Chronic hepatitis B and C in Bulgaria
why we need of screening?

L. Mateva, K. Antonov

World Hepatitis Day - 5th July 2012, Sofia,

HBV and HCV infection in Bulgaria

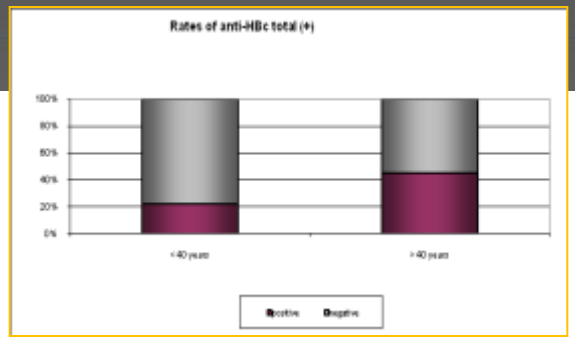
- HBV and HCV infection are a serious public health problem in Bulgaria
  - as many other countries in Europe /World
  - *High prevalence and risk of transmission*
  - *Severe liver complications (particularly HCC) and death*
  - *Diminished health-related quality of life*
- Unfortunately, systematic data for the burden of HBV/HCV infection are not available yet
    - prevalence and incidence
    - negative impact on HBV/HCV-related disease on life-expectancy, morbidity, and mortality
    - Impact on QoL
    - cost
  - There are no effective monitoring / national data base and screening program

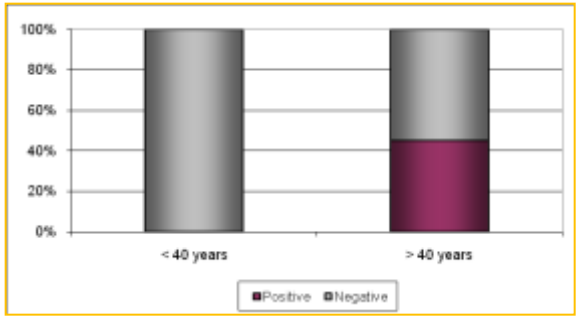
Characteristics of HBV infection in Bulgaria

Effective vaccination program in Bulgaria!

Rate of anti-HBc total

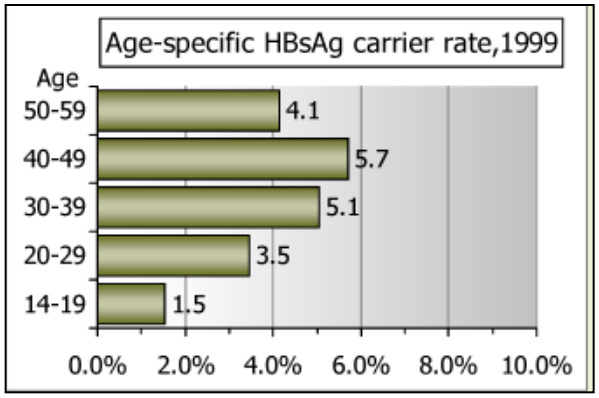
- 30 % - blood donors in Sofia (2008)
  - significantly higher mean age of anti-HBc total (+) subjects than non-reactive: 41.6 ± 2.2 vs. 35.1 ± 1.2 y.
- 30,4% - healthy volunteers (all > 40 y.), (2009)





HBsAg carrier rate

- 5.1% - blood donors (1987)
- 3.9 % - total population (1999)
- 2.2 % - blood donors in Sofia (2008) and healthy volunteers (all >40 y.), (2009)



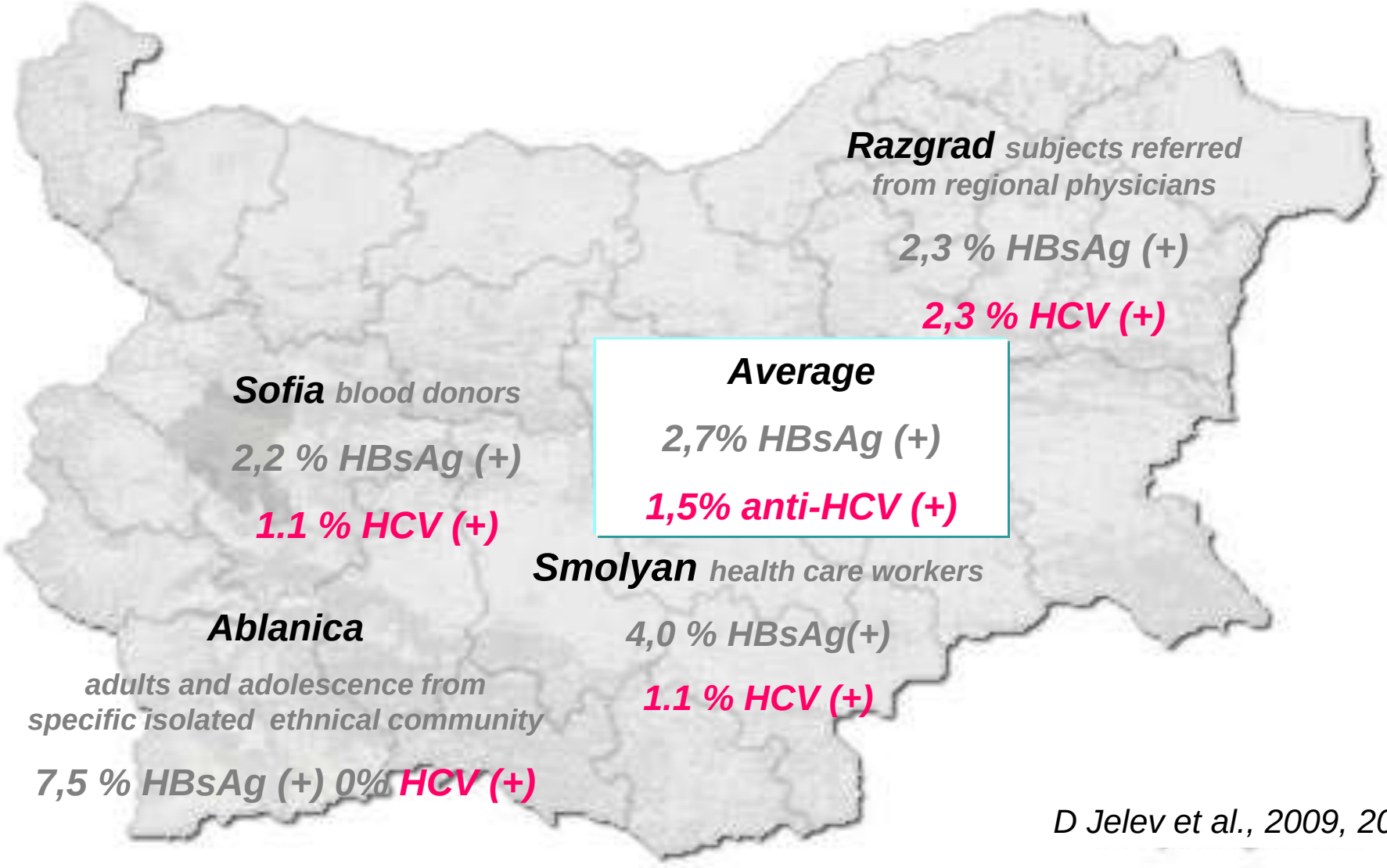
Gubev E et al, 1987, Teocharov P al.1999 Kojuharova M, P, 1999 and 2001 Jelev D et al, 2008 and 2009

The prevalence of HBsAg carrier rate is still higher among risk groups

- 11.2% - dialyzed patients
- 11.6% - hemophilia and afibrinogenemia
- < 6% - injection drug users (2006)

Vassilev ZP et al, 2006

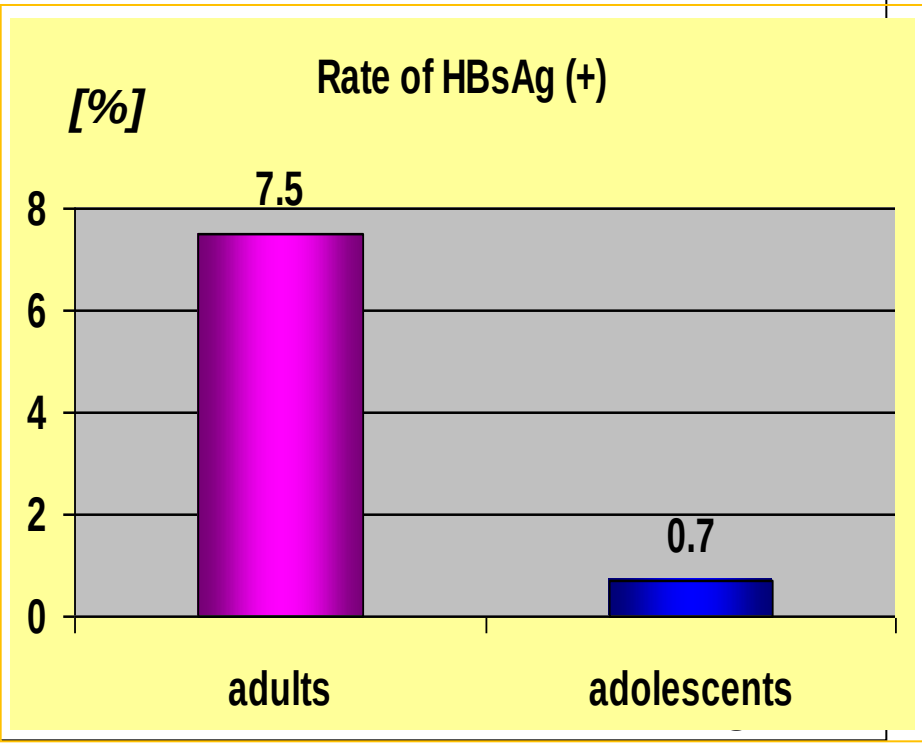
Prevalence of HBsAg(+) and anti-HCV(+) in 4 different groups from 4 different country regions



D Jelev et al., 2009, 2011

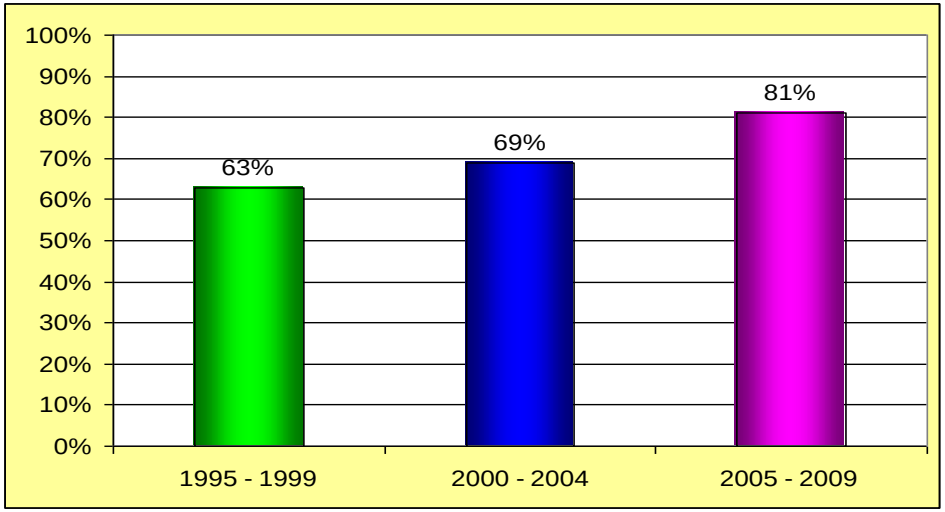
Characteristics of HBV infection in village of Ablanitza

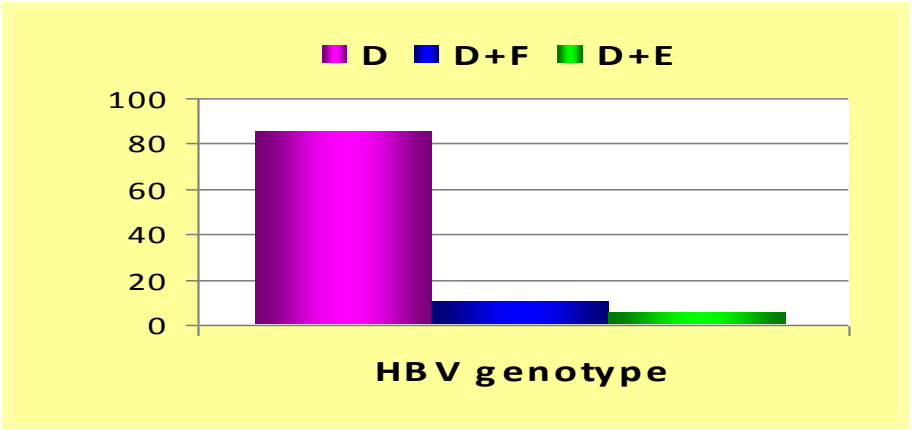
- 676 subjects were tested
  - 412 adults
  - HBsAg (+) adolescents 2/264
    - Born after 1992 from HBsAg (+) mothers



Characteristics of HBV infection in Bulgaria

- HBeAg –negative CHB
  (n= 260)
- HBV-genotype D or mixed genotypes (D+F, D+E, D+A)
- is predominant in CHB (n=58) and acute hepatitis B (21/23)





Krastev Z et al, 2006, Tcherveniakova et al, 2008, D. Jelev et al; 2009

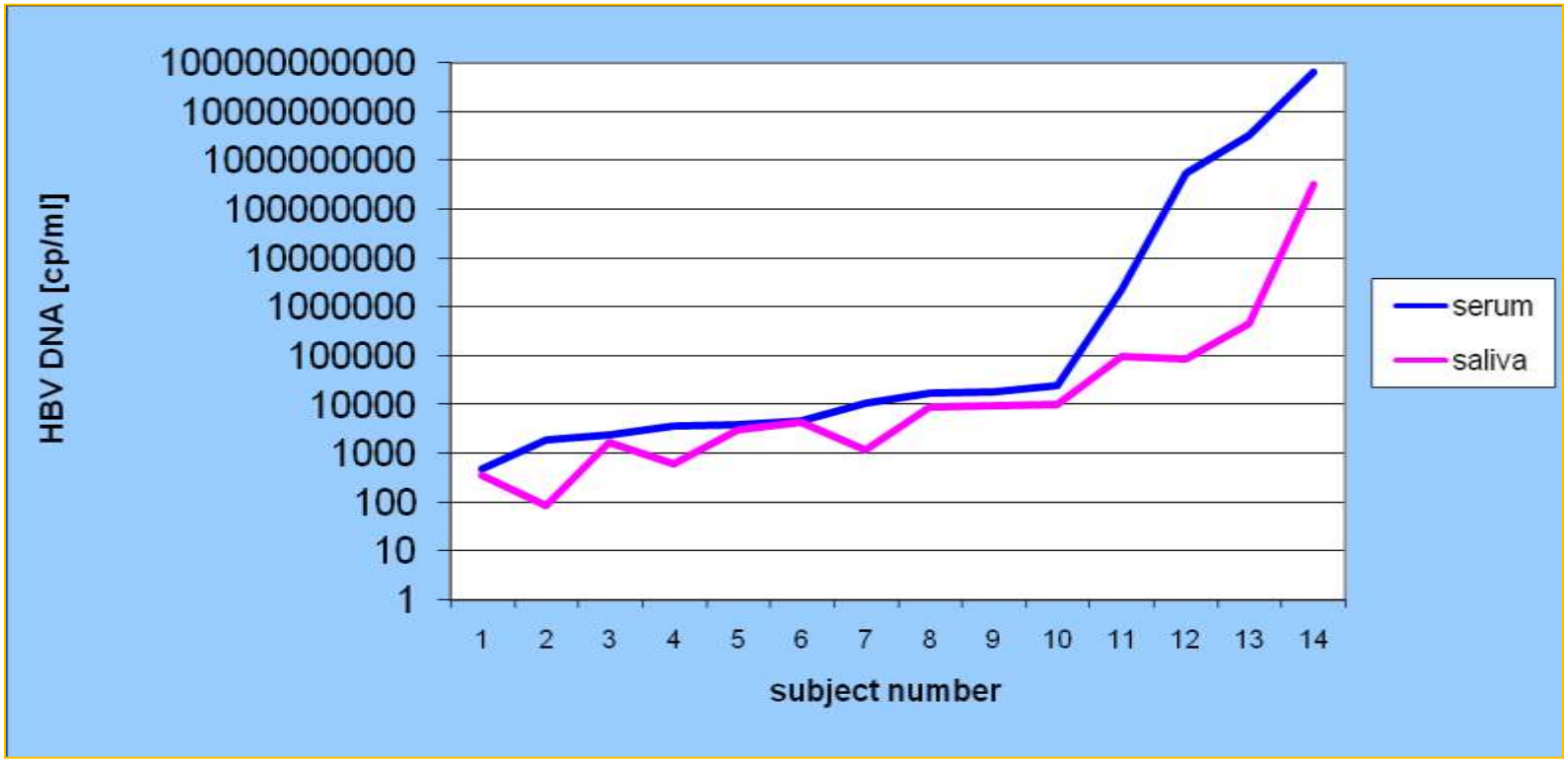
HDV infection

- 8.6% among HBsAg (+) subjects (1986)
- 16% - in active liver disease (1999)

Naoumov N et al, 1986 , Antonov K, 1999

Saliva and transmission of HBV infection?

- *HBV DNA - 14 parallel serum and saliva samples tested by RT PCR*



Ivanova A et all, 2008

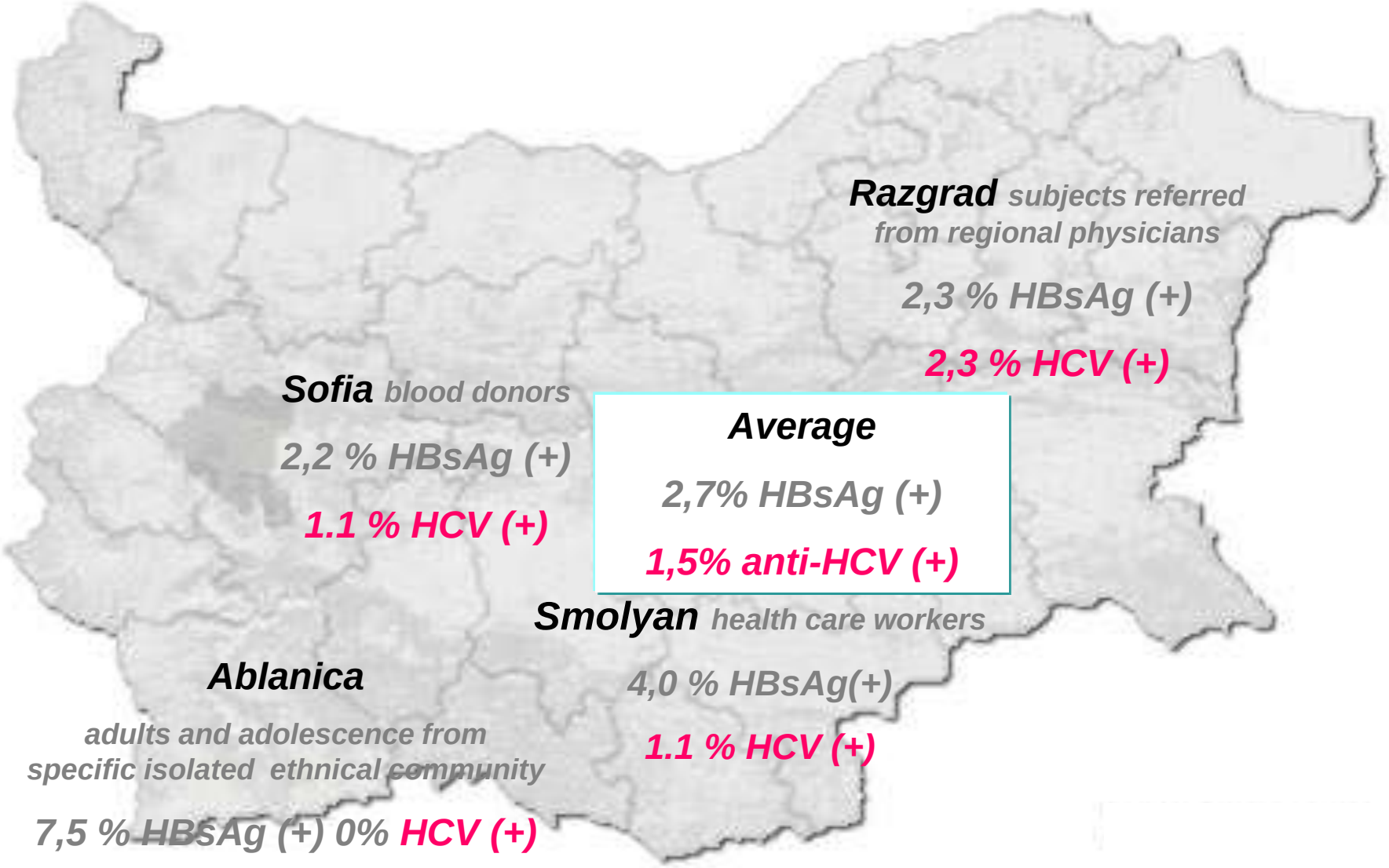
Characteristics of HCV infection in Bulgaria

The rate of HCV-Ab (+) carriers

- Bulgarian blood donors
  - 1,4 % *(1999)*
  - 1,1% Blood donors in Sofia *(2007)*
- Medical personnel in hemodialysis
  - 1.2 % *(n=114, 1994)*

P. Draganov et al.,1994, P. Teocharov Pet al.1999 N Naumov et al., 1999 V Jordanova et al, 2007, D Jelev et al 2011

Prevalence of HBsAg(+) and anti-HCV(+) in 4 different groups from 4 different country regions



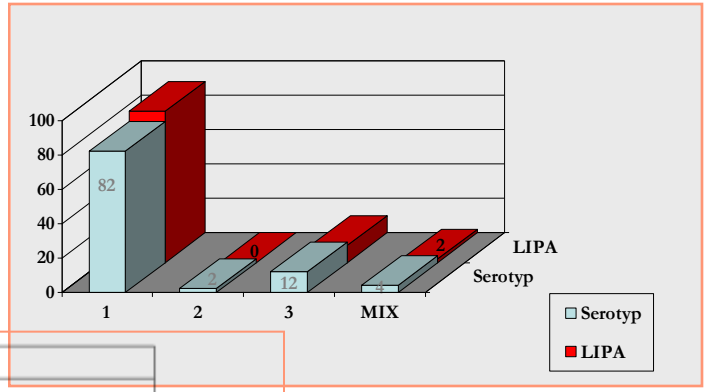
High prevalence of HCV in specific groups in Bulgaria

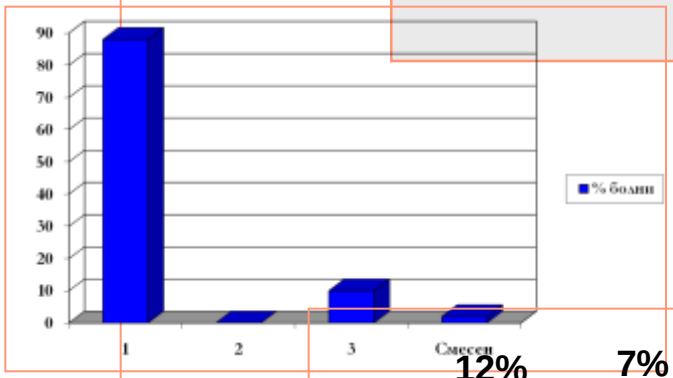
- Patients with haemophilia
  - 75% *(1991)*
- Patients on haemodialysis
  - 42% *(1994)*
- Patients with porphyria cutanea tarda
  - 52% *(1996)* - Family – 20%, sporadic - 63%

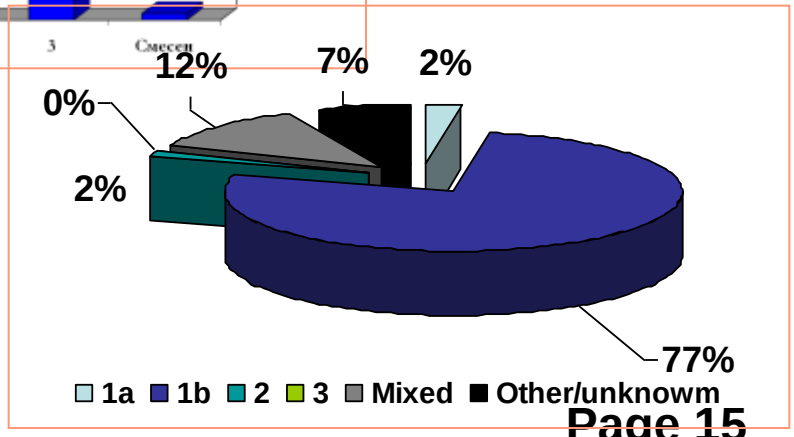
N Naumov, T.Lisichkov,, L. Mateva , 1991, P. Draganov et all.,1994, K. Antonov et all.,1996

Genotype 1b HCV - the most common infection among Bulgarian patients – 90%

- HCV genotype 1
  - 82% -88%
  - Predominantly - subgroup "b"
- Mixed infection (genotype 1 + 2 or 3)
  - Near 4%
- HCV genotype 3
  - 10-12%

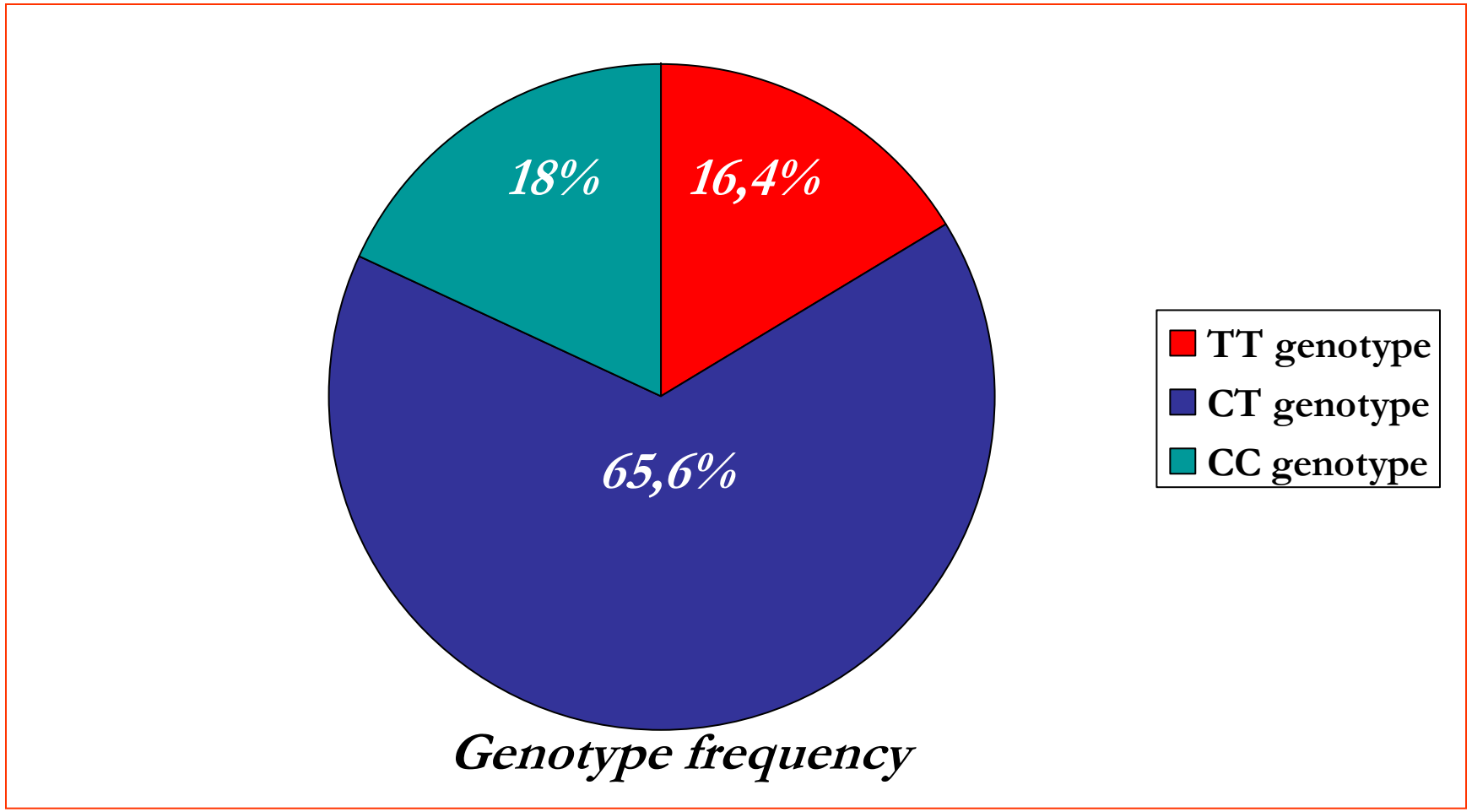






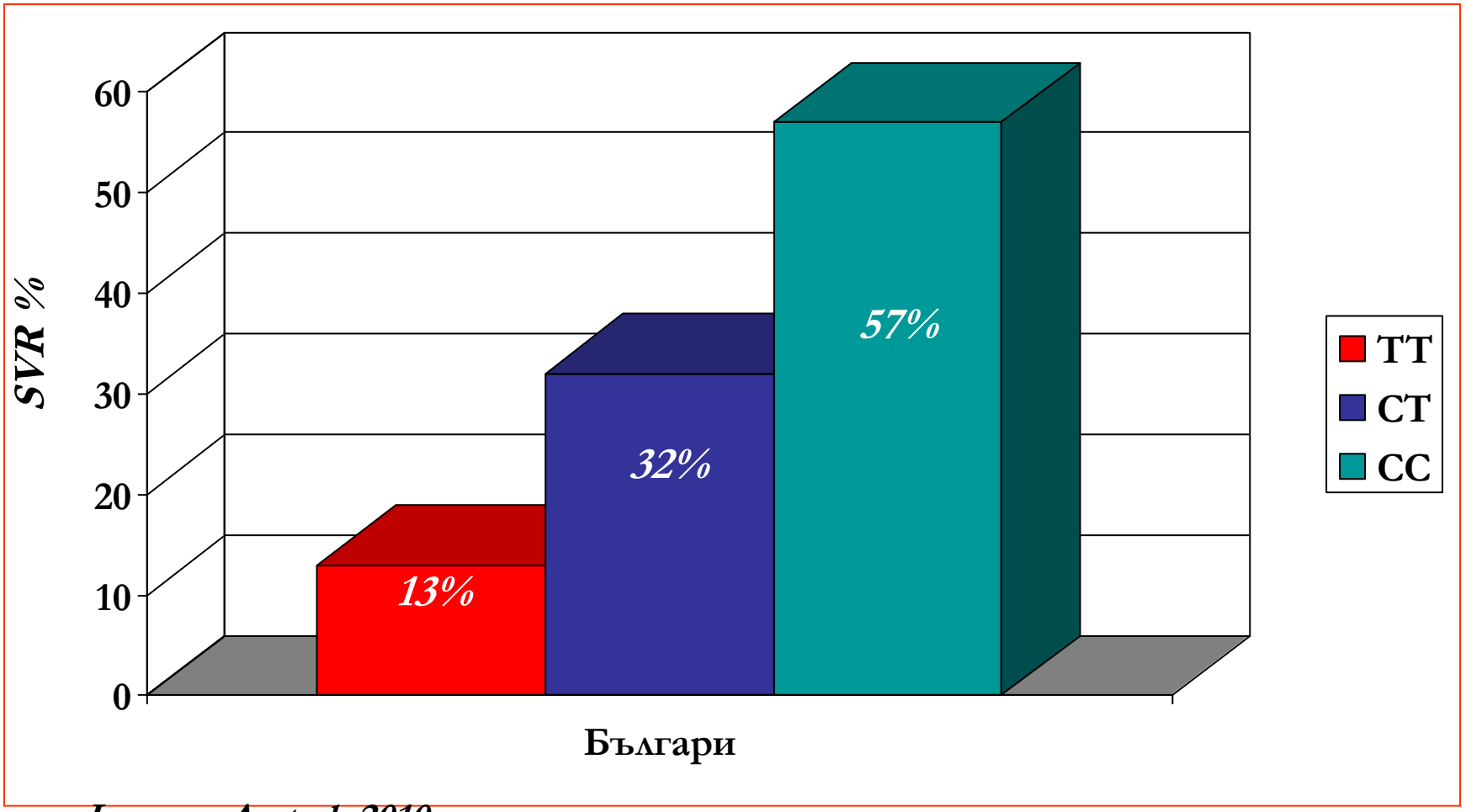
N. Naumov, 1999, I Ivanova et al., 2005. K. Antonov thesis

IL28B polymorphism (rs12979860) in Bulgarian patients with chronic genotype 1 HCV infection



Ivanova A et al. 2010

IL28B polymorphism (rs12979860) in Bulgarian patients with chronic genotype 1 HCV infection and SVR



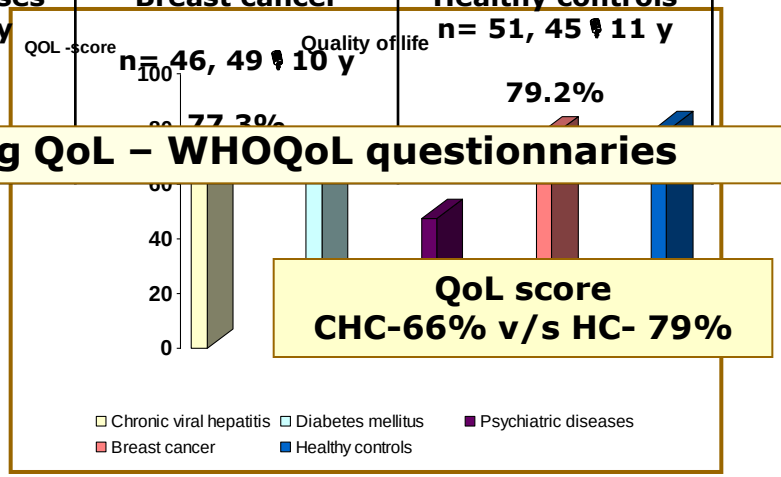
Ivanova A et al. 2010

HCV Impacts Quality of Life

No systematic data

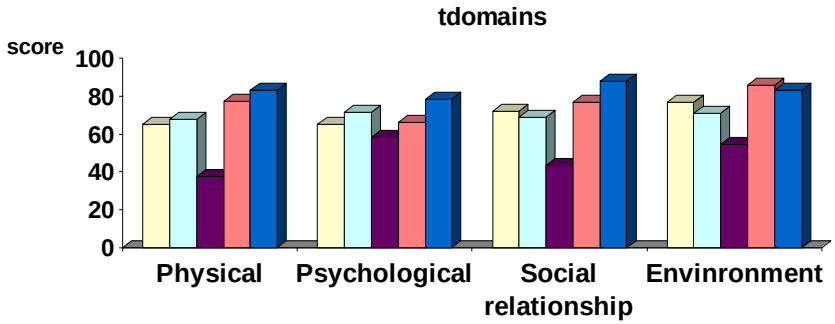
Health-related quality of life (QoL)
Reductions (-13%) in women with CHC

CHC	DM	Psychiatric diseases	Breast cancer	Healthy controls
n= 44, 45 ± 15 y	n= 40, 54 ± 13 y	n= 38, 43 ± 14 y	n= 46, 49 ± 10 y	n= 51, 45 ± 11 y
66.2%	64.6%	47.3%	77.3%	79.2%



- **Nonspecific disease Instruments for Assessing QoL – WHOQoL questionnaries**

- HCV-infected Bulgarian women had a worse QoL scores than healthy controls, and women with successfully treated breast cancer, tested by nonspecific disease WHOQoL questionnaries.
- = DM
- A reduction was found in all domains

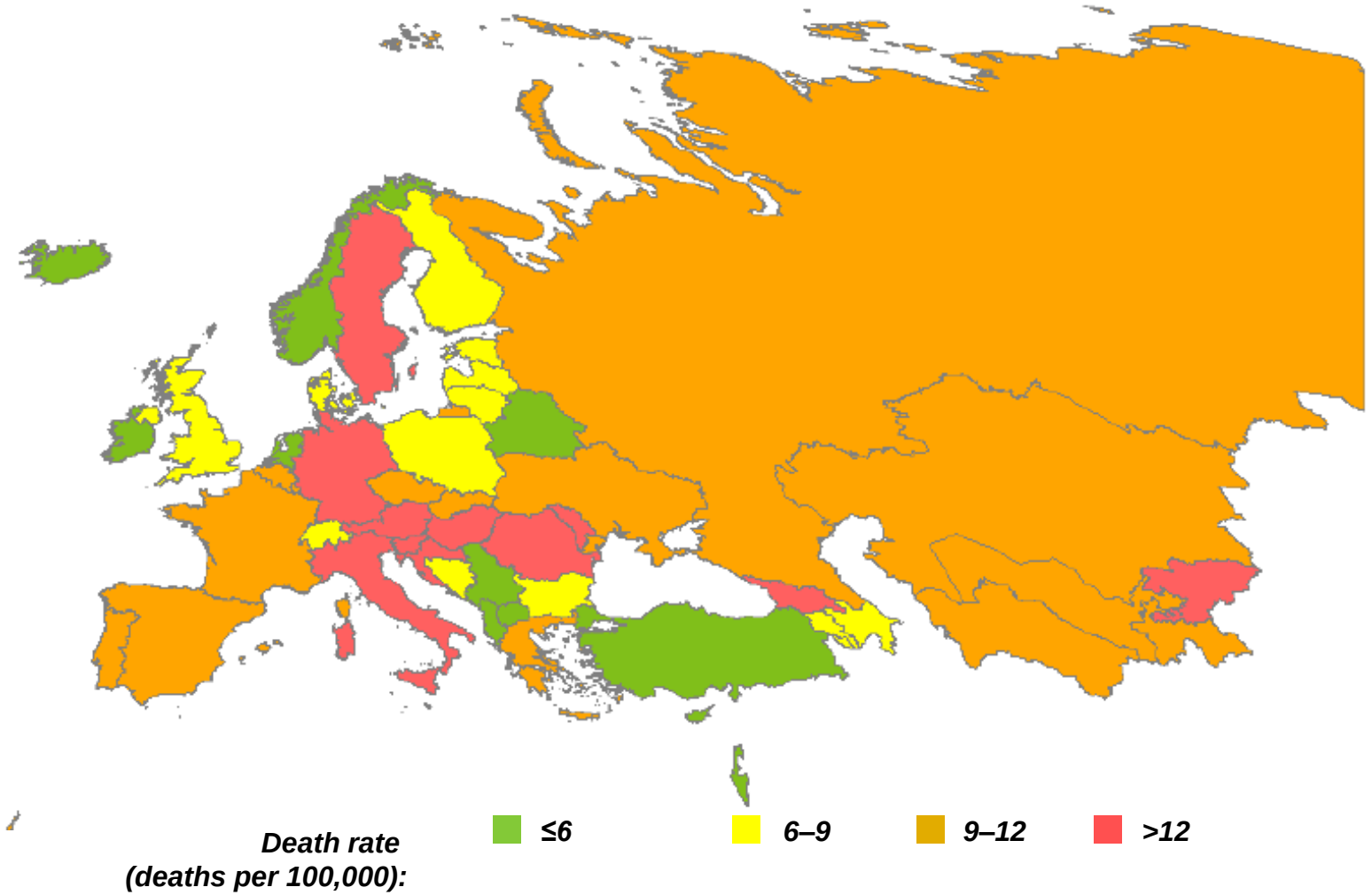


J. Mihaylova, L. Mateva et al. , 2002

Disease mortality from HBV/HCV

No systematic data

HCV-related death rates in countries of the WHO European

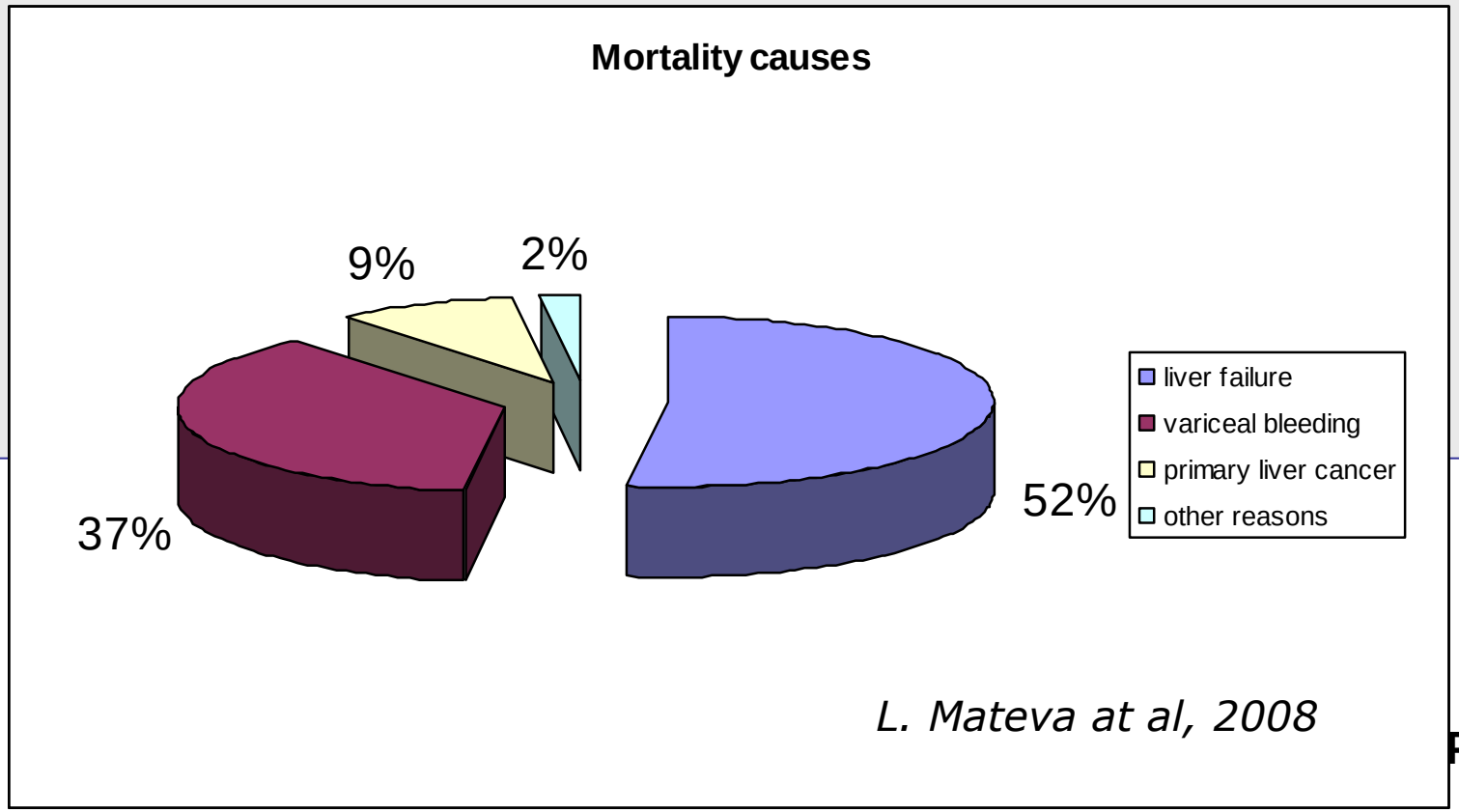


Mühlberger N, et al. BMC Public Health 2009;9:34

Causes of death

- Causes of death - 98% cirrhosis-related complications
- liver failure, UGI bleeding, HCC

- Only 2% of patients died from other reasons



L. Mateva at al, 2008

How we starts?

Test and treat

1980 – HBV infection

1990 – HCV infection

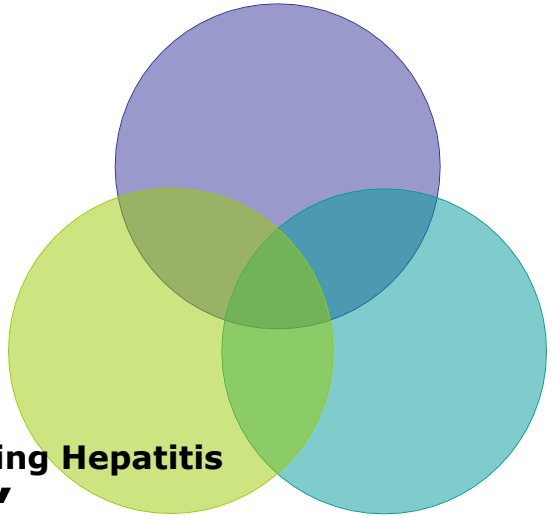
K. Antonov et al., 1994,1997, 1998, 2001, 2005, thesis

Peg-IFN α -based therapy

- HBV – Peg-IFN α
- HCV - Peg-IFN α 2a/2b + Ribavirin 2001
  - has been evaluated as cost-effective (NICE HTA, 2007)

Where we are now?

Bulgarian Society of Gastroenterology



National Association for Fighting Hepatitis
"Hepasist"

NHIF

+ support of Industry

Work together and go forward

To reduce the impact of HBV/HCV infection in Bulgaria

NHIF: National Program for Diagnosis and Antiviral Treatment of Patients with Chronic Viral Hepatitis (since 2002)

Bulgarian SGE's Practice Guidelines on the Diagnosis, Management, and Treatment of Chronic Viral Hepatitis: version 2001,2002, 2005.., and 2012

According EASL's Practice Guidelines

NHIF: National Programme for Antiviral Treatment of Patients with CVH

- 11 Centers – Clinics of Gastroenterology
  - (7- Sofia + Varna, Plovdiv, Pleven, Stara Zagora)

  Local commissions
    - Individual assessment of benefit/risks ratio of antiviral therapy -protocol
- Central committee of experts at NHIF
    - According acceptable standard criteria and selecting the right patient for treatment
    - Waiting list (up to 2009)
    - Therapy and follow up

100% REIMBURSEMENT

Antiviral therapy

HCV RNA /HBV DNA
+
Active viral infection / fibrosis

- CH C
  - Peg-IFNα + RBV
- CH B
  - Peg-IFN
  - NUCs (Lamivudine, Telbivudin, Entecavir, Tenofovir)

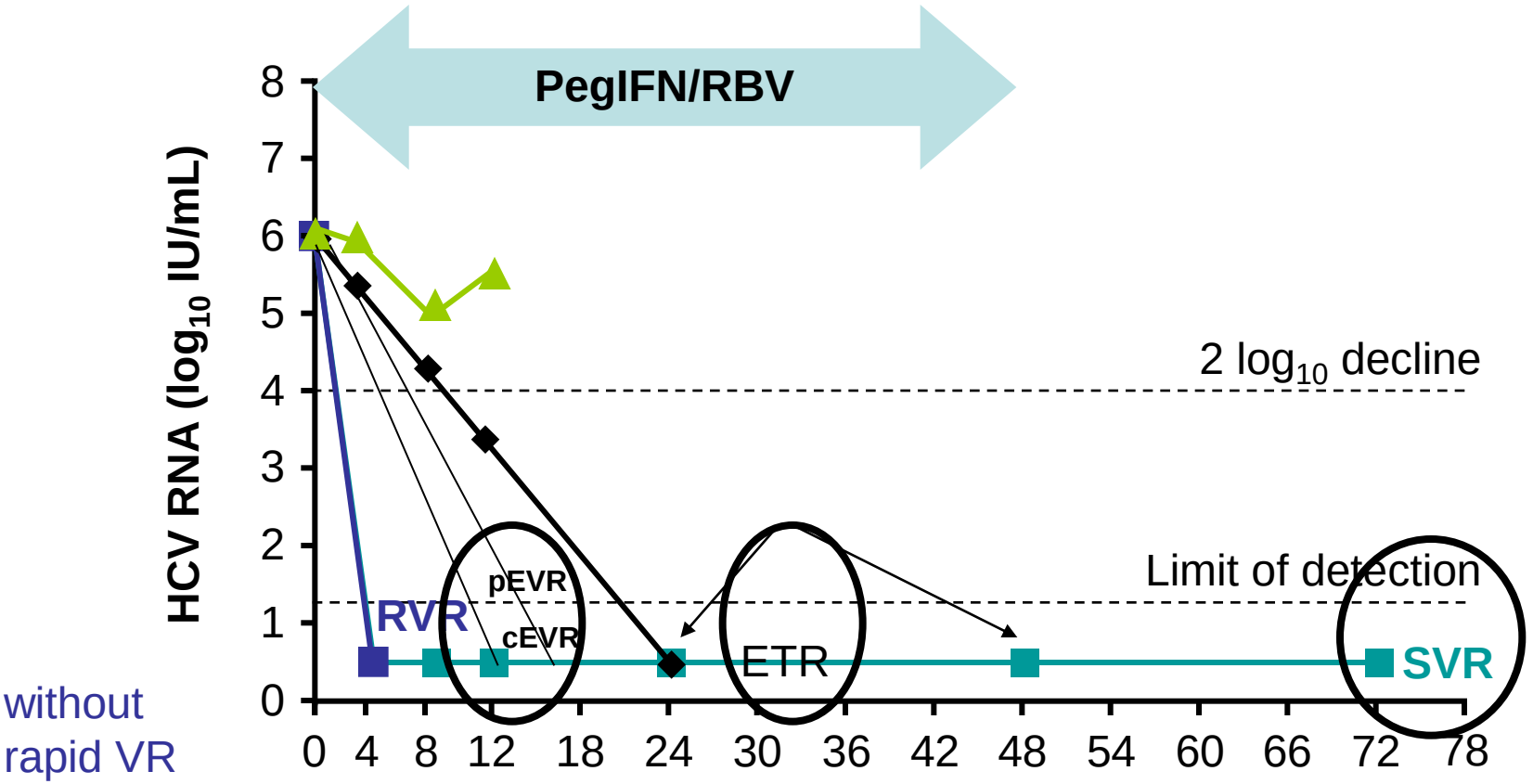
Assessment prior to treatment and monitoring during and after therapy
Schedule for follow-up

Parameters	Therapy												Follow-up	
	0	2w	1m	2m	3m	4m	5m	6m	7m	8m	9m	12m	+ 3m	+ 6m
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver enzymes	X		X	X	X	X	X	X	X	X	X	X	X	X
Standard Clin. chemistry Test+ TSH	X							X				X		
Anti-HCV /Gynotype	X													
HCV RNA (*Quantitative)*					G - 2,3			G-1				X		X
Anti-HCV /Gynotype	X													

HCV RNA negative at 6th mo after stop of therapy ⇒ + 24th mo (2nd y)

Responders, Non-responders, Relapsers

Virological responses during and after therapy



EVR –early: complete or partial, ETR, SVR – sustained
Relapse, partial / null VR – nonresponder

Clinical Endpoint

significant reduction of HCV/HBV -associated complications and mortality

CH C

- SVR = successful HCV treatment
  - undetectable serum HCV RNA levels 24 wks (6 mo) after end of treatment

  - 2 y (24th mo)

CH B

- HBV DNA < 10 000 copies/ml (2 000 IU/ml)
  - 24 wks (6 mo) after end of treatment by „real time" PCR

- Seroconversion - HBeAg and HBsAg

Regional distribution

- NHIF provides treatment of the patients from the whole country who cover the inclusion criteria

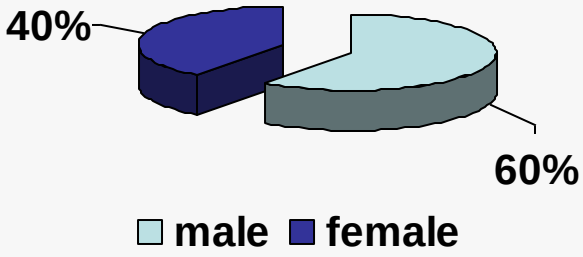
Treated patients

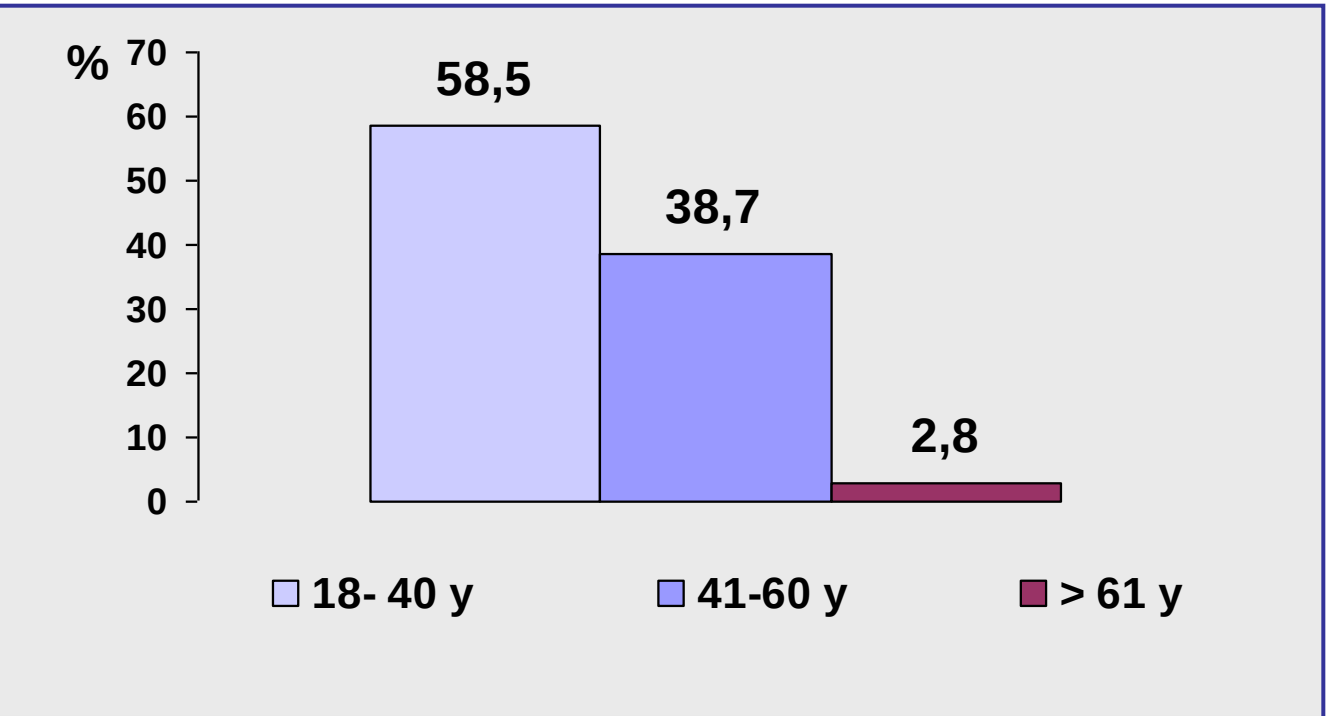
G. Kondeva, N. Tarinska,2005

NHIF: National Programme for Antiviral Treatment of Patients with CVH

Age and sex distribution

More than half are young - aged 18- 40 years

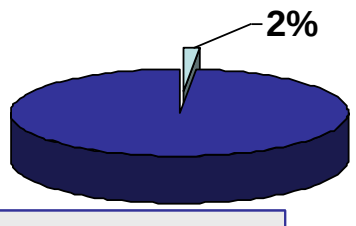




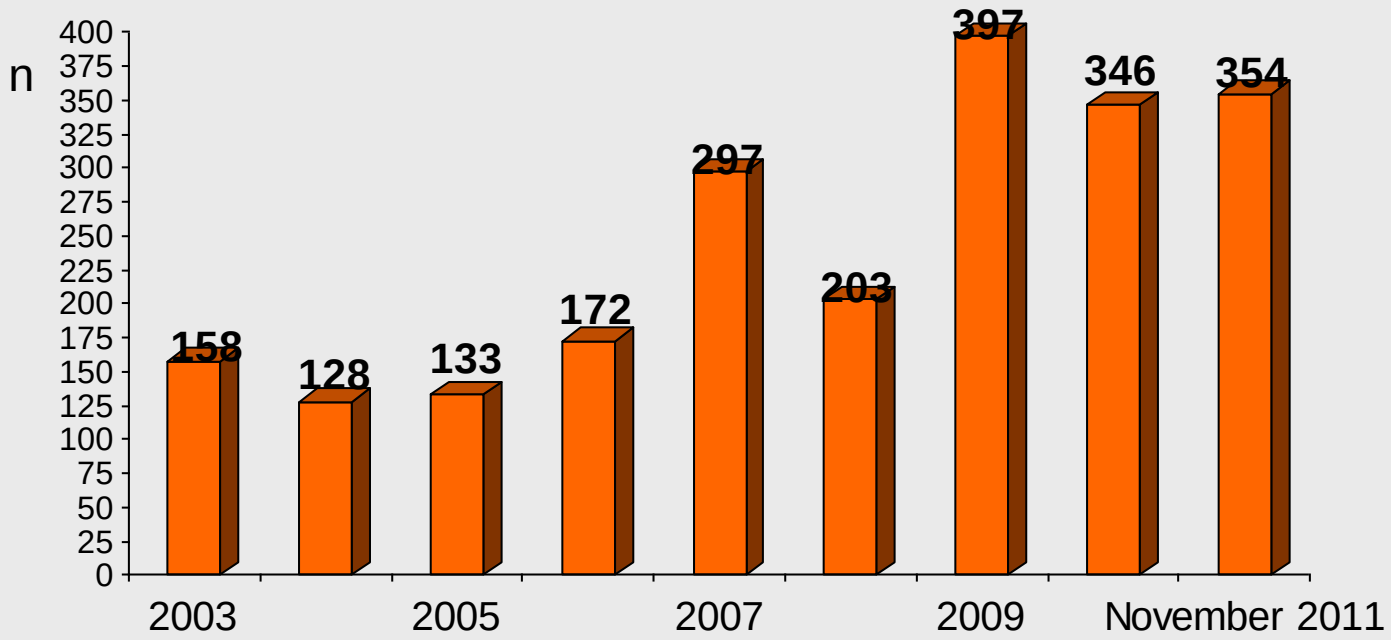
Treatment of Patients with CHC

JAN 2003-NOV 2011

- 2188 patients

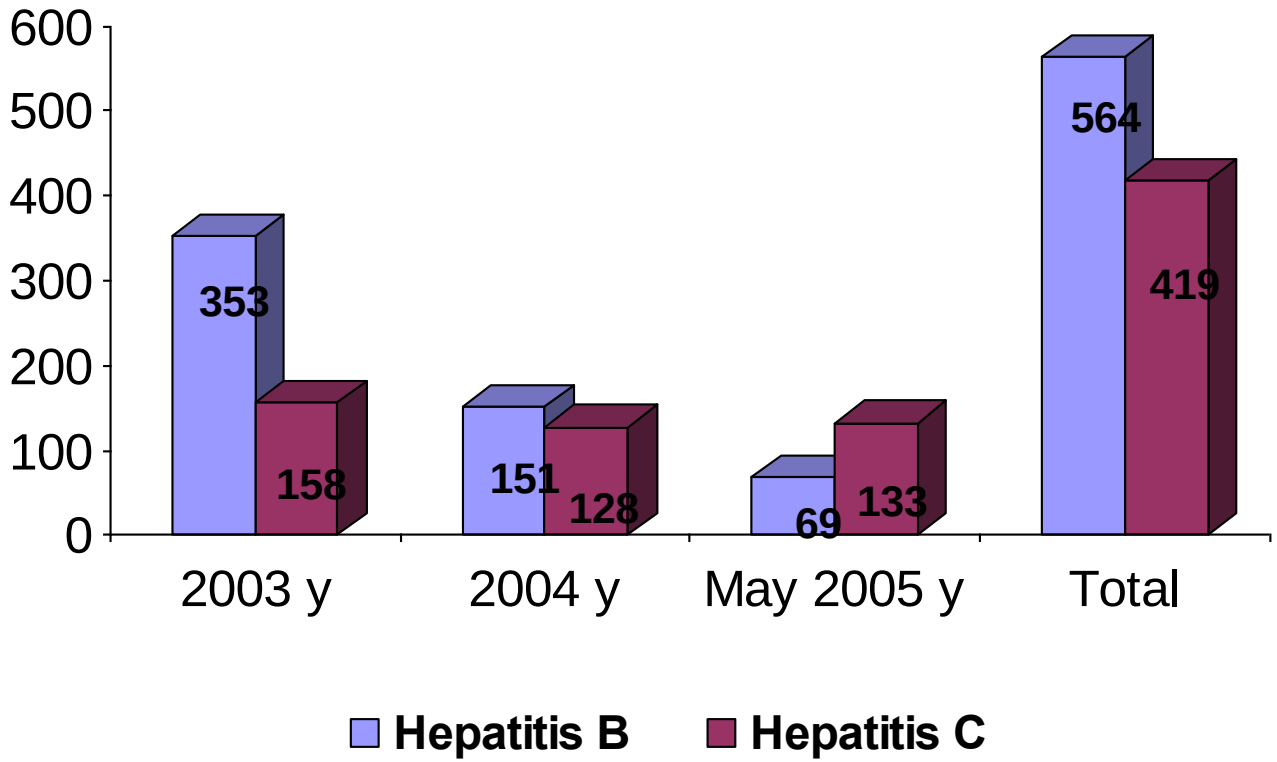


IFNa+RBV PegIFNa+RBV



NHIF: National Programme for Antiviral Treatment of Patients with CVH

From JAN 2003 to MAY 2005: 564 patients with CHB/CHD (57%) were treated



G. Kondeva, N. Tarinska,2005

Treatment of Patients with CHB 2009-20011

- Peg-IFN - 282 new cases
- NUCs (Lamivudine, Telbivudin, Entecavir, Tenofovir) - 620 new patients
  - Total: 902 new patients

Efficacy and Safety of antiviral therapy

No systematic data

CHC: Peg-IFNα + RBV

SVR = 65%- 81%

-Effective therapy

-With usual predictable adverse events

Strong selection and monitoring

Good patient's collaboration

CHB antiviral

- Peg-IFNα – effective only in selected patients with low viraemia
- NUC's therapy – continues

NHIF: National Programme for Antiviral Treatment of Patients with CVH

- Based on firm criteria
- Leading in centers wit highly qualified specialists with experience in the treatment of CVH
- Therapy with proved efficacy
- Total reimbursement

Effective

- It may be expanded and optimized according to the new development in the world practice

White Paper

- The Burden of Hepatitis C in CEE and CIS: An Epidemiological and Economic Assessment

Centre for European Policy Studies, CEPS

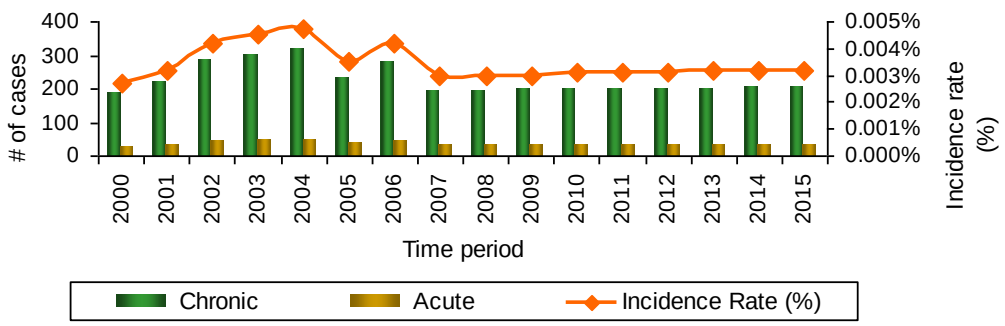
BULGARIA, Draft, September 2009

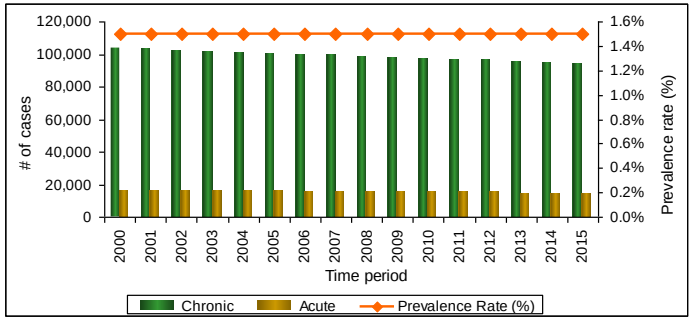
Z. G Ökem, PhD , Seval Akgün, MD, PhD, Prof. of Public Health and Medicine, Baskent University

Epidemiology 2000 – 2015 r.

- *New cases: about 230*
  0.0030%
  or 3.0-3.2 /100000
- *Prevalence 1.5%*
  About 110 000 cases
- *87% - Chronic HCV infection*

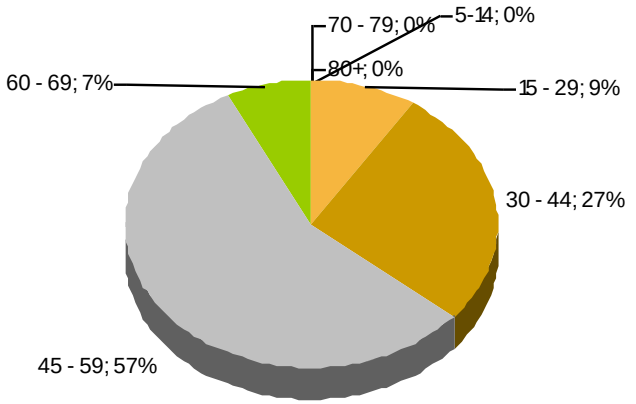
Year	HCV – Number of cases	Incidence per 100,000	Number of HCV infected cases – Prevalence (1.5%)	Acute HCV cases – Proportion (13%)	Chronic HCV cases – Proportion (87%)
2000	218	2.7	120,135	16,018	104,117
2001	256	3.2	119,316	15,909	103,407
2002	333	4.2	118,497	15,800	102,697
2003	350	4.5	117,678	15,690	101,988
2004	367	4.7	116,859	15,581	101,278
2005	268	3.5	116,040	15,472	100,568
2006	326	4.2	115,317	15,376	99,941
2007	226	3.0	114,594	15,279	99,315
2008	227	3.0	113,871	15,183	98,688
2009	228	3.0	113,148	15,086	98,062
2010	229	3.1	112,425	14,990	97,435
2011	231	3.1	111,738	14,898	96,840
2012	232	3.1	111,051	14,807	96,244
2013	233	3.2	110,364	14,715	95,649
2014	234	3.2	109,677	14,624	95,053
2015	236	3.2	108,990	14,532	94,458



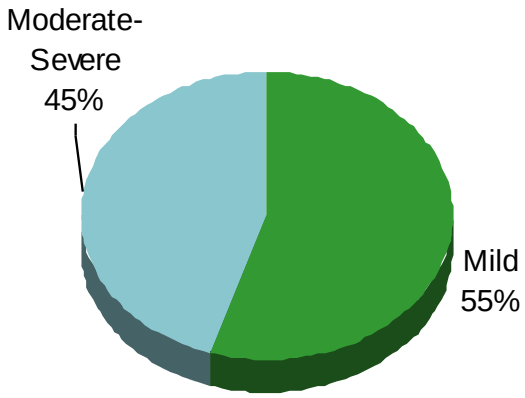


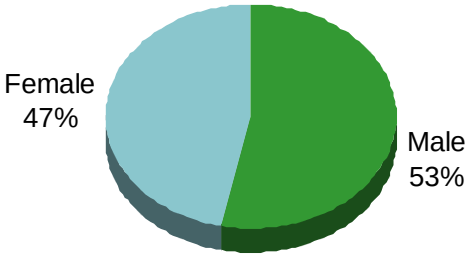
Characteristics of HCV infection

- .93% - between 15-59 г.
- 53% - male



- 55% - mild disease

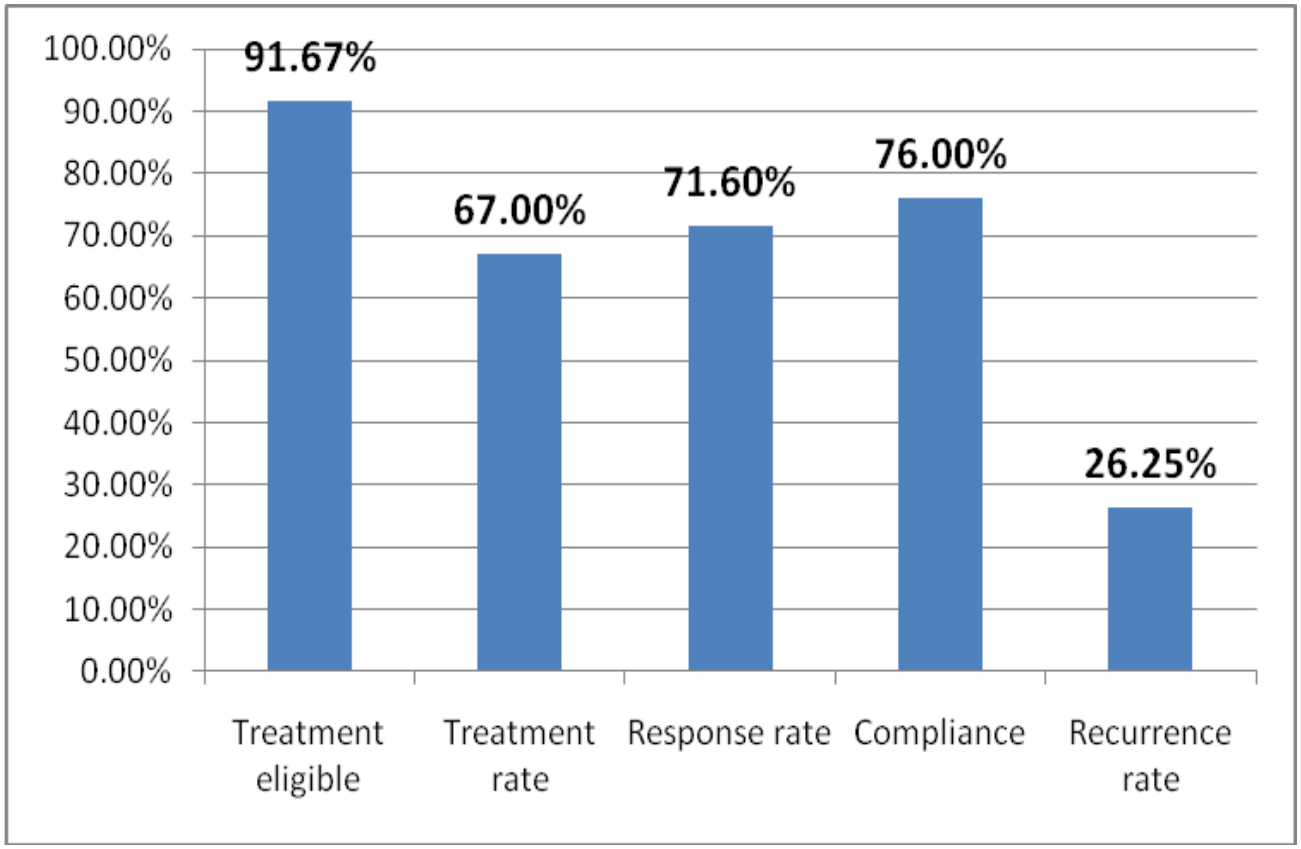




HCV -related mortality

- All-cause mortality rate was 8.05 / 100,000
- 1,494 – liver cirrhosis (34 / 100,000)
- 802 – HCC 1.50 / 100,000).

HCV treatment



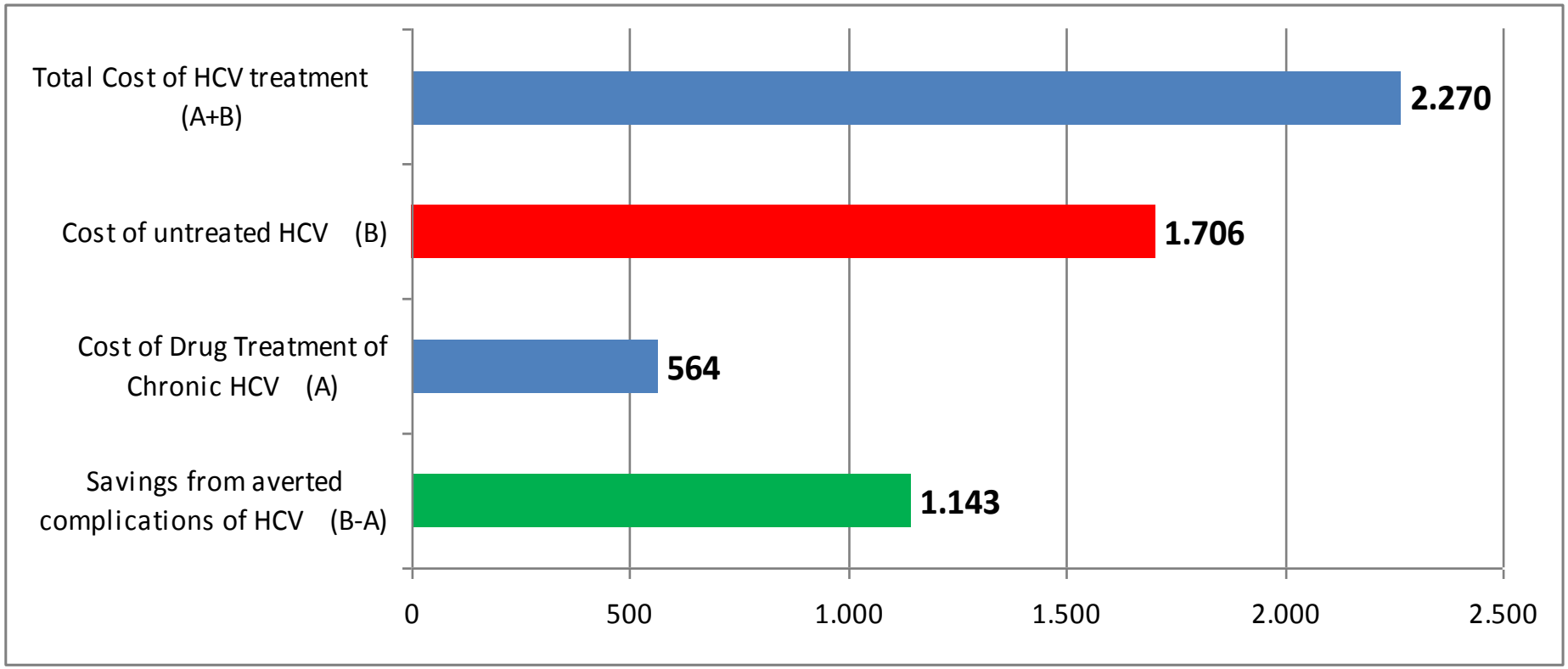
Treatment rates in Bulgaria

Costs of HCV treatment

- NHIF (2008)
- Without costs of diagnosis

Costs of HCV treatment per patient in Bulgaria in 2008	(€)
Per outpatient visit	15
Average drug cost per patient treated with HCV	12,132
Treating cirrhosis	7,968
Treating hepatocellular carcinoma	1,036
Treating ascites	7,968
Treating esophageal varices	7,968
Treating hepatocellular encephalopathy	6,129
Liver transplant	25,000
Treating post-liver transplant	4,000

Long-term costs and savings from HCV treatment in Bulgaria, 2008-2015 (€ million)



Long-term costs and savings from HCV treatment in Bulgaria, 2008-2015 (€ million)

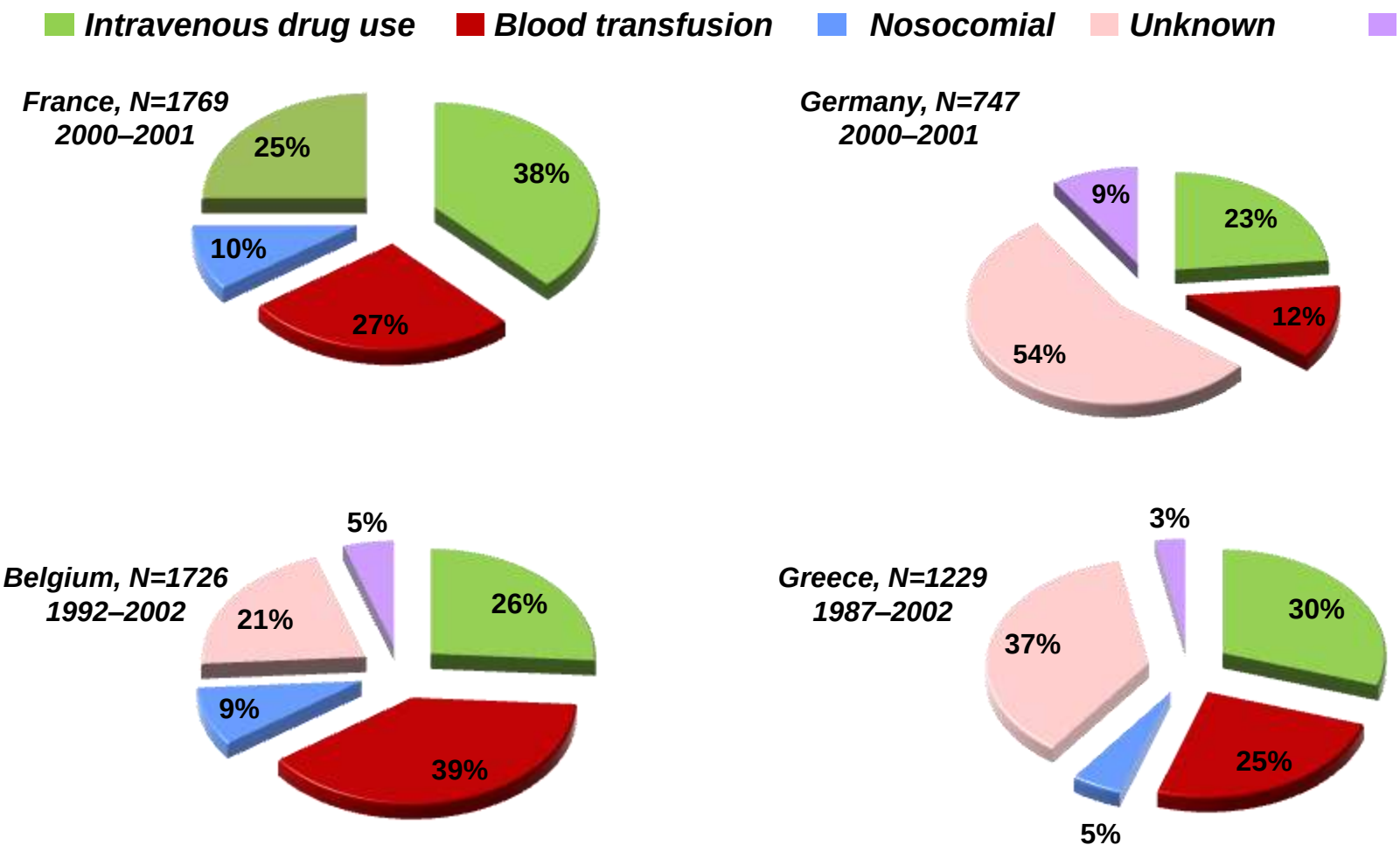
What we need ?

- National Screening program and National register (data base)
  - To decrease rate of infections
  - Early diagnosis - to identifying patients for treatment
  - Early treatment associated with better response rates
  - To follow-up the infected subjects and monitoring therapy
  - To decrease the cost

Why we need of screening program?

- Many of infected persons do not know the risk factors

Risk factors among patients diagnosed with chronic hepatitis C



Why we need of screening program?

A large proportion of patients with chronic HBV/HCV infection remain undiagnosed

- Asymptomatic disease
- Nonspecific symptoms
- First diagnosis – advanced liver cirrhosis

Early diagnosis = screening
ALT
HBsAg, anti-HCV

Thank you!