	3	Chronic hepatitis, cirrhosis
This article	55 H	210	197§	<1.6	Yes	−/−	+ (6.3)	+ (>10)	+	3c (GQ427014)	Resolved in <6 months
This article	42 F	55	269	<1.6	Yes	−/−	−	+ (2.1)	+	3f (GQ426999)	Resolved in <6 months
This article	43 H	390	432	<1.6	Yes	−/−	+ (9.8)	+ (3.2)	+	3f (GU994211)	Resolved in <6 months

*Optical density ratio, Adaltis EIAGen kits (Adaltis Italia, Casalecchio di Reno, Italy); †interrupted 6 months earlier; ‡remained <200/mm^3; §279/mm^3 2 months later.

Colson et al., J Viral Hep 2010

Plan

- Intérêt accru pour l'hépatite E chez les patients VIH+
- Anciennes études de séroprévalence (<2000)
- Cas rapportés d'hépatite E
- **Etudes récentes de prévalence (>2008)**
- Discussion/Conclusion

Lack of hepatitis E virus infection in HIV patients with advanced immunodeficiency or idiopathic liver enzyme elevations

A. Madejón,[1,2] E. Vispo,[1] M. Bottecchia,[1,2] M. Sánchez-Carrillo,[1,2] J. García-Samaniego[2] and V. Soriano[1] [1]*Department of Infectious Diseases; and* [2]*Department of Hepatology, Hospital Carlos III and CIBERehd, Madrid, Spain*

Received February 2009; accepted for publication February 2009

SUMMARY. Hepatitis E virus (HEV) is an enterically transmissible RNA agent that causes self-limited acute hepatitis. Recent reports have highlighted that organ-transplant recipients may develop chronic hepatitis E and progress to cirrhosis. Similar cases could occur in HIV patients. We have investigated 50 HIV-infected individuals with CD4 counts <200 cells/mm^3 and 43 with cryptogenic hepatitis. None of them showed HEV viremia. Thus, HEV infection does not seem to be prevalent in the HIV population and accordingly universal HEV vaccination is not warranted in these patients.

Keywords: chronic hepatitis, hepatitis E, HIV.

Madejon et al., J Viral Hepat 2009

Journal of Viral Hepatitis, 2009 doi:10.1111/j.1365-2893.2009.01219.x

LETTER TO THE EDITOR

Hepatitis E in HIV-positive patients in a low-endemic country

To the Editor:

Hepatitis E virus (HEV) infection has emerged as a special topic of interest in recent years as cases of chronic hepatitis E have been described in organ transplant recipients [1,2]. We

homosexual. The age of the anti-HEV-positive patients ranged between 39 and 51 years and CD4+ counts between 417 and 923 cells per μL. HIV-RNA was negative in five patients. Importantly, all six anti-HEV-positive patients tested negative for HEV RNA by nested RT-PCR. Five of the six patients had normal ALT levels, and one patient had a moderately elevated ALT level of 94 U/L.

Pischke et al., J Viral Hepat 2011

Hepatitis E virus in HIV-infected patients: a prospective sero-virological study in France

Christophe Renou[a], Alain Lafeuillade[b], Jean-François Cadranel[c], Nicole Pavio[d], Alexandre Pariente[e], Thierry Allègre[f], Cécile Poggi[g], Guillaume Pénaranda[h], François Cordier[i] and Elisabeth Nicand[j] for the ANGH*

Objectives: Many cases of acute autochthonous hepatitic E virus (HEV) hepatitis have been reported in France, mainly from the South. Chronic HEV infection has recently been described in immunosuppressed patients. Although a potential risk of chronicity exists in HIV-infected patients, no survey has been conducted in this population. The aim of this study was to assess the sero-virological prevalence of HEV in French HIV-infected patients.

Methods: Two hundred and forty-five HIV-infected patients followed at two Infectious Diseases Departments (one in the South, one in the North) were included from January to March 2009. Sera were collected from all patients and tested using anti-HEV IgG and IgM kits. HEV RNA was systematically amplified in the ORF2 region with an in-house method. The IgG avidity index of all IgG-positive samples was determined.

Results: Three of the 133 southern patients showed both anti-HEV IgG and IgM positivities, along with cytolysis and biological cholestasis; HEV RNA was amplified in two of these cases, whereas a low IgG avidity index was observed in all three samples. Twelve of the 130 remaining southern patients (9%) showed anti-HEV IgG positivity. The serological prevalence in the 112 northern patients was 3%, which was significantly lower than in the southern patients ($P = 0.04$). No case of acute hepatitis was reported in the North, whereas the prevalence of patients with biochemical liver abnormalities was similar in both areas ($P = 0.22$).

Conclusions: In France, HIV-infected patients are at risk of HEV infection with a serological North-to-South gradient. No case of chronic HEV infection was detected in this study.

AIDS 2010, **24**:000–000

Keywords: co-infection, geographic, hepatitis E, liver, prevalence

Renou et al., AIDS 2011

Table 1. Epidemiological, biochemical, HIV, and HEV characteristics of the three cases of acute hepatitis E observed in the South of France.

Case	1	2	3
Age (years)	50	61	45
Clinical presentation	Fever, arthralgia, myalgia	Jaundice	Jaundice
Duration of HIV infection (years)	17	22	19
Source of HEV contamination	Unknown	Unknown	Unknown
Pre-existing chronic liver disease	No	No	No
CDC Status	C3	B3	B2
CD4+ (cells/μl)	470	1216	464
CD8+ (cells/μl)	504	4018	1630
CD4+ (%)	28	17	17
HIV viral load (IU)	<40	<40	<40
ALT (xN)	12	25	80
Bilirubin (xN)	5	12	13
IgG (cut-off = 1)	6,7	8,5	6,9
IgM (cut-off = 1)	10,6	11,5	8,1
IgG avidity (%)	11	18	17
HEV RNA (sera)	Negative	Positive (genotype 3c)	Positive
Chronic hepatitis E	No	No	No

ALT, alanine transaminase; HEV hepatitis E virus; N, upper normal limit.

Renou et al., AIDS 2011

Hepatitis E Virus infection in HIV-infected patients with elevated serum transaminases levels

Table 1: Demographic and biological characteristics of patients seropositive for HIV-1 with acute or past HEV infection

Patient N°	Sex	Age (years)	ALT (xULN)	AST (xULN)	CD4 + T lymphocytes absolute count/mm^3	Plasmatic HIV RNA (log_{10} copies/mL)	Sample N°	Time from onset of transaminasitis (months)	Anti HEV IgM OD/CO	Anti HEV IgG OD/CO	IgG avidity index (%)	RNA HEV	Conclusion
					At onset of transaminasitis								
1	M	34	1	1			1	- 1	0.5	0.6		NEG	No HEV infection
			20	12	286	3.4	2	0	10.8	4.2	7.5	POS	Acute HEV
			1	1			3	+1	10.8	4.2	11	NEG	infection
			1	1			4	+12	2.2	3.9	34	NEG	
2	F	32	8	3	215	4.1	1	0	0.1	4.3	86	NEG	Past infection
3	M	57	2.5	2.5	223	5.1	1	0	0.2	7.2	73	NEG	Past infection
4	M	52	2	2.5			1	- 4	0.7	4.8	90	NEG	Past infection
			4	3	246	3.0	2	0	0.9	5.4	88	NEG	
			1	1			3	+ 12	0.7	7.1	93	NEG	
			1	1			4	+ 18	0.6	7.0	100	NEG	

OD/CO : Optical density/Cut Off; the results were considered as positive if OD/CO exceeded 1.
ULN : Upper Limit of Normal values, 50 I.U./mL. ALT : alanine aminotransferases. AST : aspartate aminotransferases.

Sellier et al.,Virol J 2011

Hepatitis E Virus Seroprevalence and Chronic Infections in Patients with HIV, Switzerland

Alain Kenfak-Foguena,[1] Franziska Schöni-Affolter,[1] Philippe Bürgisser, Andrea Witteck, Katharine E.A. Darling, Helen Kovari, Laurent Kaiser, John-Marc Evison, Luigia Elzi, Vanina Gurtner-De La Fuente, Josef Jost, Darius Moradpour, Florence Abravanel, Jacques Izopet,[2] Matthias Cavassini,[2] and the Swiss HIV Cohort Study

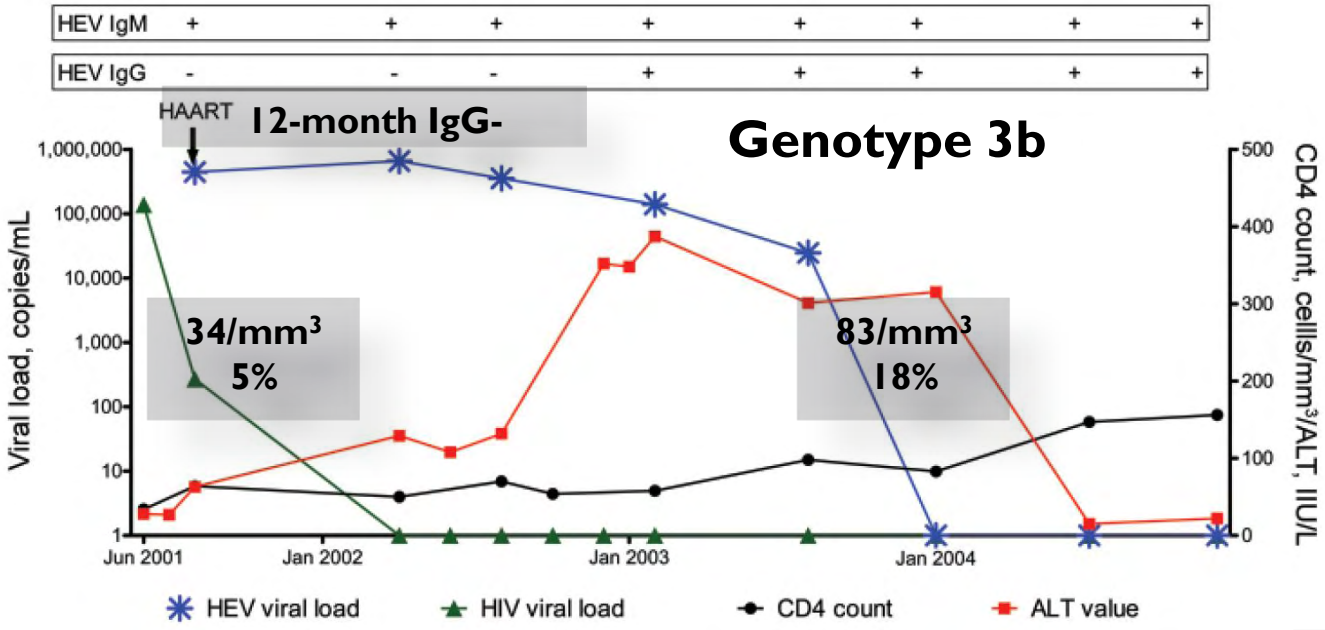
We screened 735 HIV-infected patients in Switzerland with unexplained alanine aminotransferase elevation for hepatitis E virus (HEV) immunoglobulin G. Although HEV seroprevalence in this population is low (2.6%), HEV RNA can persist in patients with low CD4 cell counts. Findings suggest chronic HEV infection should be considered as a cause of persistent alanine aminotransferase elevation.

Table 2. Logistic regression derived odds ratios/estimates for positive HEV serology in study of prevalence and role of HEV infection among participants in the Swiss HIV Cohort Study, Switzerland, 2008*

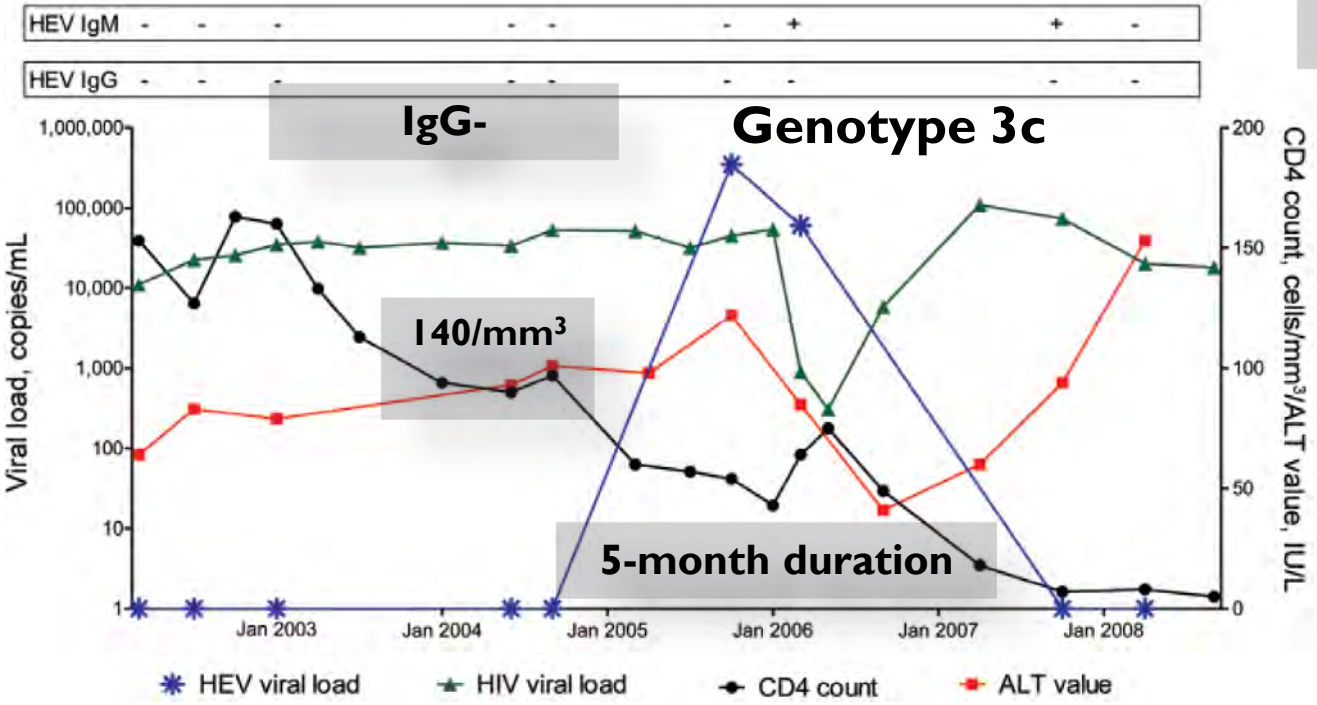
Variable	Odds ratio (95% CI)	p value
Male vs. female	0.207 (0.041–1.016)	0.0523
CD4 100–350 vs. CD4 <100 per mm^3	4.683 (1.268–17.295)	0.0206
CD4 ≥350 vs. CD4 <100 per mm^3	2.448 (0.522–11.468)	0.256
Other ethnicity vs. Asian ethnicity	0.295 (0.073–1.191)	0.0864
Alcohol history, no vs. yes	1.802 (0.582–5.581)	0.3071
Risk group, other vs. MSM	0.422 (0.100–1.774)	0.2392
Age at ALT elevation	1.017 (0.966–1.070)	0.5257
Duration of ALT elevation	1.001 (1.000–1.002)	0.0207

*HEV, hepatitis E virus; MSM, men who have sex with men; ALT, alanine aminotransferase.

M/48 MSM



M/59 MSM



135 samples from 54 pts with CD counts < 150 cells/mm ^{3}

Chronic hepatitis E virus infection in HIV-infected patients in South-eastern France

Table 1. HEV antibodies and HEV RNA detection in the serum samples of HIV-infected patients

Characteristics	HIV-1-infected patients			HIV-2-infected patients	P-value
	Group I	Group II	Group III		
Number of patients tested	73	69	31	17	-
Age, Mean, Year	41	41	45	46	-
Sex (Male/Female)	54/19	38/31	21/10	8/9	NS
CD4-cells count, Mean, No. (cells/mm^3)*	27	386	375	481	-
IgG anti-HEV antibodies, No. (%)	6 (8)	2 (3)	5 (13.9)	2 (12.5)	NS
IgM anti-HEV antibodies, No. (%)	3 (4)	1 (1.4)	2 (5.6)	1 (6.3)	NS
HEV RNA in sera, No. (%)	1 (1.3)	0 (0.00)	0 (0.00)	0 (0.00)	-
HEV genotype/subtype	3 f	Nd	Nd	Nd	-

Nd, Not done ; **NS,** Not significant; **Group I,** HIV-1-infected patients with low CD4-cells count (<50/mm^3); **Group II,** HIV-1-infected patients diagnosed in 2006; **Group III,** HIV-1-infected patients with cirrhosis. **Note:** * The rate of CD4-cells count were available for 173 patients.

Kaba M, Brouqui P, Richet H, *et al.*, Clin Microbiol Infect 2009;15(s4):S584

Plan

- Intérêt accru pour l'hépatite E chez les patients VIH+
- Anciennes études de séroprévalence (<2000)
- Cas rapportés d'hépatite E
- Etudes récentes de prévalence (>2008)
- **Discussion/Conclusion**
- Cas clinique

HEV-associated chronic hepatitis in organ-tranplant recipients

Table 3. Patients with Resolving HEV Infection and Those in Whom the Infection Evolved to Chronic Hepatitis.

Variable	Patients with Resolving Infection (N=6)	Patients with Chronic Infection (N=8)	P Value
	median (range)		
At diagnosis			
Time since transplantation — mo	78.5 (25–168)	37.5 (6.0–63.0)	0.03
Leukocyte count — $\times 10^{-3}/mm^3$	8.85 (6–9.66)	4.31 (2.19–7.20)	0.004
Lymphocyte count — $\times 10^{-3}/mm^3$			
Total	1.73 (1.12–2.33)	0.75 (0.63–1.04)	0.004
CD2+	1.59 (0.84–2.25)	0.66 (0.58–0.92)	<0.001
CD3+	1.54 (0.70–1.88)	0.61 (0.49–0.79)	0.01
CD4+	0.93 (0.49–1.07)	0.22 (0.16–0.40)	0.004
Platelet count — $\times 10^{-3}/mm^3$	261 (190–285)	155.5 (75.0–250.0)	0.01
Serum creatinine — mg/dl*	2.15 (1.31–2.84)	1.33 (1.08–1.89)	0.01
At last follow-up			
Aspartate aminotransferase — IU/liter	25.5 (7–35)	55.5 (39.0–238.0)	0.002
Alanine aminotransferase — IU/liter	25 (13–45)	108.0 (59.0–298.0)	0.002

* To convert values for creatinine to micromoles per liter, multiply by 88.4.

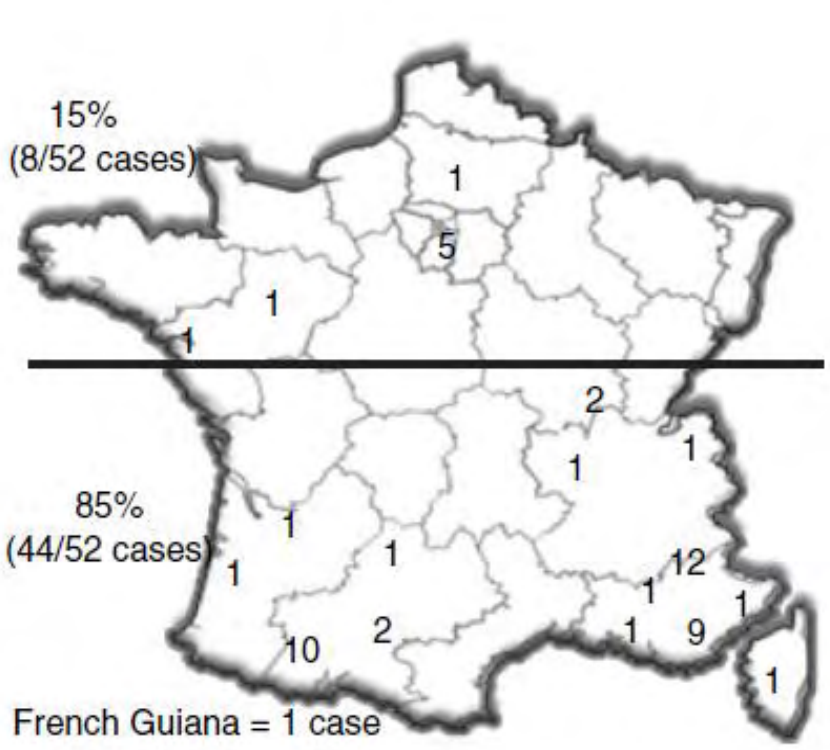
Kamar N, Selves J, Mansuy JM, *et al*. N Engl J Med 2008;358:811-7

HEV transmission through sexual intercourse or intravenous drug use (the two major routes of HIV transmission among adults)?

- No data has been published that documented such transmission using molecular assays.

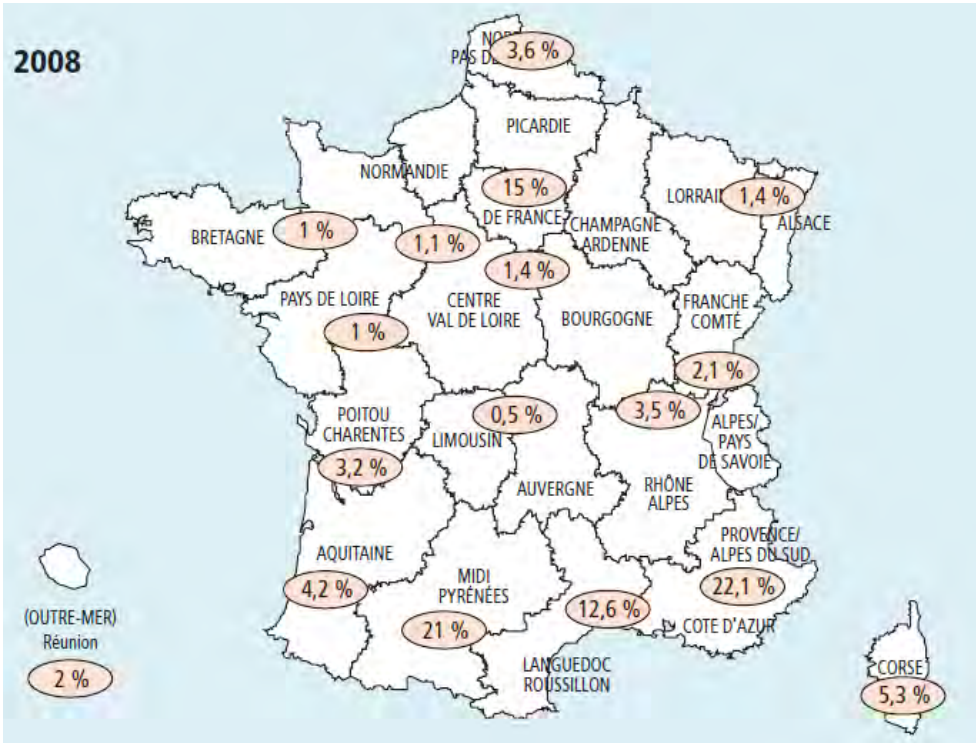
- In the studies by Renou et al.'s study [2010] and Kenfak-Foguena et al.'s study [2011]: HEV seroprevalence did not differ statistically significantly according to the risk of HIV transmission.

Gradient Nord-Sud pour l'hépatite E en France



Number of cases of acute hepatitis E reported by hospitals in southern and northern France.

Renou *et al.*, Aliment Pharmacol Ther 2008;27:086–1093



Distribution des cas d'hépatites E autochtones en France en 2008

Nicand *et al.*, BEH 31-32 / 2009

In blood donors: anti-HEV IgG prevalence :

- 3% in the North (3%) [Boutrouille et al., 2007]
- 8-16% in the South [Mansuy et al., 2008; Colson et al., 2010]

Immunosuppression may jeopardize the production of detectable levels of anti-HEV antibodies

- [Pischke et al., 2009]: **all six patients who harbored detectable anti-HEV IgG had CD4 counts between 417 and 923 cells/mm^3**
- [Sellier et al., 2011]: **the four patients with anti-HEV antibodies had CD4 counts >200 cells/mm^3**
- [Kenfak-Foguena et al., 2011]: using multivariate logistic regression, **patients infected with HIV whose CD4 counts were 100-350 cells/mm3 were ~5 times more likely to be infected with HEV compared to those with CD4 counts <100 cells/mm^3**
- In contrast: [Renou et al., 2010]: **relative CD4 counts were statistically significantly lower in patients from South of France with than without anti-HEV IgG (23.1% versus 30.2%; *p*= 0.04**

Incidence and Risk Factors for Chronic Elevation of Alanine Aminotransferase Levels in HIV-Infected Persons without Hepatitis B or C Virus Co-Infection

Helen Kovari,[1] Bruno Ledergerber,[1] Manuel Battegay,[2] Andri Rauch,[3] Bernard Hirschel,[4] Alain Kenfak Foguena,[5] Pietro Vernazza,[6] Enos Bernasconi,[7] Nicolas J. Mueller,[1] and Rainer Weber,[1] for the Swiss HIV Cohort Study[a]

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Background. Chronic liver disease in human immunodeficiency virus (HIV)–infected patients is mostly caused by hepatitis virus co-infection. Other reasons for chronic alanine aminotransferase (ALT) elevation are more difficult to diagnose.

Methods. We studied the incidence of and risk factors for chronic elevation of ALT levels (greater than the upper limit of normal at ≥2 consecutive semi-annual visits) in participants of the Swiss HIV Cohort Study without hepatitis B virus (HBV) or hepatitis C virus (HCV) infection who were seen during the period 2002–2008. Poisson regression analysis was used.

Results. A total of 2365 participants were followed up for 9972 person-years (median age, 38 years; male sex, 66%; median CD4$^+$ cell count, 426/μL; receipt of antiretroviral therapy [ART], 56%). A total of 385 participants (16%) developed chronic elevated ALT levels, with an incidence of 3.9 cases per 100 person-years (95% confidence interval [CI], 3.5–4.3 cases per 100 person-years). In multivariable analysis, chronic elevated ALT levels were associated with HIV RNA level >100,000 copies/mL (incidence rate ratio [IRR], 2.23; 95% CI, 1.45–3.43), increased body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) (BMI of 25–29.9 was associated with an IRR of 1.56 [95% CI, 1.24–1.96]; a BMI ≥30 was associated with an IRR of 1.70 [95% CI, 1.16–2.51]), severe alcohol use (1.83 [1.19–2.80]), exposure to stavudine (IRR per year exposure, 1.12 [95% CI, 1.07–1.17]) and zidovudine (IRR per years of exposure, 1.04 [95% CI, 1.00–1.08]). Associations with cumulative exposure to combination ART, nucleoside reverse-transcriptase inhibitors, and unboosted protease inhibitors did not remain statistically significant after adjustment for exposure to stavudine. Black ethnicity was inversely correlated (IRR, 0.52 [95% CI, 0.33–0.82]). Treatment outcome and mortality did not differ between groups with and groups without elevated ALT levels.

Conclusions. Among patients without hepatitis virus co-infection, the incidence of chronic elevated ALT levels was 3.9 cases per 100 person-years, which was associated with high HIV RNA levels, increased BMI, severe alcohol use, and prolonged stavudine and zidovudine exposure. Long-term follow-up is needed to assess whether chronic elevation of ALT levels will result in increased morbidity or mortality.

Should HIV-Infected Patients with Unexplained Chronic Liver Enzyme Elevations Be Tested for Hepatitis E Virus?

To the Editor—We read with interest the report by Kovari et al [1] describing 385 human immunodeficiency virus (HIV)–infected individuals with incident chronic elevations of alanine aminotransferase levels, in the absence of hepatitis C or B virus coinfection. The authors found that chronic alanine aminotransferase elevation in their population was associated with high body mass index, frequent alcohol consumption, and cumulative exposure to combination antiretroviral therapy, especially to stavudine.

Despite its many strengths, an important limitation of this study is that they did not exclude hepatitis E virus (HEV) as a potential cause of chronic viral hepatitis in this population. HEV, a significant global agent of viral hepatitis, was first identified in 1980 [2, 3] and is generally

Kovari et al., Clin Infect Dis 2010; Kuniholm et al., Clin Infect Dis 2010

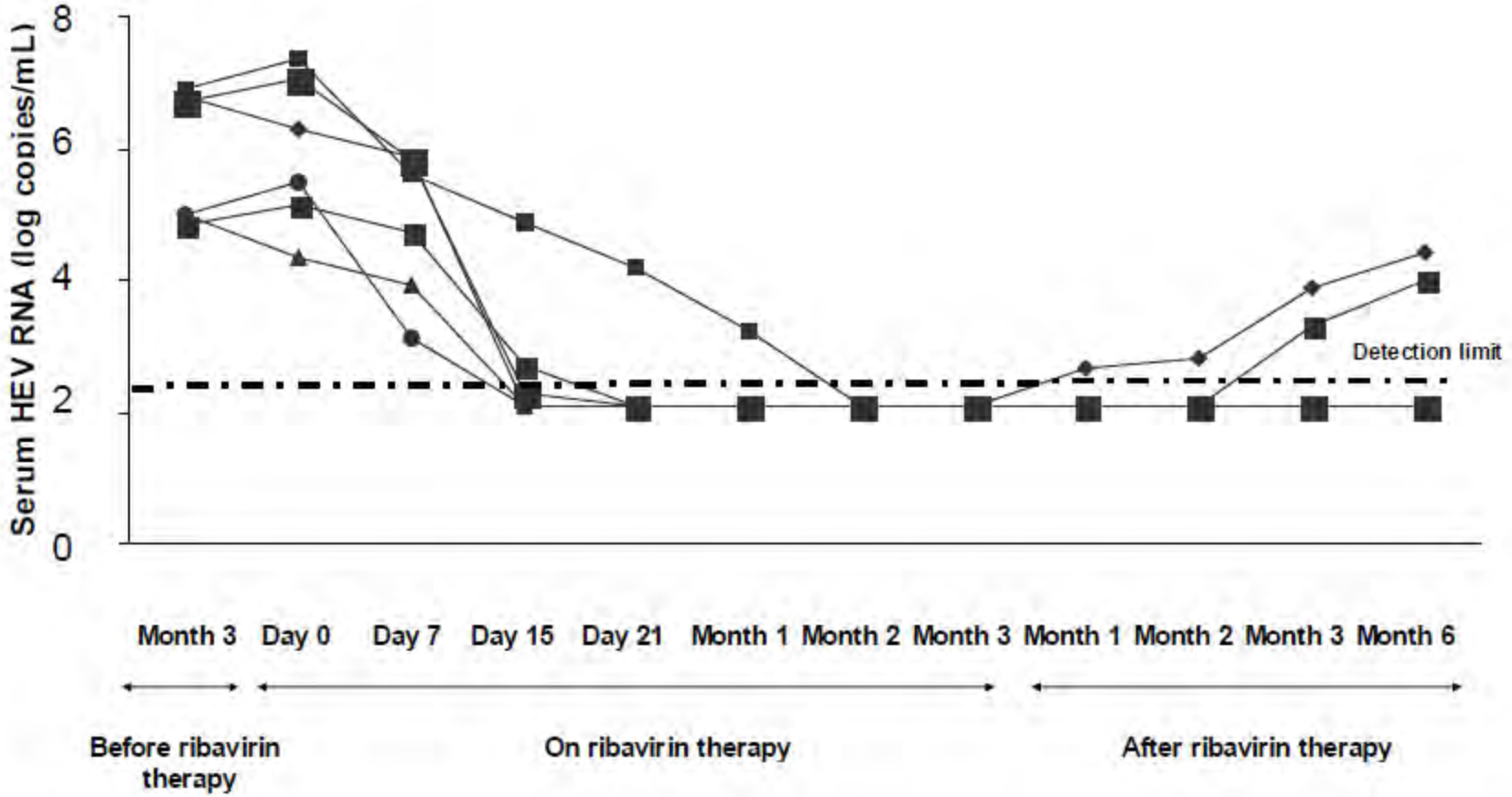
- 3.9 cases per 100 person-years [Kovari et al., Clin Infect Dis 2010]
- 01-03/2009: 40/133 (30%) HIV+ patients had liver cytolysis (ALT≥ 3xN in only three cases) [Renou et al., AIDS 2010].
- 2005-2008: 108/1,250 (8.6%) HIV+ patients had ≥1 episode of ALT≥ 2xN [Sellier et al., Virol J 2011].

Comparison of effects of hepatitis E or A viral superinfection in chronic hepatitis B

	CHB + HAV superinfection ($n = 52$)	CHB + HEV superinfection ($n = 136$)	P value[a]
Age (years)[b]	37.0 (23.0, 48.5)	40.0 (33.0, 51.5)	0.022*
Sex[c]			0.004*
Male	39 (75.0)	124 (91.2)	
Female	13 (25.0)	12 (8.8)	
Family history of hepatitis B[c]	19 (36.5)	58 (42.7)	0.446
Chronic hepatitis B carrier[c]	13 (25.0)	24 (17.7)	0.257
Chronic hepatitis[c]	20 (38.5)	73 (53.7)	0.062
Compensated cirrhosis[d]	2 (3.9)	16 (11.8)	0.099
Decompensated cirrhosis[d]	4 (7.7)	10 (7.4)	1.000
Inactive HBsAg carrier[c]	13 (25.0)	12 (8.8)	0.004*
Alcoholic hepatitis[d]	3 (5.8)	3 (2.2)	0.350
Alcoholic cirrhosis[c]	6 (11.5)	19 (14.0)	0.660
Complications[c]	32 (61.5)	129 (94.9)	<0.001*
Liver fluke[d]	2 (3.9)	7 (5.2)	1.000
Chronic gastrointestinal disease[d]	5 (9.6)	12 (8.8)	1.000
G6PD deficiency[d]	3 (5.8)	7 (5.2)	1.000
Hepatic failure[c]	6 (11.5)	54 (39.7)	0.002*
Other diseases[c,e]	4 (7.69)	15 (11.0)	0.497
Death[c]	1 (1.9)	46 (33.8)	<0.001*

Zhang et al., Hepatol Int (2010) 4:615–620

Serum hepatitis E virus RNA concentrations before and during the study period Including ribavirin therapy



Kamar et al., Gastroenterology 2010

Geographic distribution of hepatitis E genotypes from humans and swine

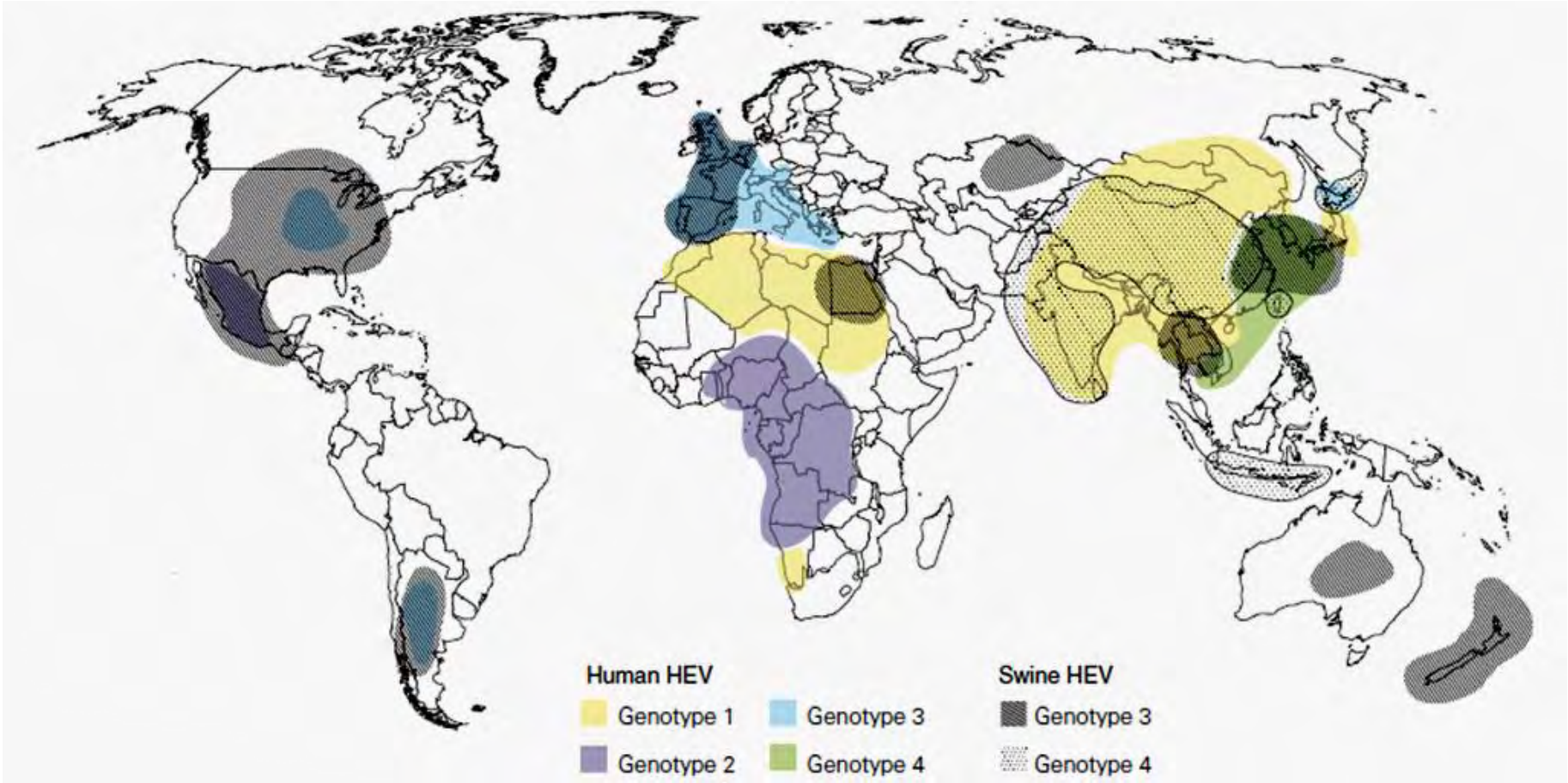


Figure 3 Map showing geographical distribution of hepatitis E virus genotypes among (a) human isolates, and (b) swine isolates. (Modified from Purcell and Emerson. *J. Hepatol.* 2008; **48**: 494–503.)

R Aggarwal and S Naik. J Gastroenterol Hepatol 2009

Conclusion

- **Diagnostic:**
  - « Un virus peut en cacher un autre »
  - Besoin d'évaluer l'ensemble des tests commerciaux en parallèle
  - PCR indispensable; l'élimination virale doit être vérifiée (3-6 mois)
- **Epidémiologie**
  - Pas de modes spécifique de transmission identifié
  - Incidence/prévalence réelle ? Apparemment faibles: PCR indispensable
  - Hépatite E et infection VIH hors-Europe? Dans pays à forte co-endémicité VIH-VHE ? Hépatites E chroniques
- **Clinique:**
  - Sévérité en cas d'hépatopathie sous-jacente chez un patient VIH: peu documentée
  - Interférence avec les autres hépatites virales?
  - Agent causal d'hépatite aiguë et chronique (CD4 <200/mm^3)
  - Différence selon le génotype?
  - Traitement (PEG-IFN?; ribavirine?)
- **Prévention:**
  - Cuisson « à cœur » des produits à base de porc/sanglier (foie)
  - Lavage des mains; salive
  - Vaccin

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