What a difference the age makes? Clinical course of chronic hepatitis C in the elderly

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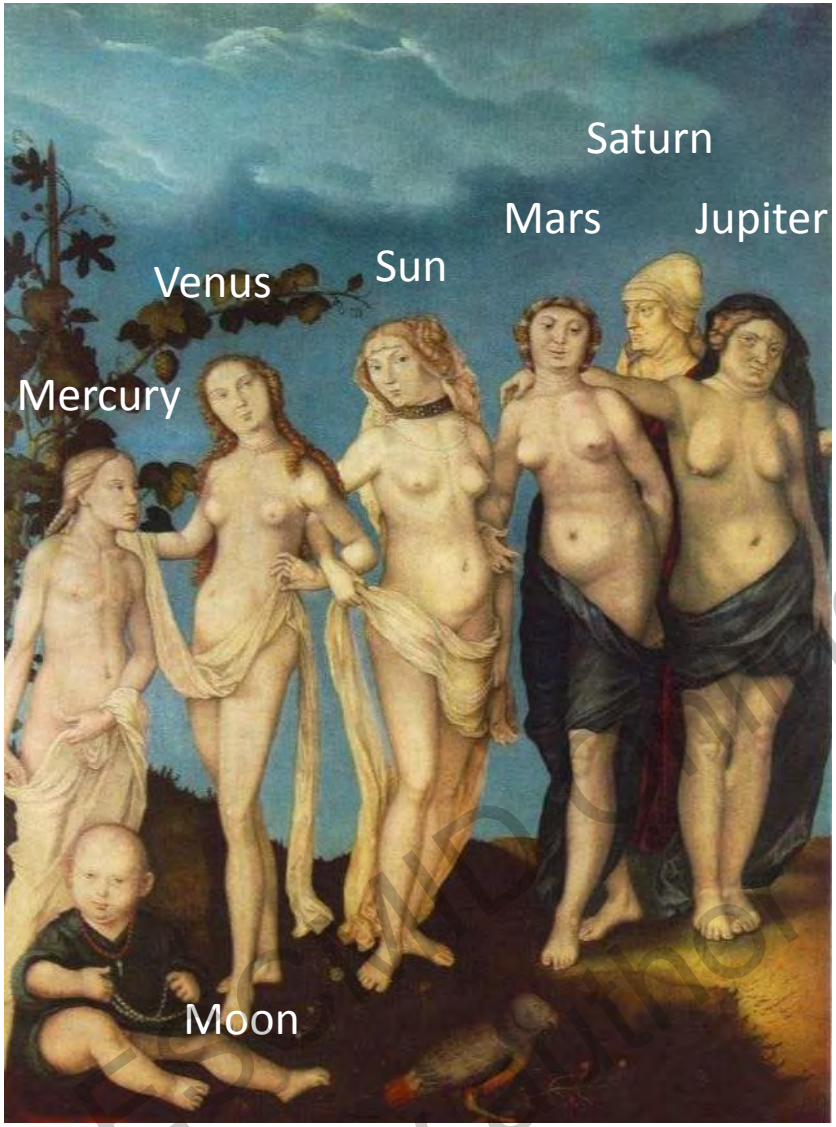


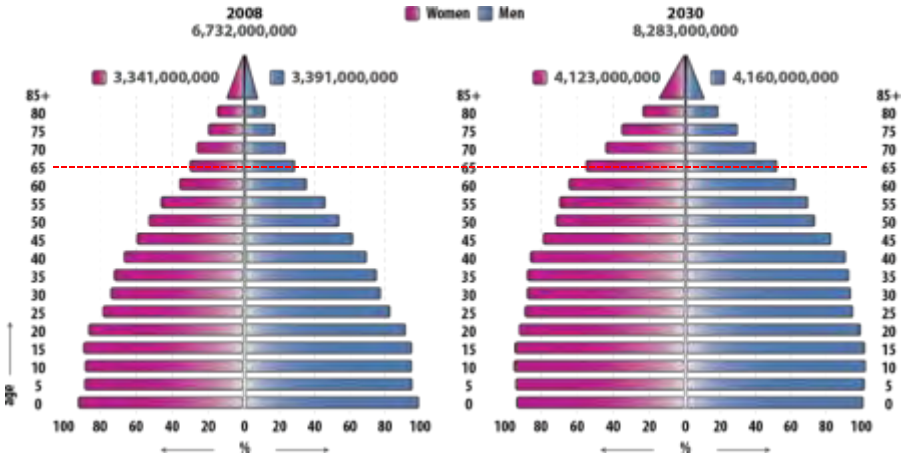
BALDUNG GRIEN, Hans
b. 1484/85, Schwäbisch-Gmünd, 1545, Strassburg
The Seven Ages of Woman
Museum der Bildenden Künste, Leipzig

AGES OF MAN

In 12th century, life span divided in 7 phases:
7-14-21-28-35-42-49-56-72 years old
Old age > 56 years old

Currently: elderly >65 years old
but for Africa>50 years old (WHO)

Retirement age in many European countries:
67 years old



Estimates of global population by gender and age, 2000 and 2030
Source: State of Oncology 2013 Report

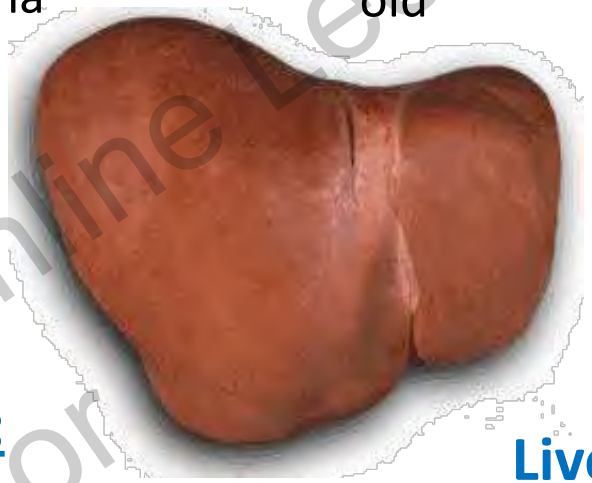
Liver physiology in the elderly

Morphology:

- Liver volume reduced by 20-40%
- Liver blood flow reduced by 35-50%
- Decreased nr of mitochondria
- Lipofuscin accumulation (chronic oxidative stress)

Drug metabolism:

- Cyp P450 activity reduced by 32% in >70yo compared to 20-29 years old



Hepatic function:

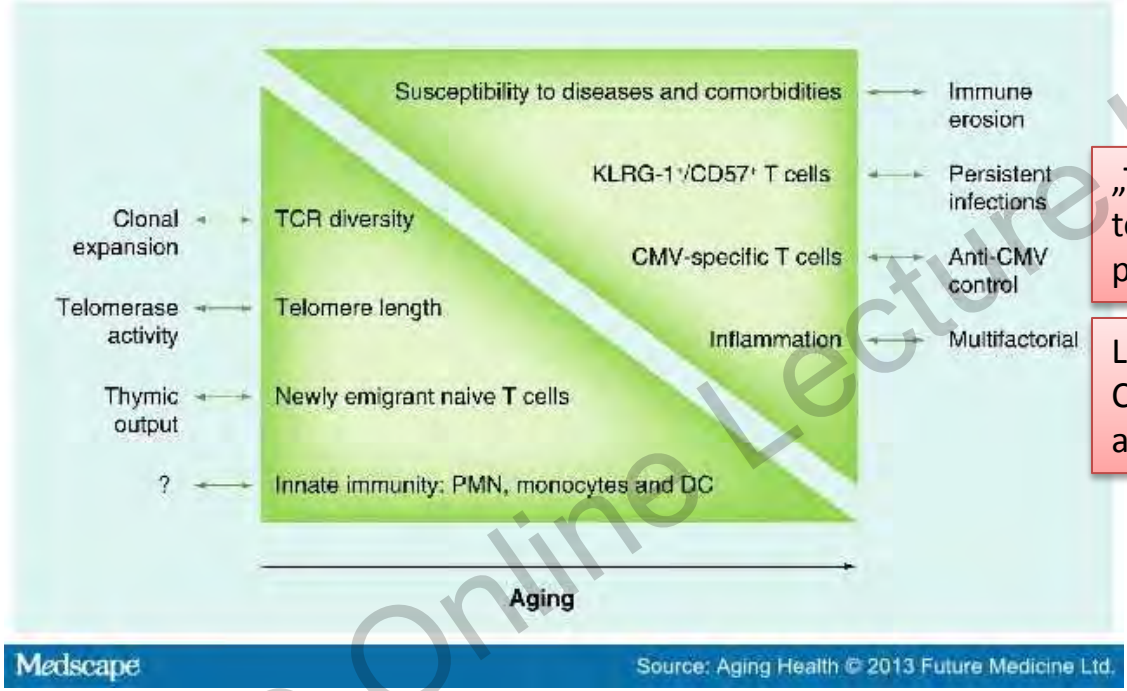
- Rather well preserved with age
- Albumin, GGT may decrease, bilirubin increase
- ALT – reported to decrease with age

Liver regeneration:

- Decline with age
- Reduced levels of EGF
- Reduced telomere length, especially when liver disease is present

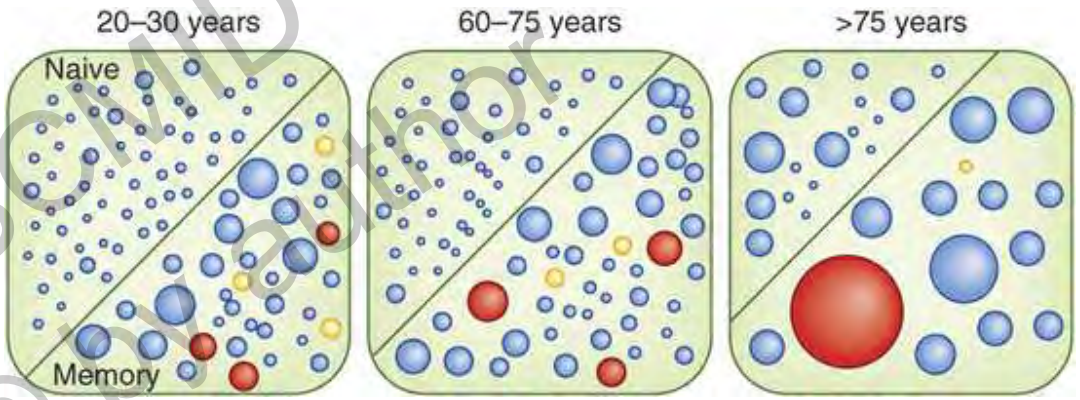
Tajiri et al., WJG 2013

Immune system in the elderly „immunosenescence”



„The price paid by adaptive system to maintain CMV in a latent phase is very high”

Low grade inflammation: Coronary arterial disease, atherosclerosis, liver cirrhosis?



T-cell evolution

TERMA cells (terminally differentiated memory cells, CD3+/CD28- with re-expression of CD45RA)

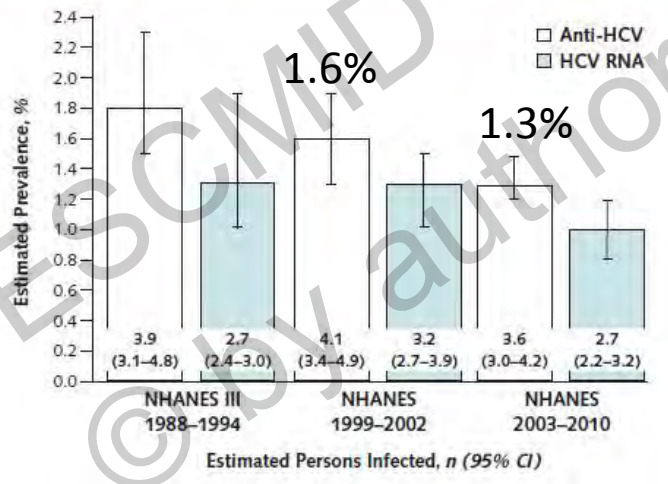
Labri et al. Aging Healt 2013, Fulop et al Front Immun 2013

Hepatitis C epidemiology in the elderly - US

Table 1. Demographic Characteristics by HCV Status for Participants Aged ≥20 y: NHANES 2003–2010 (n = 19 901)

Characteristic	HCV Status				*P* Value*
	Anti-HCV–Negative		HCV RNA–Positive		
	Participants, *n*	Proportion (95% CI)	Participants, *n*	Proportion (95% CI)	
Age at interview					<0.001
20–29 y	3501	19.3 (18.3–20.4)	5	1.2†‡ (0.3–5.2)	
30–39 y	3320	19.0 (18.1–19.9)	28	10.1 (6.4–15.6)	
40–49 y	3284	20.4 (19.5–21.4)	89	40.7 (34.0–47.8)	
50–59 y	2746	17.5 (16.7–18.4)	93	38.3 (31.6–45.4)	
≥60 y	6779	23.8 (22.5–25.1)	56	9.7 (6.8–13.6)	

Figure. Estimated prevalence of anti-HCV and HCV RNA in persons aged ≥6 y, according to NHANES III (1988–1994), NHANES 1999–2002, and NHANES 2003–2010.

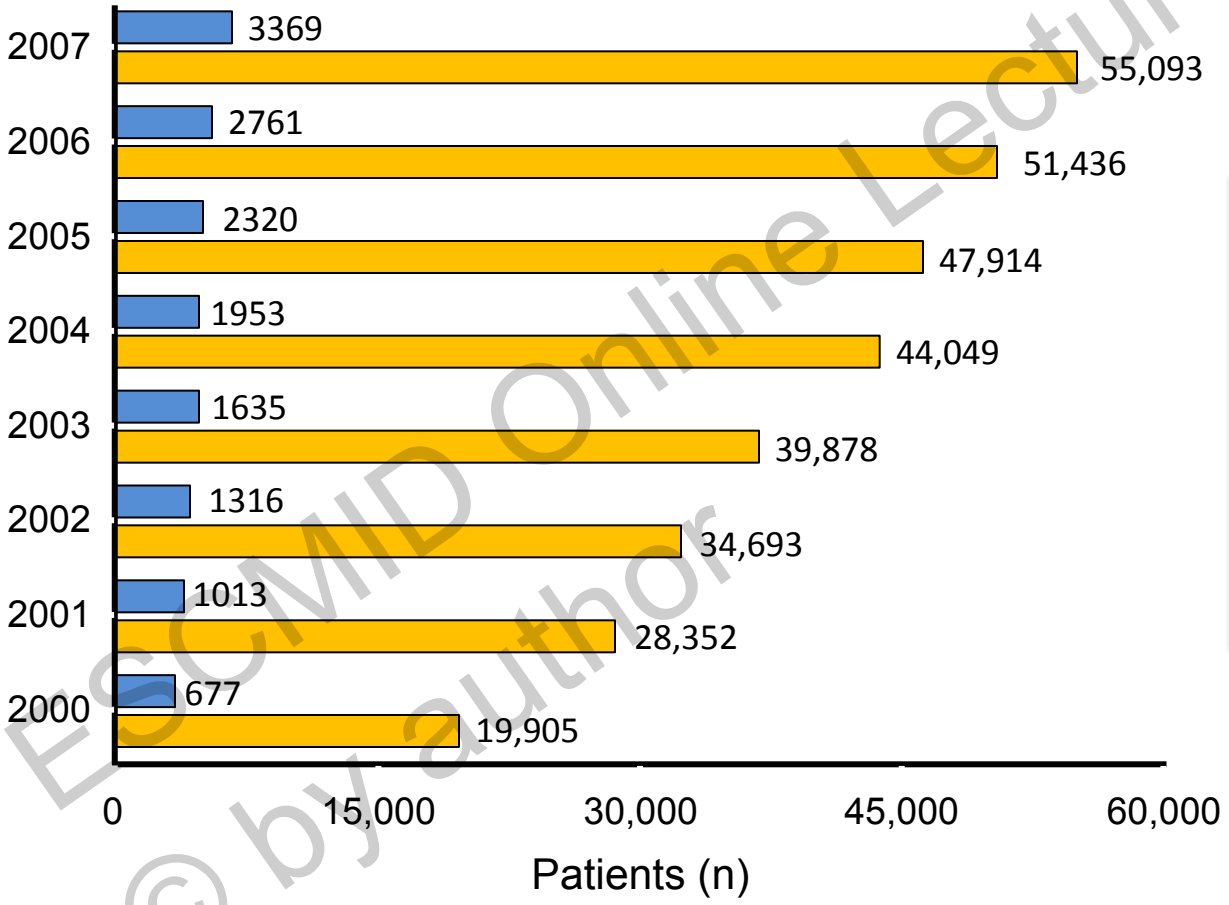


- Decrease in prevalence probably reflects increasing mortality from HCV-related conditions
- These deaths largely occur in the age group born between 1945 and 1965 (the "Baby Boom" generation)
- The urgency of addressing this underappreciated national epidemic

Denniston et al., Ann Intern Med. 2014

Cirrhosis and HCC in Veterans: A Perfect Storm

- Most of HCV infected veterans were born in the baby boom, served in Vietnam war era and were infected in their 20s
- ***Average duration of infection is now 30-40 yrs***



Over an 8-yr period (2000-2007) the number of veterans diagnosed with **cirrhosis increased 2.5-fold and with HCC 5-fold**

Davison J, et al. Public Health Matters. 2009;4:2-4. Slide from CCO

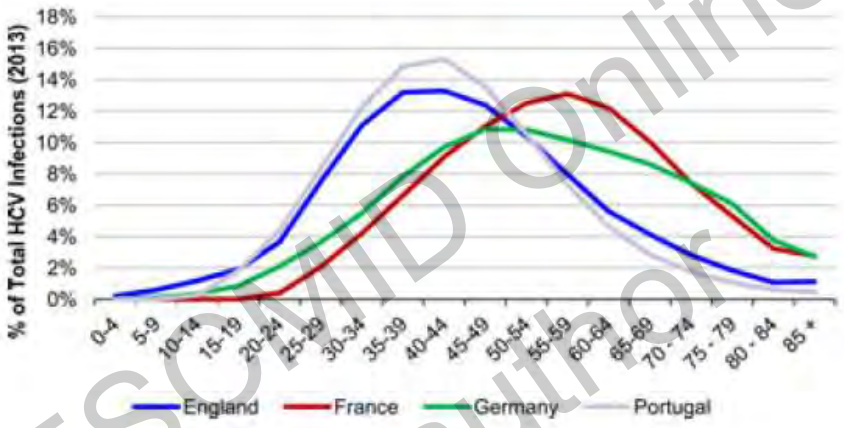
Hepatitis C epidemiology in the elderly - Europe

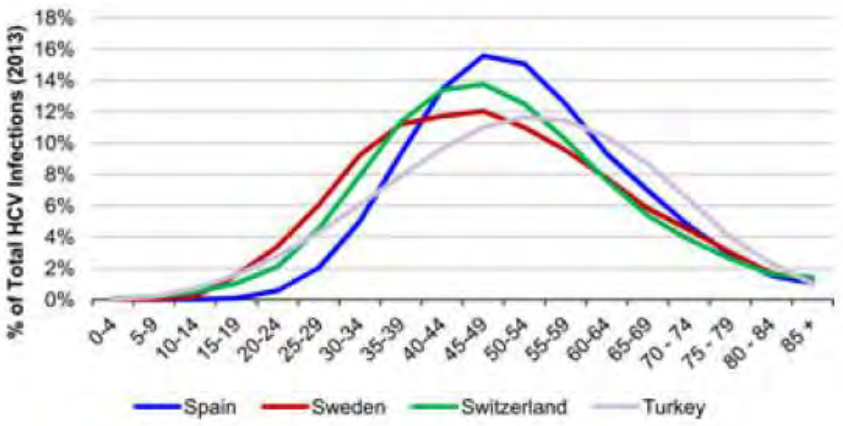
In southern Europe (Italy, Spain, France) and Japan, the elderly are the most affected group by HCV-infection[1]

Southern Europe (Italy, Spain, France): prevalence of 16% to 42% in people ≥60 years of age, and approximately 33%-50% of people over 80 years[1-3]

Japan: 41% of people aged 80-89 years were found to have anti-HCV antibodies in a community-based prospective study between 1984 and 1995[1,4]

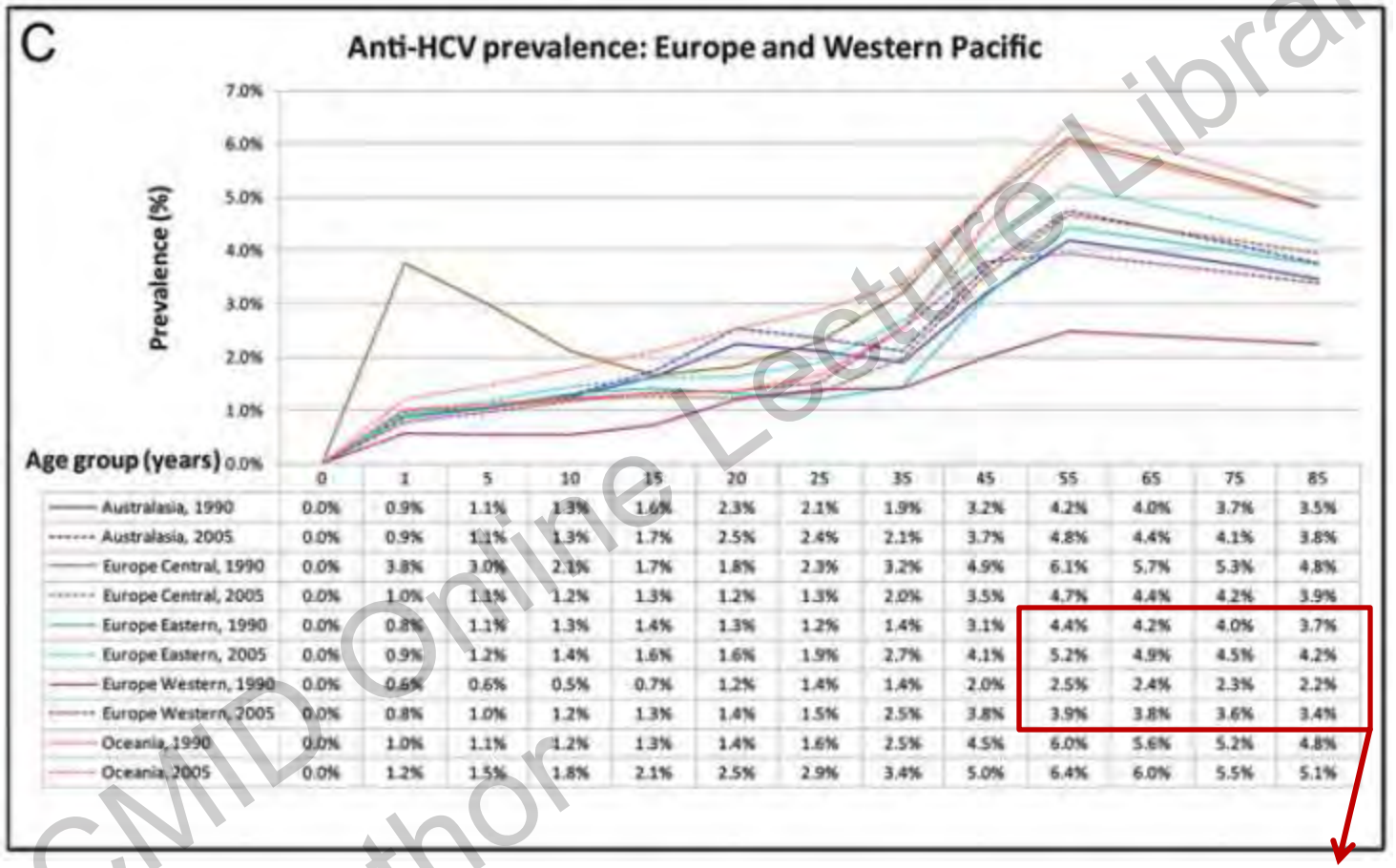
Distribution of HCV-infected population by age as a % of total number of cases[5]





1. Cainelli F. Hepatitis C virus infection in the elderly: epidemiology, natural history and management. Drugs Aging. 2008;25(1):9-18. 2. Maggi G, Armitano S, Brambilla L, et al. Hepatitis C infection in an Italian population not selected for risk factors. Liver. 1999;19(5):427-431. 3. Maio G, d'Argenio P, Stroffolini T, et al. Hepatitis C virus infection and alanine transaminase levels in the general population: a survey in a southern Italian town. J Hepatol. 2000;33(1):116-120. 4. Okayama A, Stuver SO, Tabor E, et al. Incident hepatitis C virus infection in a community-based population in Japan. J Viral Hepatitis. 2002;9:43-51. 5. Razavi H, Present epidemiology of hepatitis C cases, Journal of Viral Hepatitis 2014, 21:34.

Hepatitis C epidemiology in the elderly - Europe



Age group (years)	0	1	5	10	15	20	25	35	45	55	65	75	85
Australasia, 1990	0.0%	0.9%	1.1%	1.3%	1.6%	2.3%	2.1%	1.9%	3.2%	4.2%	4.0%	3.7%	3.5%
Australasia, 2005	0.0%	0.9%	1.1%	1.3%	1.7%	2.5%	2.4%	2.1%	3.7%	4.8%	4.4%	4.1%	3.8%
Europe Central, 1990	0.0%	3.8%	3.0%	2.1%	1.7%	1.8%	2.3%	3.2%	4.9%	6.1%	5.7%	5.3%	4.8%
Europe Central, 2005	0.0%	1.0%	1.1%	1.2%	1.3%	1.2%	1.3%	2.0%	3.5%	4.7%	4.4%	4.2%	3.9%
Europe Eastern, 1990	0.0%	0.8%	1.1%	1.3%	1.4%	1.3%	1.2%	1.4%	3.1%	4.4%	4.2%	4.0%	3.7%
Europe Eastern, 2005	0.0%	0.9%	1.2%	1.4%	1.6%	1.6%	1.9%	2.7%	4.1%	5.2%	4.9%	4.5%	4.2%
Europe Western, 1990	0.0%	0.6%	0.6%	0.5%	0.7%	1.2%	1.4%	1.4%	2.0%	2.5%	2.4%	2.3%	2.2%
Europe Western, 2005	0.0%	0.8%	1.0%	1.2%	1.3%	1.4%	1.5%	2.5%	3.8%	3.9%	3.8%	3.6%	3.4%
Oceania, 1990	0.0%	1.0%	1.1%	1.2%	1.3%	1.4%	1.6%	2.5%	4.5%	6.0%	5.6%	5.2%	4.8%
Oceania, 2005	0.0%	1.2%	1.5%	1.8%	2.1%	2.5%	2.9%	3.4%	5.0%	6.4%	6.0%	5.5%	5.1%

Age group	55	65	75	85
Europe Eastern 1990	4.4%	4.2%	4.0%	3.7%
Europe Eastern 2009	5.2%	4.9%	4.5%	4.2%
Europe Western 1990	2.5%	2.4%	2.3%	2.2%
Europe Western 2005	3.9%	3.8%	3.6%	3.4%

Hanafiah et al. Hepatology 2013

What a difference the age makes?
Is it duration or age at acquisition that matters?

Table 3. Retrospective-Prospective Cohort Studies of the Natural History of Hepatitis C

Study	Group	Exposure interval (*y*)	Cirrhosis (%)	HCC (%)	Liver death (%)
Vogt[22]	Children	17	0.3	0	0
Kenny-Walsh[23]	Young women	17	2.0	0	0
Wiese[24]	Young women	20	0.4	0	0
Seeff[25]	Young men	45–50	5.9	0	0
Thomas[26]	IDU	9–15	1.1	0	2.1
Rodger[27]	Comm acq	25	4.0	0	1.0
Seeff[28]	PTH	23	15.0	1.9	2.8

NOTE. Reproduced from Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002;36:S35–S46.[13]

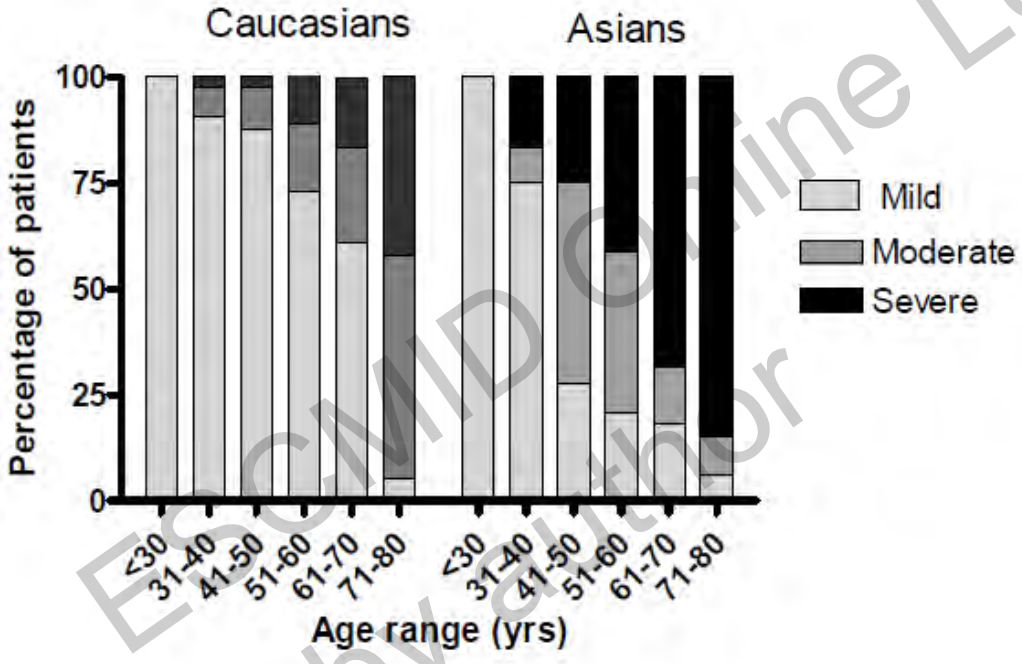
Table 1. Factors Associated with Disease Progression in Chronic Hepatitis C

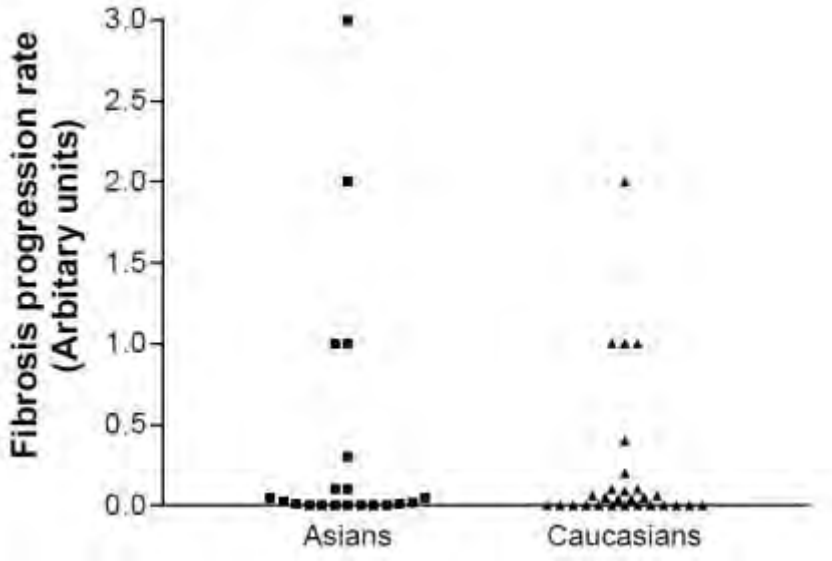
Nonmodifiable factors	Potentially modifiable factors
Age at acquisition of infection	ALT level
Duration of infection	Activity on liver biopsy
Male sex	Alcohol consumption
Race	Coinfection with HBV or HIV
Host genetic factors	Coinfection with schistosomiasis
Viral genotype	Metabolic factors (steatosis, insulin resistance)
	Cigarette smoking
	Daily cannabis use
	Iron overload

Missiha et al., Gastroenterology 2008

Increased risk of cirrhosis with duration of infection

- A retrospective study in London: 143 adult Asian patients who presumably had been infected with HCV for many decades were compared with 239 Caucasian patients.
- Of Asian patients aged 61–80 years (n =55) 78% had cirrhosis, whereas 25% of Caucasian patients aged 61–80 years (n =55) had cirrhosis





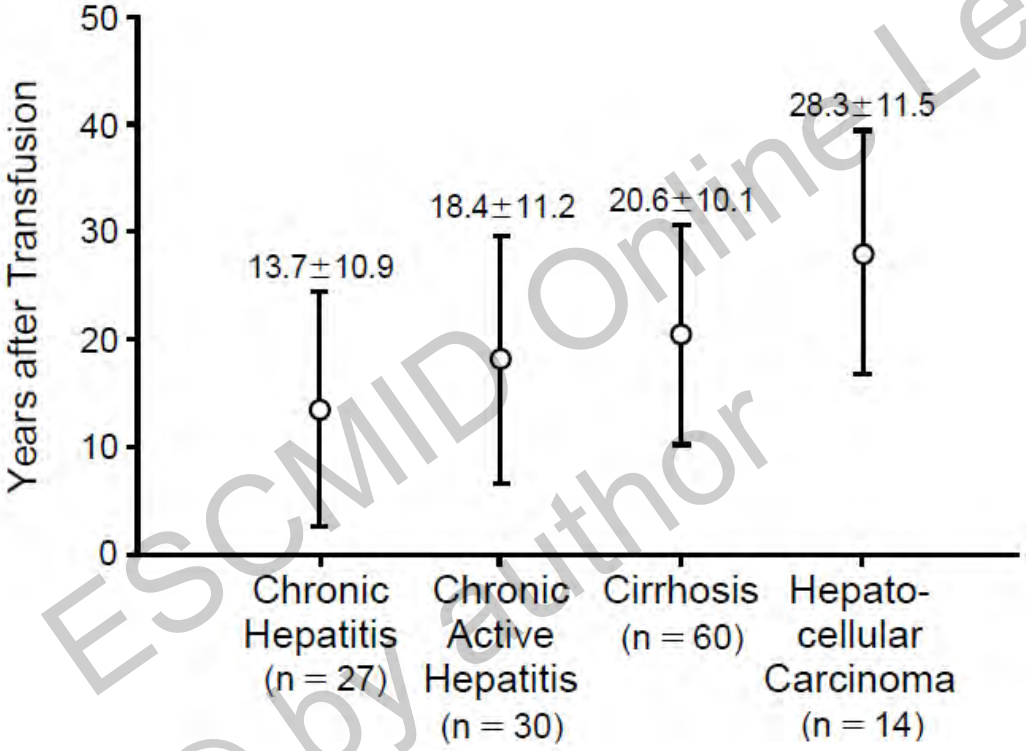
Fibrosis progression by paired liver biopsies

D'Souza et al., Clin Gastro Hepatol 2005

CLINICAL OUTCOMES AFTER TRANSFUSION-ASSOCIATED HEPATITIS C

MYRON J. TONG, PH.D., M.D., NEVEEN S. EL-FARRA, B.S., ANDREW R. REIKES, M.D., AND RUTH L. CO, R.N.

103 patients received a transfusion before the age of 50 (average age, 29.2 years) and 28 when they were 50 or older (average age, 58.5 years).



Time of developing of complications by age at infection (yrs)

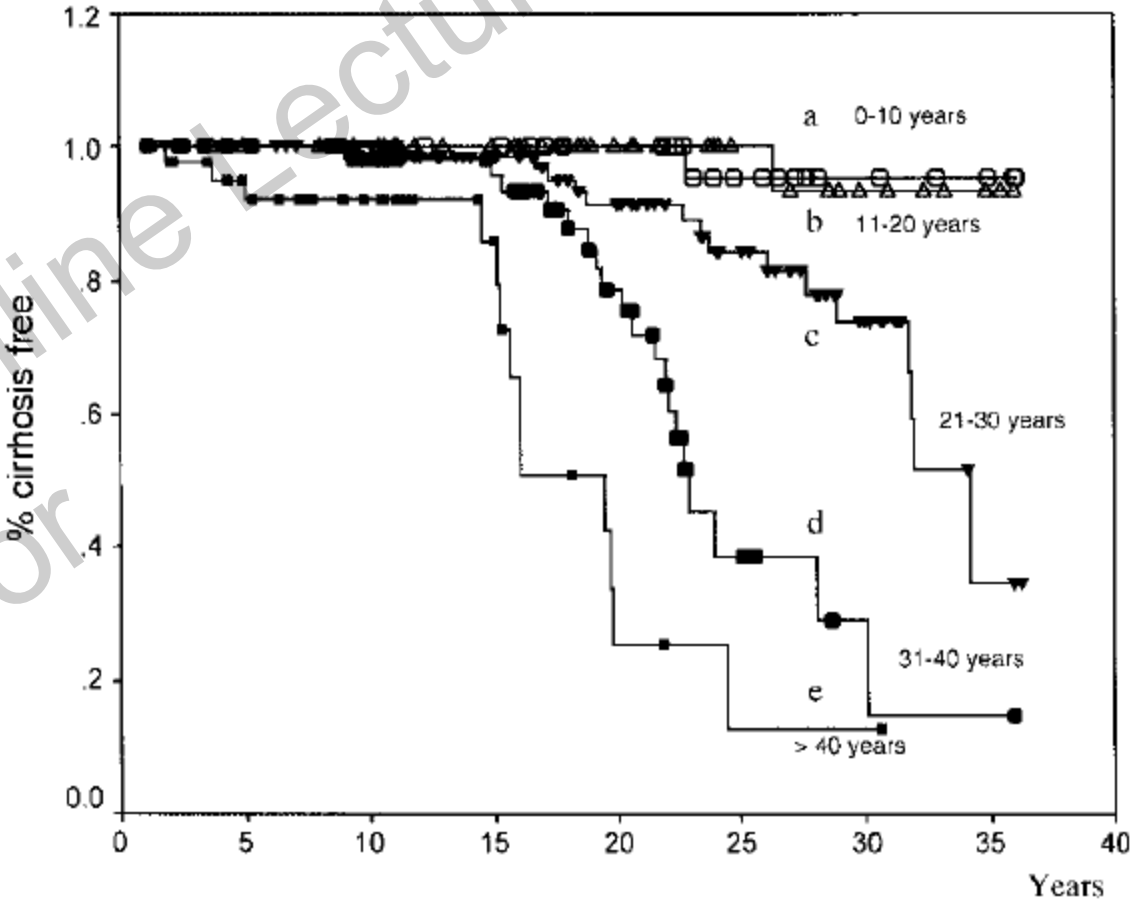
	<50 yo	≥50 yo
Hepatitis	15.9	6.3
Cirrhosis	23.6	9.8
HCC	31.5	14.7

Twofold faster progression

Age at infection is a significant factor for liver cirrhosis development

- 392 subjects with anamnestic evidence of a single and precisely dated transfusion event, and showed no other causes of chronic liver disease
- After a mean interval of 18.4 years, 54 patients (20.1%) had cirrhosis

Time to have 50% probability of liver cirrhosis development by age at infection:
21-30: 33 years
31-40: 28 years
>40: 16 years



Minola et al, Blood 2002

Risk factors for extensive fibrosis in a large cross-sectional study from France

- 6,865 patients ≥65 yr old were included, 2,169 patients underwent liver biopsy

Table 6. Factors Associated with Fibrosis Stage in 2,169 Patients with an Available Liver Biopsy (Univariate Analysis) in DOSVIRC Patients

	Low Fibrosis (F0 or F1) N = 1,112	Extensive Fibrosis (F2, F3 or F4) N = 1,057	*p*
Male gender, %	53	61	<0.001
HIV positive antibodies, %	12	12	0.95
Alcohol consumption ≥50 g/day %	9	17	<0.001
Age at biopsy (yrs)*	41.8 (11.1)	48.6 (13.6)	<0.001
≥65 yrs %	4	14	<0.001
Age at infection*,†	25.4 (11.2)	29.8 (14)	<0.001
Diabetes, %	1.85	5.46	<0.001
Body Mass Index*	23.0 (3.8)	24.3 (4.3)	<0.001

* Mean (SD).
† Data available for 1412 patients.

Thabut et al. Am J Gastroenterol 2006

Higher proportion of patinets with normal ALT and significant fibrosis in the elderly

Table 12. Percentages of Patients with Normal ALT According to Fibrosis Stage at Fibrotest and Age at Sampling*

	<65 yrs	65–79 yrs	>80 yrs	Total	*p*
F0	6,198 (65)	290 (83)	10 (91)	6,498 (66)	<0.001
F0-F1	1,297 (55)	154 (80)	8 (80)	1,459 (56)	<0.001
F1	726 (52)	98 (71)	4 (80)	828 (53)	<0.001
F1-F2	2,332 (45)	474 (65)	42 (78)	2,848 (48)	<0.001
F2	962 (40)	327 (58)	29 (81)	1,318 (44)	<0.001
F3	971 (33)	451 (46)	51 (53)	1,473 (36)	<0.001
F3-F4	94 (24)	56 (41)	6 (40)	156 (29)	<0.001
F4	1,033 (26)	557 (30)	112 (36)	1,702 (27)	<0.001

*Missing data for fibrosis stage, N = 7.

In the study of Monica et al. among HCV-RNA+ elderly subjects normal ALT was observed in 46% vs 11% in younger adults (10 years follow-up)

Thabut et al. Am J Gastroenterol 2006, Monica et al Dig Liver Dis 2006

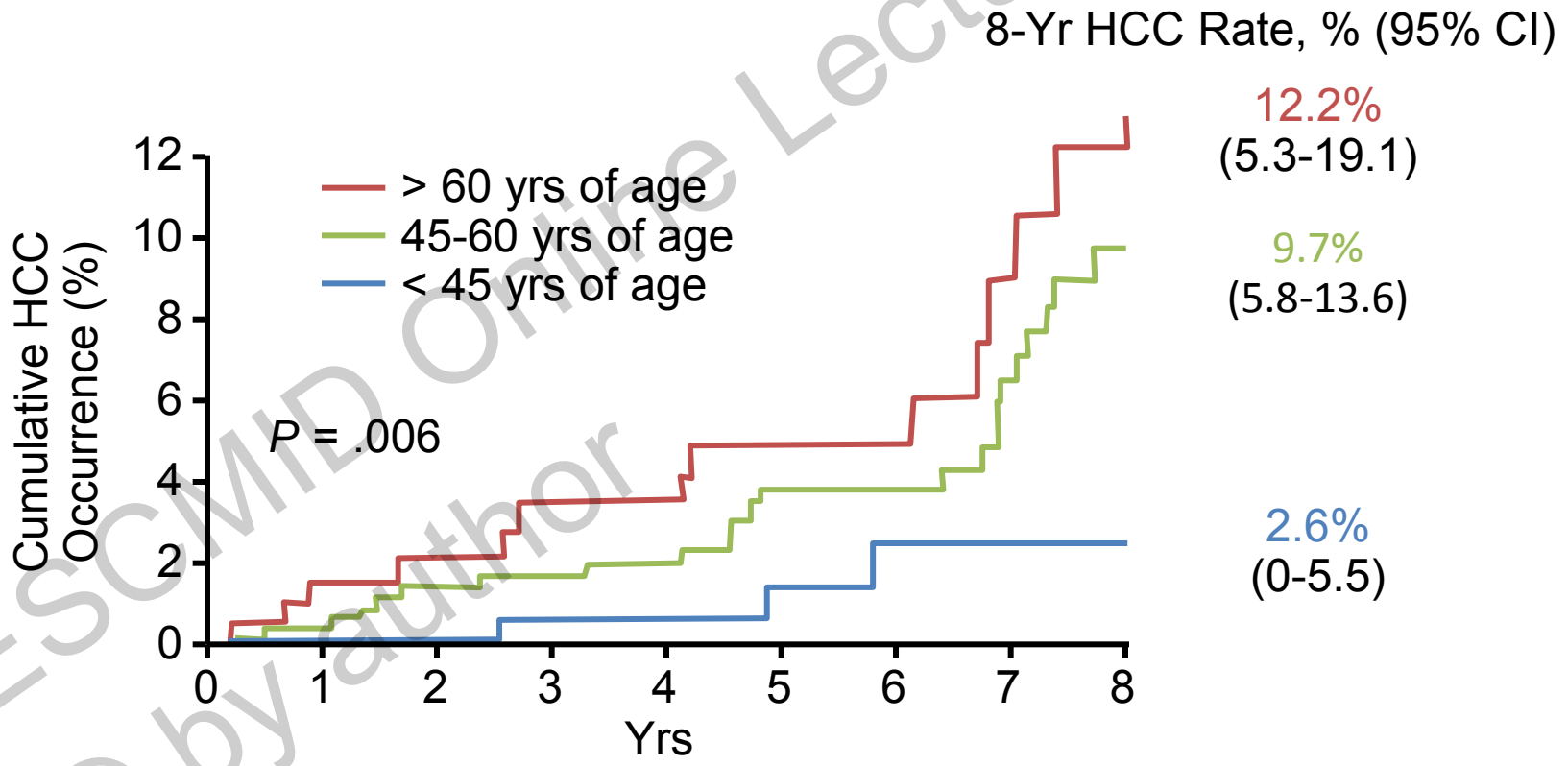
HCV-infection is diagnosed at more advanced stage and with higher prevalence of comorbidities in the elderly

Characteristics	<65 years (n = 386)	≥65 years (n = 174)	P
HCV awareness (%)	279 (72)	96 (55)	<0.0001
Diagnosis			
Chronic hepatitis (%)	284 (74)	86 (49)	0.000
Liver cirrhosis (%)	84 (22)	67 (39)	0.000
Hepatocellular carcinoma (%)	18 (5)	21 (12)	0.000
Mode of diagnosis			
Histological (%)	137 (35)	34 (20)	0.000
Clinical (%)	249 (65)	140 (80)	
Normal ALT (%)	133 (34)	58 (33)	ns
Asymptomatic patients (%)	362 (94)	149 (86)	0.002
Complication as initial manifestation (%)	6 (2)	9 (5)	0.02
Presence of comorbid conditions (%)	267 (69)	148 (85)	<0.0001
Main comorbid conditions			
Cardiovascular diseases (%)	27 (7)	30 (17)	0.0002
Chronic pulmonary diseases (%)	8 (2)	20 (11)	<0.0001
Hypertension (%)	88 (23)	87 (50)	<0.0001
Diabetes (%)	76 (20)	47 (27)	0.05
Cancer other than HCC (%)	8 (2)	12 (7)	0.004
Chronic renal failure (%)	3 (1)	2 (1)	ns
Cerebrovascular diseases (%)	1 (0.3)	7 (4)	0.002
Psychiatric disorders (%)	42 (11)	10 (6)	0.05
Metabolic syndrome (%)	56 (14)	33 (19)	ns
Hematologic diseases (%)	29 (8)	22 (13)	0.05

Gramenzi et al. Journal of Viral Hepatitis, 2010

Age as a risk factor for HCC following SVR in HCV pts with advanced fibrosis

- 1000 patients with bridging fibrosis or cirrhosis who achieved SVR following IFN-based HCV therapy followed for median of 5.7 yrs



Van der Meer AJ, et al. AASLD 2013. Abstract 143. Slide from CCO.

Donor age and fibrosis progression after OLTx

- Post-transplant liver biopsies were examined in 56 HCV-infected LT-patients

Table 3 Comparison of recipients who experienced graft fibrosis at a fast (greater than 0.8 fibrosis units per year) or slow (less than 0.8 units per year) rate

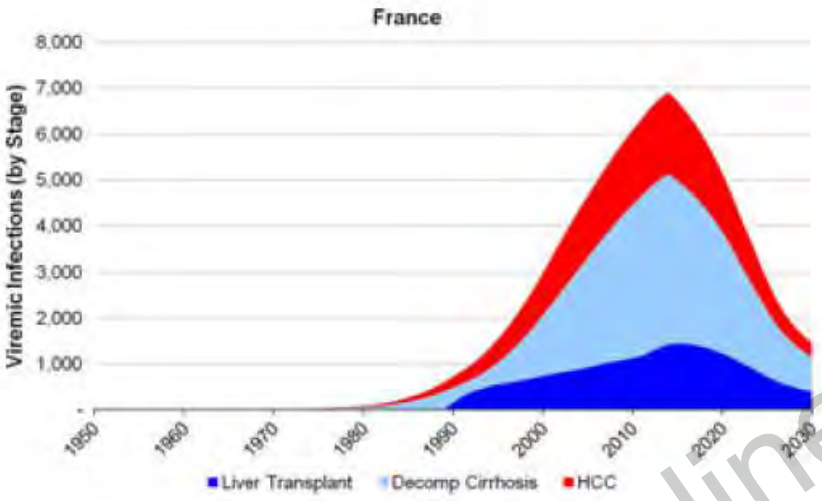
	Slow fibrosis (<0.8 units/year)	Fast fibrosis (>0.8 units/year)	Univariate analysis	Multivariate analysis
n	29	27		
Recipient age (y)	50 (34–67)	46 (28–65)	0.3	0.7
Recipient sex (M/F)	24/5	21/6	0.6	0.8
Caucasian	15	14	0.4	0.5
Cyclosporin/tacrolimus	26/3	23/4	0.6	0.4
Treated rejection	10	11	0.6	0.12
>1 episode rejection	3	0	0.2	0.8
HBsAg positive*	3	2	0.7	0.5
Cold ischaemic time (min)	787 (261–1280)	780 (353–1055)	0.7	0.4
Warm ischaemic time (min)	44 (25–58)	51 (33–76)	0.02	0.01
Donor sex (M/F)	18/11	20/7	0.34	0.34
Donor age (y)	38 (15–64)	45 (17–67)	0.09	0.02
Date of transplantation (pre/post 11/96)	16/13	12/15	0.42	0.96

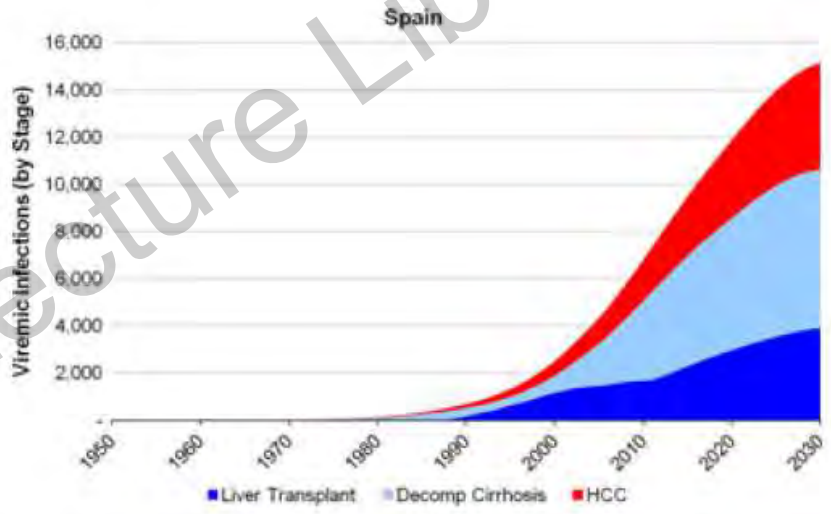
HBsAg, hepatitis B virus surface antigen.
*Serum status pre-transplant—all were serum HBsAg negative post-transplant.
Data are median (range).

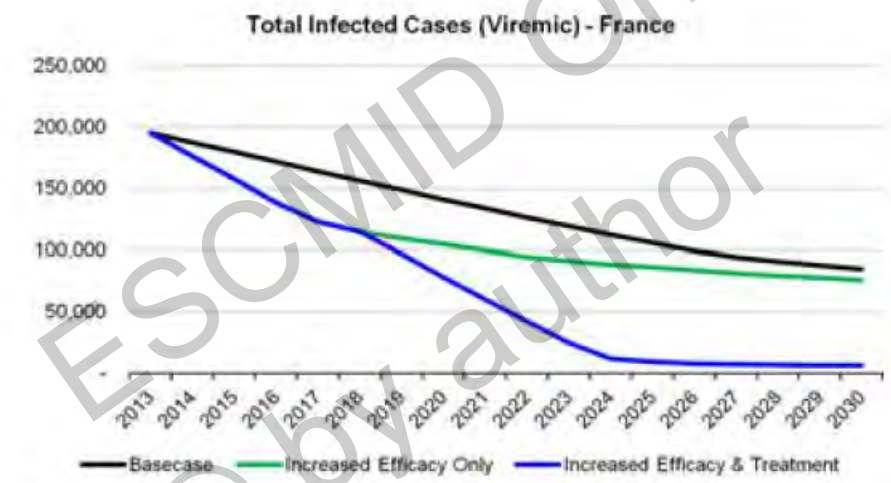
Predicted interval form transplantation to graft cirrhosis according to <u>donor age</u>
<40: 10 years
40-49: 6.7 years
>49: 2.7 years

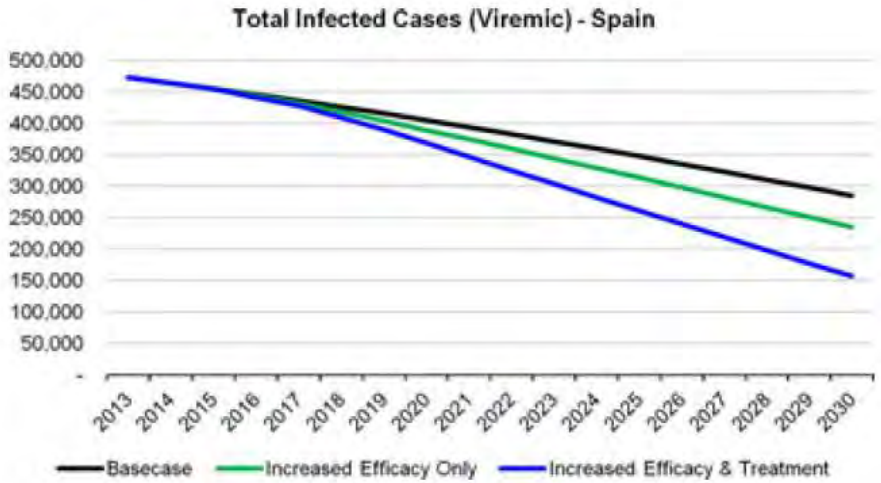
Wali et al. Gut 2002

The most important is to screen and treat as many patients as possible!





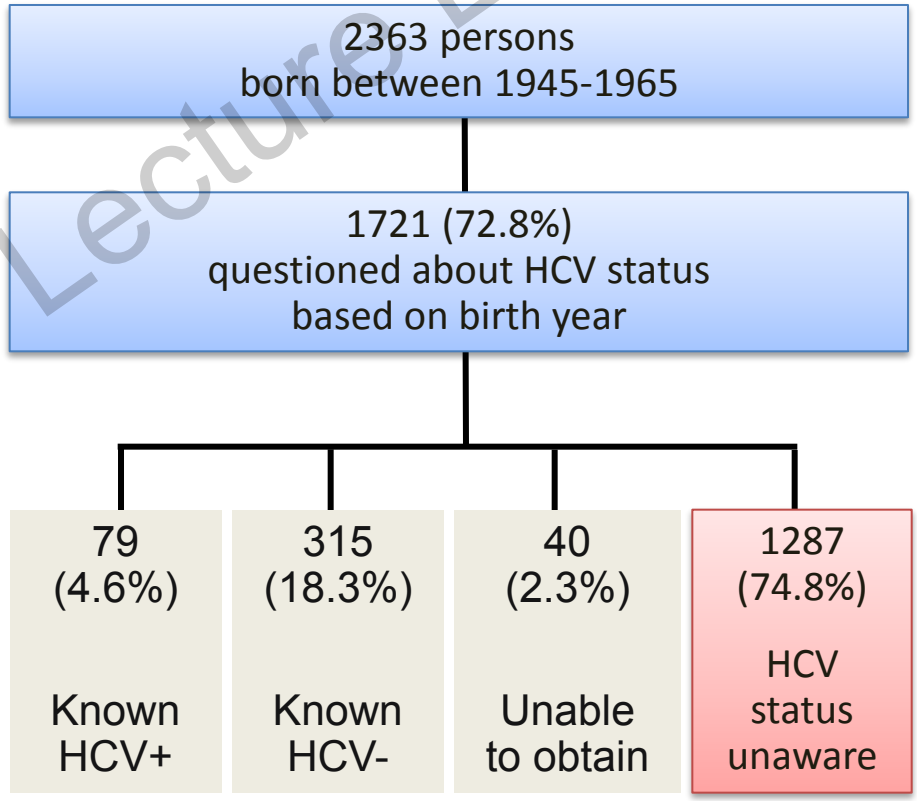




Razavi H et al. J Viral Hep 2014; Wedemeyer H et al. J Viral Hep 2014

Opt-Out HCV Screening of Baby Boomers in Urban Emergency Department

- University of Alabama ED
  - Interim report: screening from 9/3/13 to 10/17/13
- Screening population and methods
  - Born between 1945-1965 and medically and surgically stable
  - Verbal questionnaire administered by ED nurse
  - Anti-HCV testing provided results within 29 mins
  - Quantitative HCV RNA testing followed



Galbraith JW, et al. AASLD 2013. Abstract LB-6. Slide from CCO.

Conclusions

- Physiological **changes occur in the liver with age** (decreased liver regeneration, detoxication), immunosenescence but also cumulative environmental exposure for hepatotoxins which can influence natural course of liver disorders
- Elderly constitute the **most affected age group** by HCV-infection in Europe (>40%) with increasing prevalence
- **Duration of infection** but also **age at acquisition** of HCV-infection are significant risk factors for liver cirrhosis and HCC development
- HCV-infection is not only **diagnosed at later stages** in the elderly but also with **various comorbidities** which may limit therapeutic options but also affect disease progression