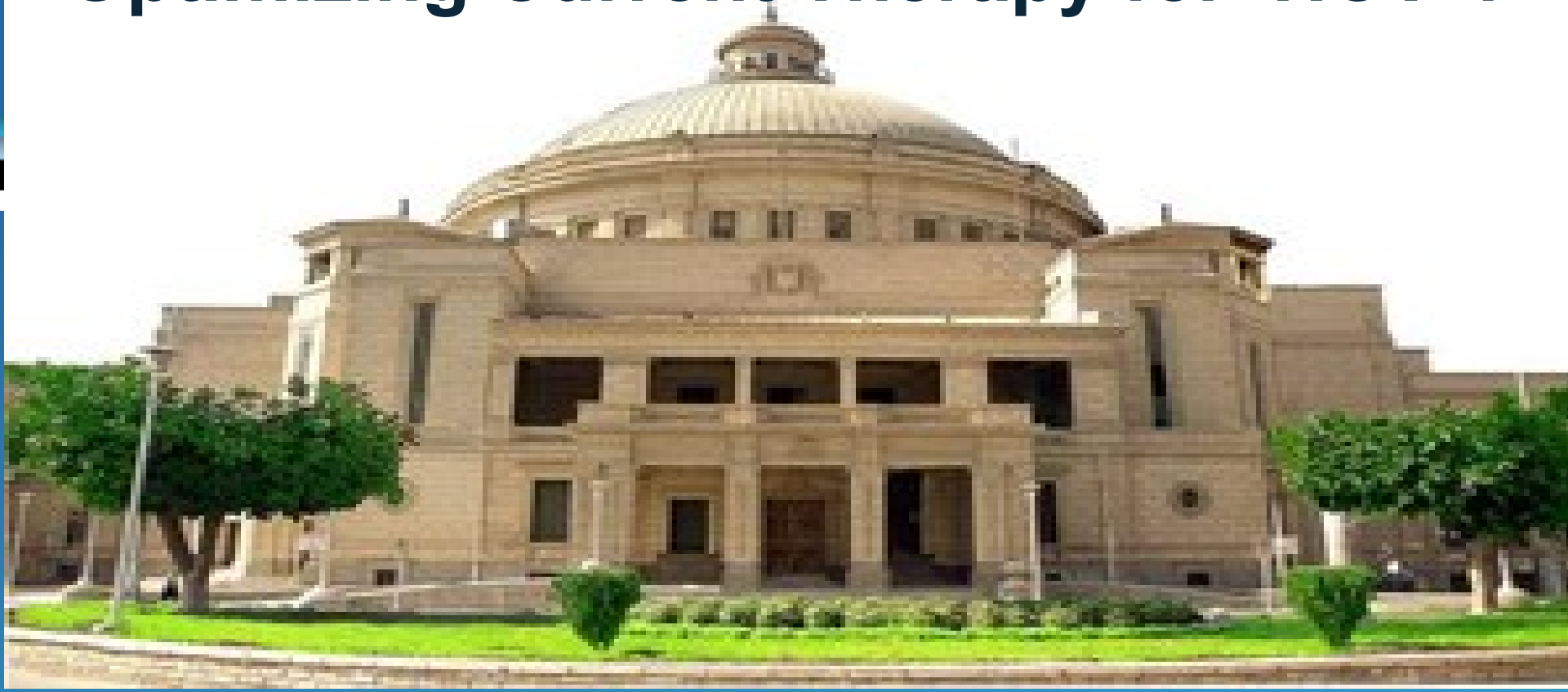
Optimizing Current Therapy for HCV 4



Prof. Gamal Esmat

Endemic Medicine and Hepatology, Cairo University

Founder of Viral Hepatitis Treatment Centers,Egypt

www.gamalesmat.com

HCV is a worldwide disease with an estimated prevalence of 3%.

Hepatitis C virus 4 is prevalent in Africa and the Middle East, especially Egypt.

More than 90% of HCV Egyptian patients are genotype 4

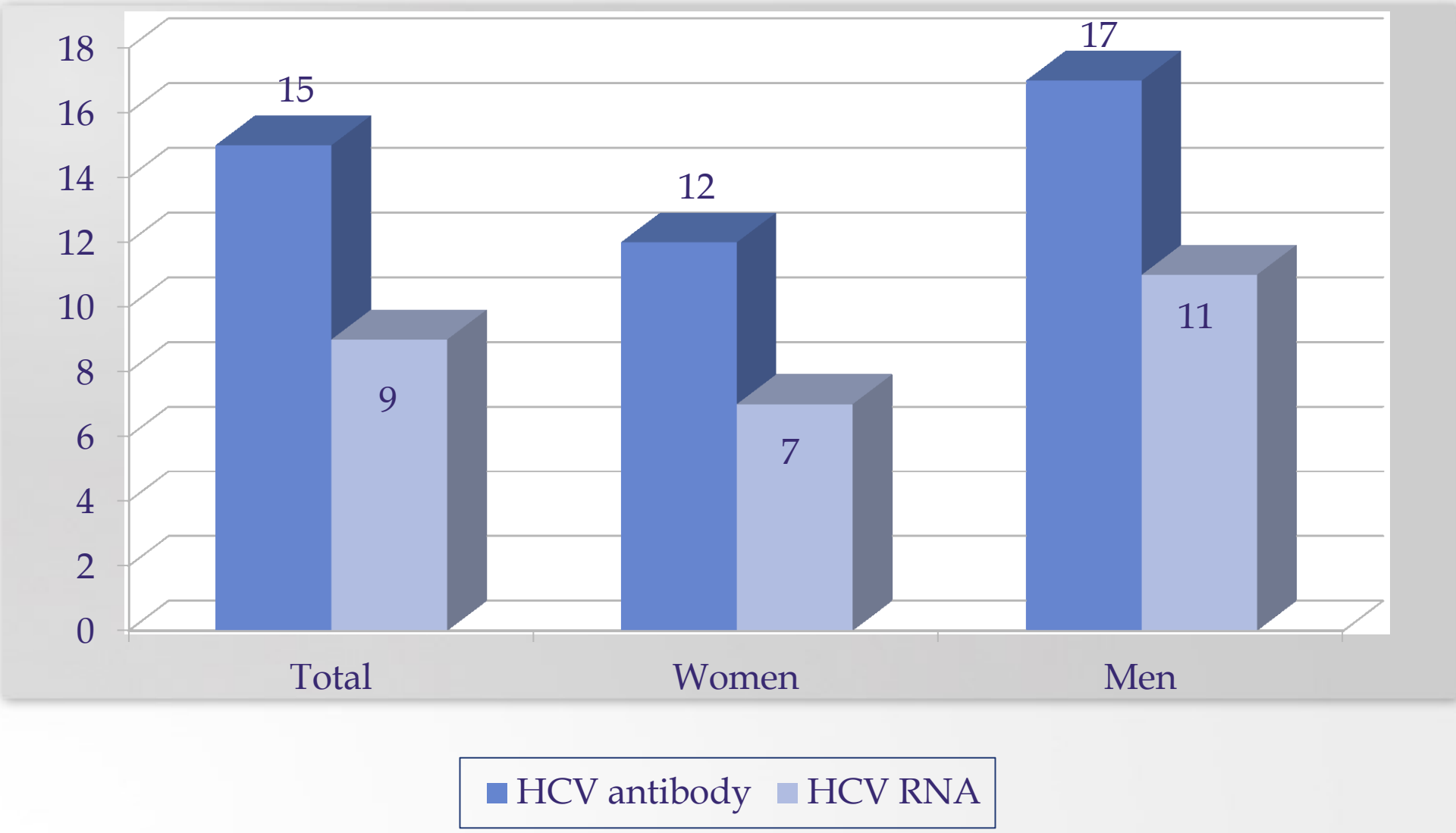
NATIONAL HCV SURVEY
EGYPT 2008

WWW.MEASUREDHS.COM

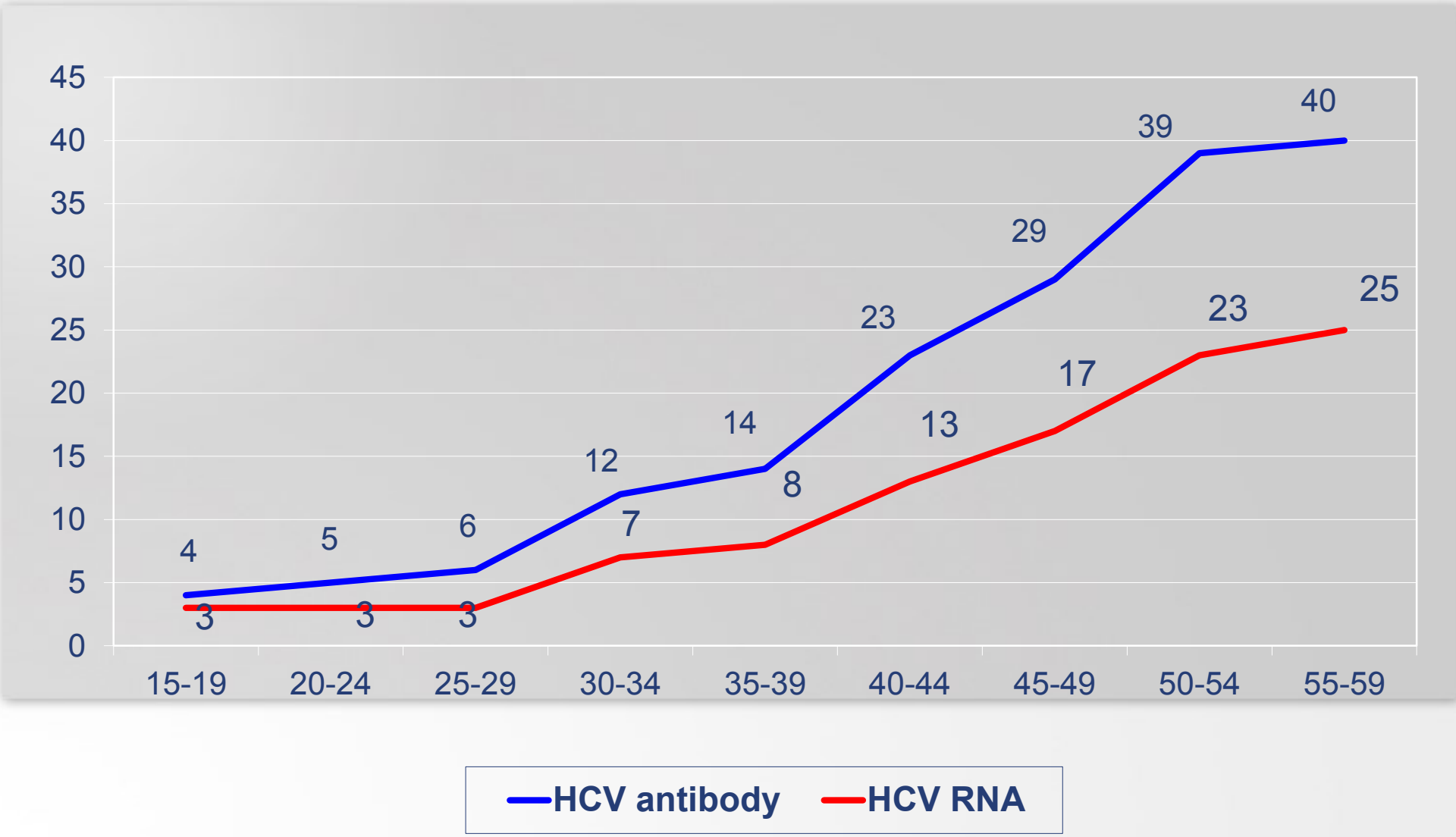
Hepatitis C testing

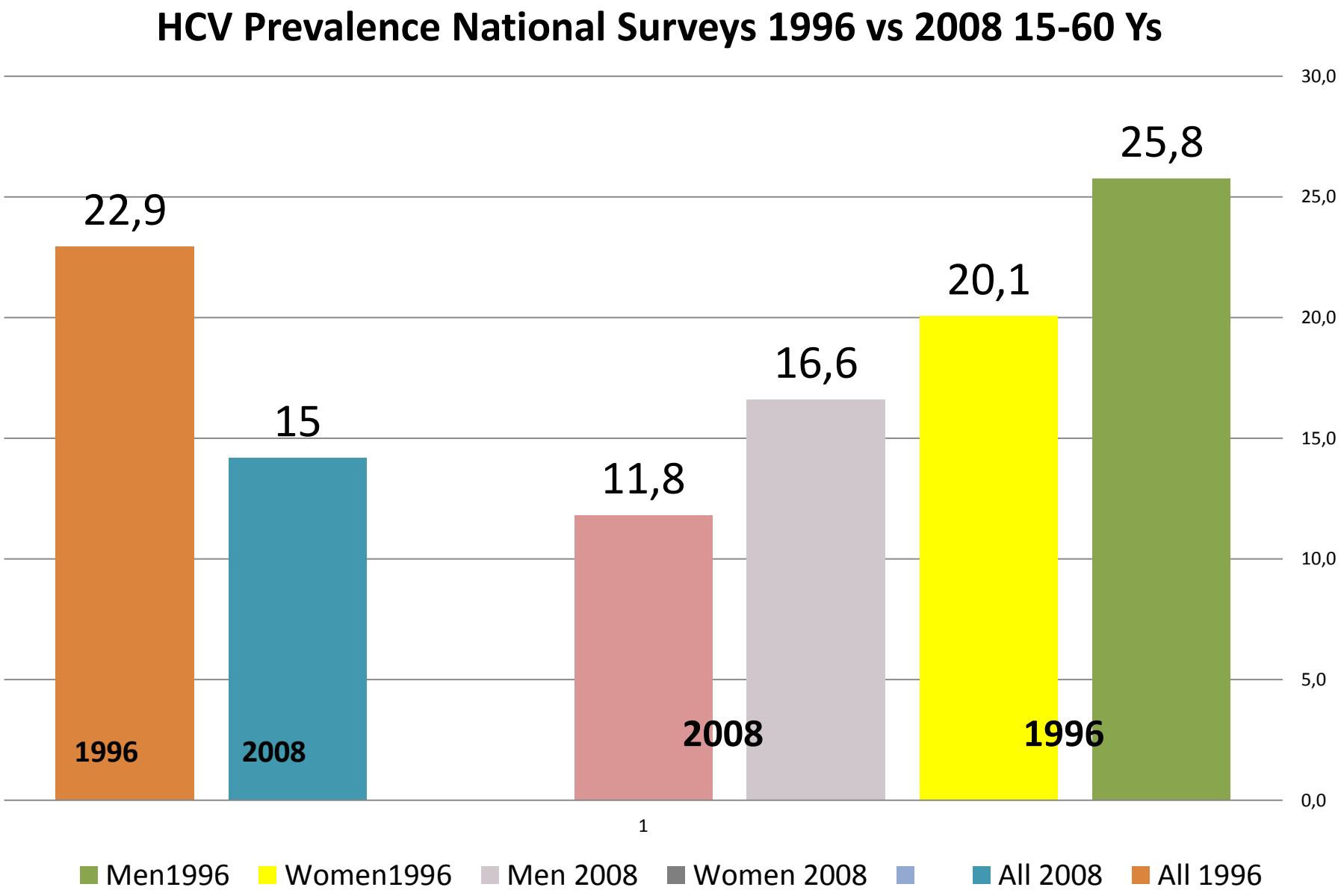
- Household survey in the 28 governorates of Egypt.
- Total of 12,780 women and men aged 15 – 59 consented to blood sampling.
- ELISA test used to determine presence of antibodies.
- Real time PCR testing for HCV RNA for all antibody positive samples to detect active infections.

Prevalence of Hepatitis C, Egypt 2009

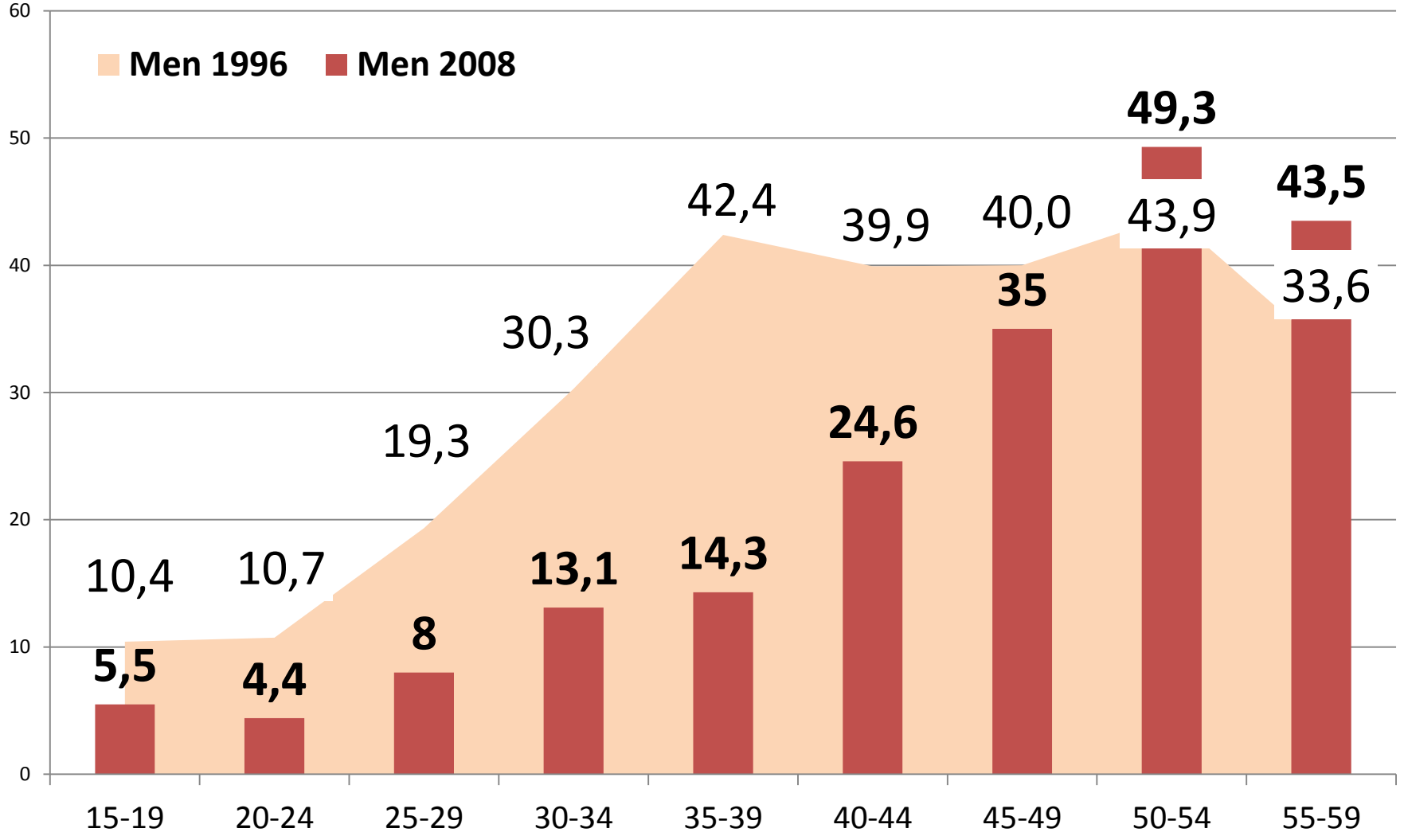


Prevalence of Hepatitis C by Age in Egypt 2009

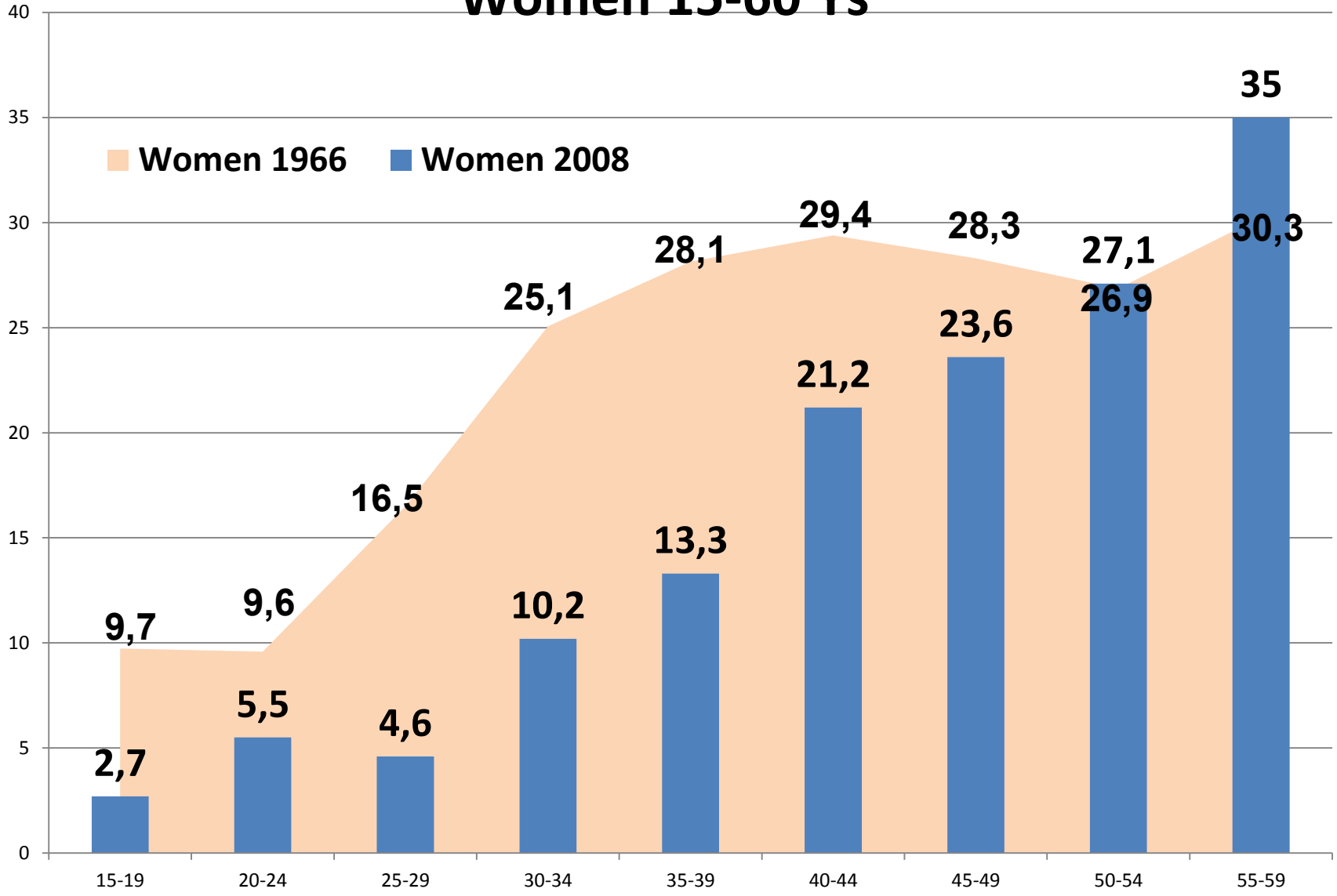



HCV Prevalence National Surveys 1996 vs 2008 15-60 Ys
30,0
25,0
20,0
15,0
10,0
5,0
0,0
22,9
15
11,8
16,6
20,1
25,8
1996
2008
2008
1996
1
Men1996
Women1996
Men 2008
Women 2008
All 2008
All 1996

HCV Prevalence National Surveys 1996 vs 2008
Men 15-60 Ys



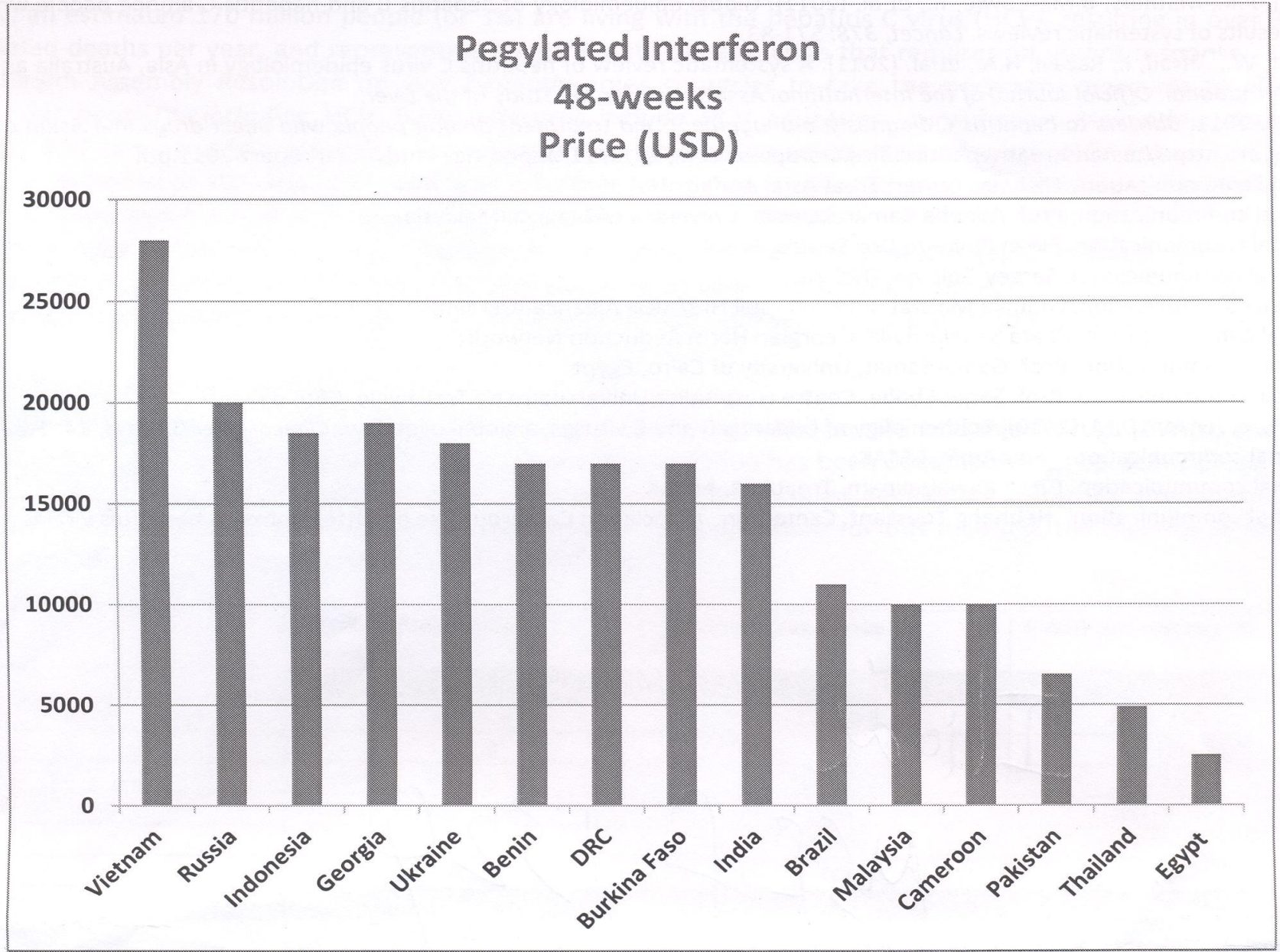
HCV Prevalence National Surveys 1996 vs 2008
Women 15-60 Ys

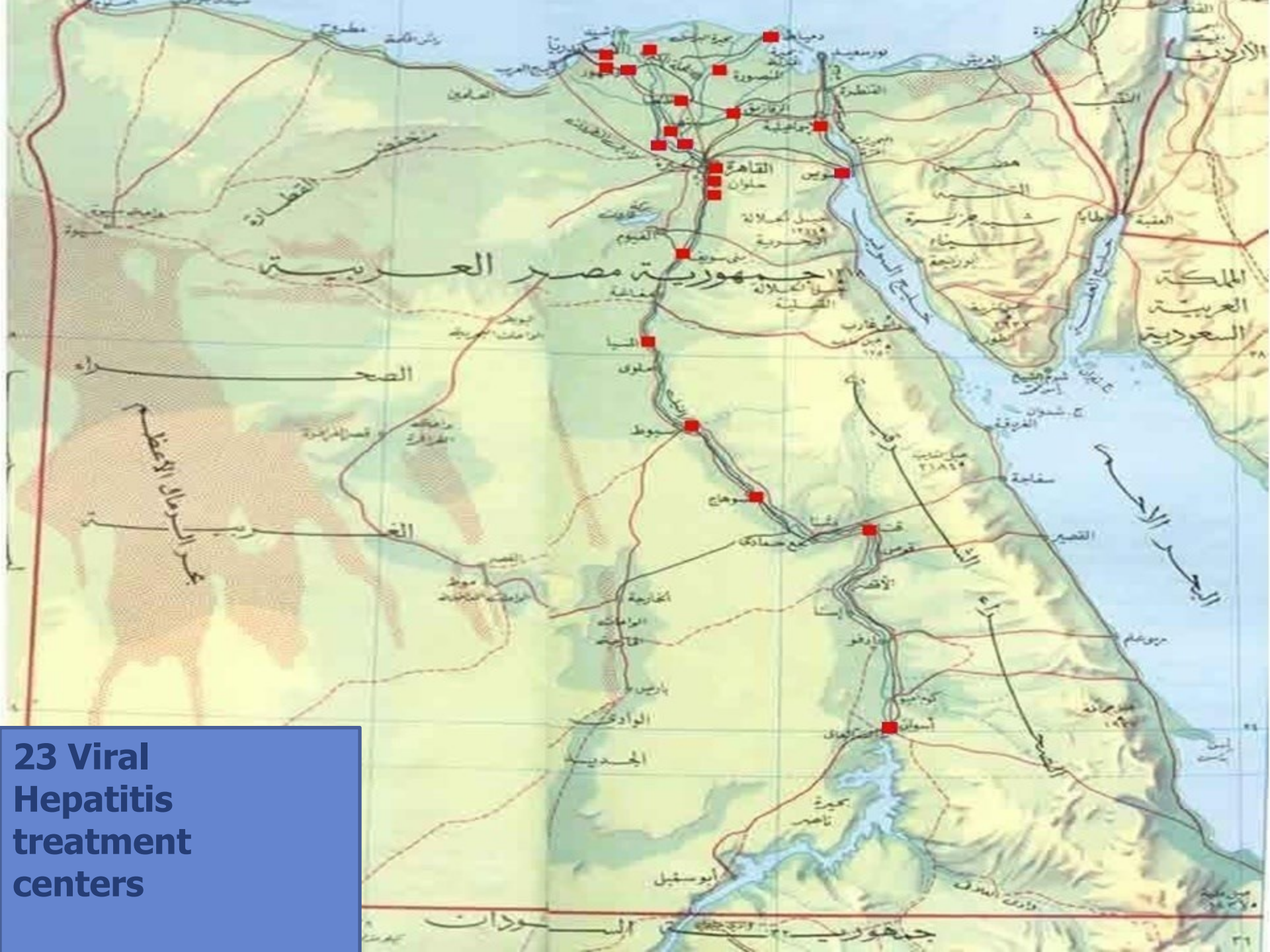


Total Number of HCV Positive Cases in 1996-2008

	Female cases	Male cases	1996All cases	Female cases	Male cases	2008All cases	Chronic HCV 1996	Chronic HCV 2008
15-19	343277	379167	722443	111401	248022	359423	469588	269568
20-24	307380	361766	669146	165686	145006	310692	434945	233019
25-29	453044	585024	1038067	130382	209033	339416	674744	254562
30-34	609555	785683	1395238	256019	326960	582980	906904	437235
35-39	605653	899449	1505101	319858	340967	660825	978316	495619
40-44	552251	732549	1284800	415505	493044	908550	835120	681412
45-49	456226	631200	1087426	376939	608519	985458	706827	739093
50-54	356239	558439	914678	344490	614785	959275	594541	719457
55-59	308571	319133	627704	304771	427713	732483	408008	549363
Total	3992196	5252409	9244604	2425052	3414050	5839102	6008993	4379326

National Egyptian Program for Management of Chronic HCV Patients


Pegylated Interferon
48-weeks
Price (USD)
30000
25000
20000
15000
10000
5000
0
Vietnam
Russia
Indonesia
Georgia
Ukraine
Benin
DRC
Burkina Faso
India
Brazil
Malaysia
Cameroon
Pakistan
Thailand
Egypt



23 Viral Hepatitis treatment centers

National HCV Treatment Program

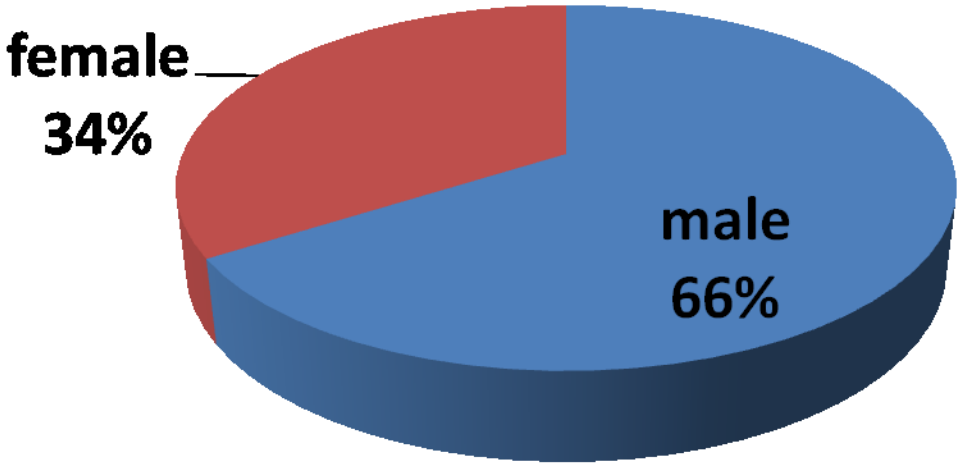
- Total no of patients treated with PEG-IFN (2006-2012): 220,000

- No of new patients annually now is: 45,000

National Network for Treatment Centers (NNTC)

- A Network for all patients' data from the Viral Hepatitis Treatment Centers nation-wide, was established with the main server located in National Hepatology Institute in Cairo.
- When fully functioning, the NNTC will have full data for pre-enrollment and treatment of 220,000 HCV patients

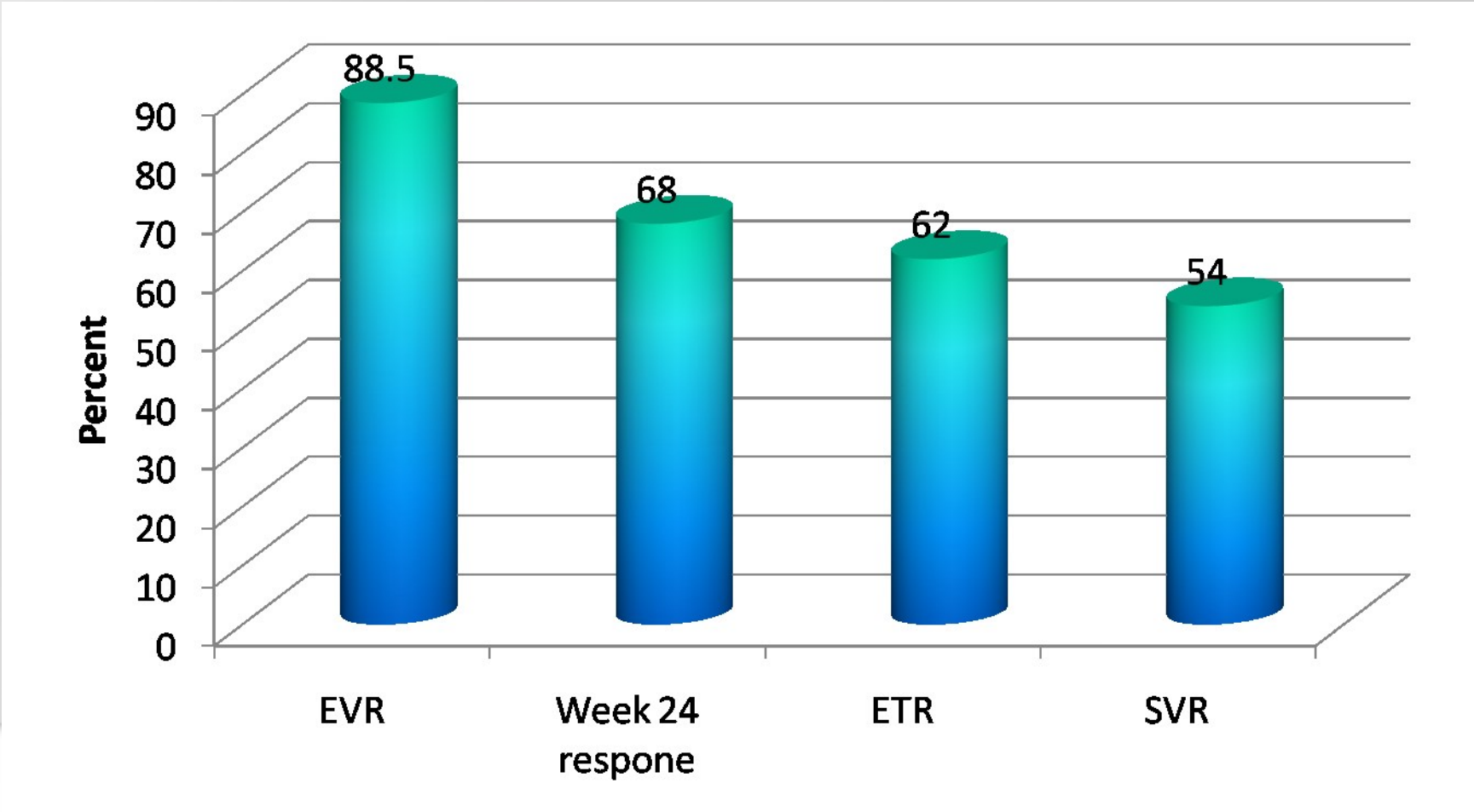
Patients' Gender



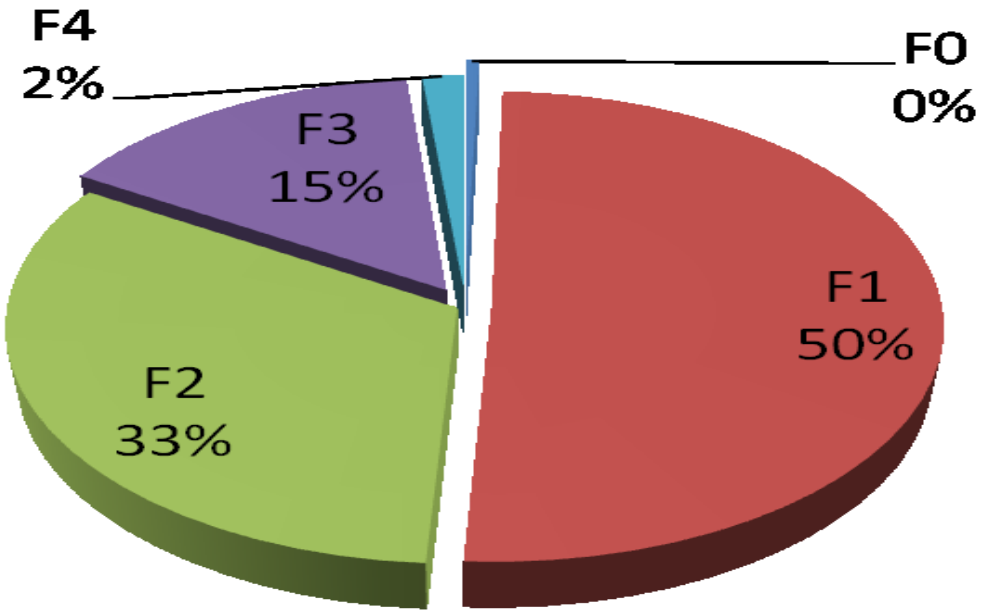
Patients' Age and BMI

	Mean (SD)
Age	40 (10)
BMI	27 (4)

Response Rates of treated patients



Liver biopsy (METAVIR)



Fibrosis

Activity

Impact of different treatment scale-up and eligibility scenarios on HCV mortality in Egypt in the next five years

D.Obach, Y.Yazdanpanah, G Esmat, V Canva, S. Dewedar, WA. Anwar, W Doss, A Mostafa, S Pol, M Buti, U Siebert, A Fontanet, M.K. Mohamed, S.Deuffic-Burban . AASLD 2012

Dept. of Tropical Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt
Dept. of Community, Environmental and Occupational Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt
National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

anRS
French National Agency for Research on AIDS and Viral Hepatitis
An autonomous agency at Inserm

Conclusion and recommendations of this analysis (1)

- Should we treat F4 patients (**no decompensation**, no co-infection) :
  - It is more expensive than non treating **but is cost-effective**
  - If we do not have enough money it is better to treat F4 patients than F0 or F1 patients (in term of life-years saved)

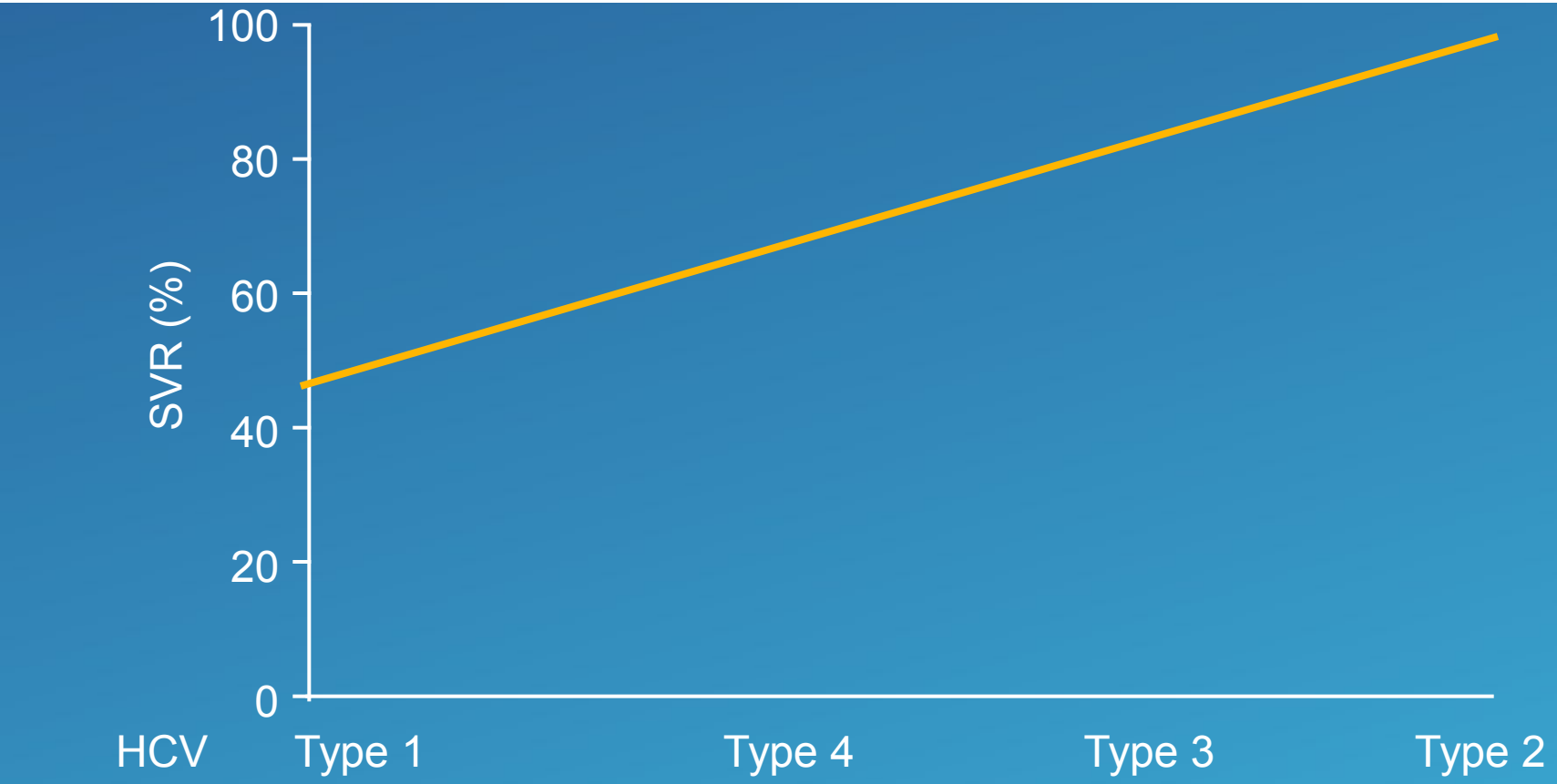
Conclusion and recommendations of this analysis (2)

- Should we treat F0-F1 patients (**with elevated ALT**) :
  - If we do not have enough money : better to treat F4 patients than F0 or F1 patients (in term of life-years saved)
  - If we do have enough money and considering that more efficacious drugs will be available in 2017,
    - It would be more effecive and more cost-effective to wait .

Optimizing Treatment for HCV Genotype 4

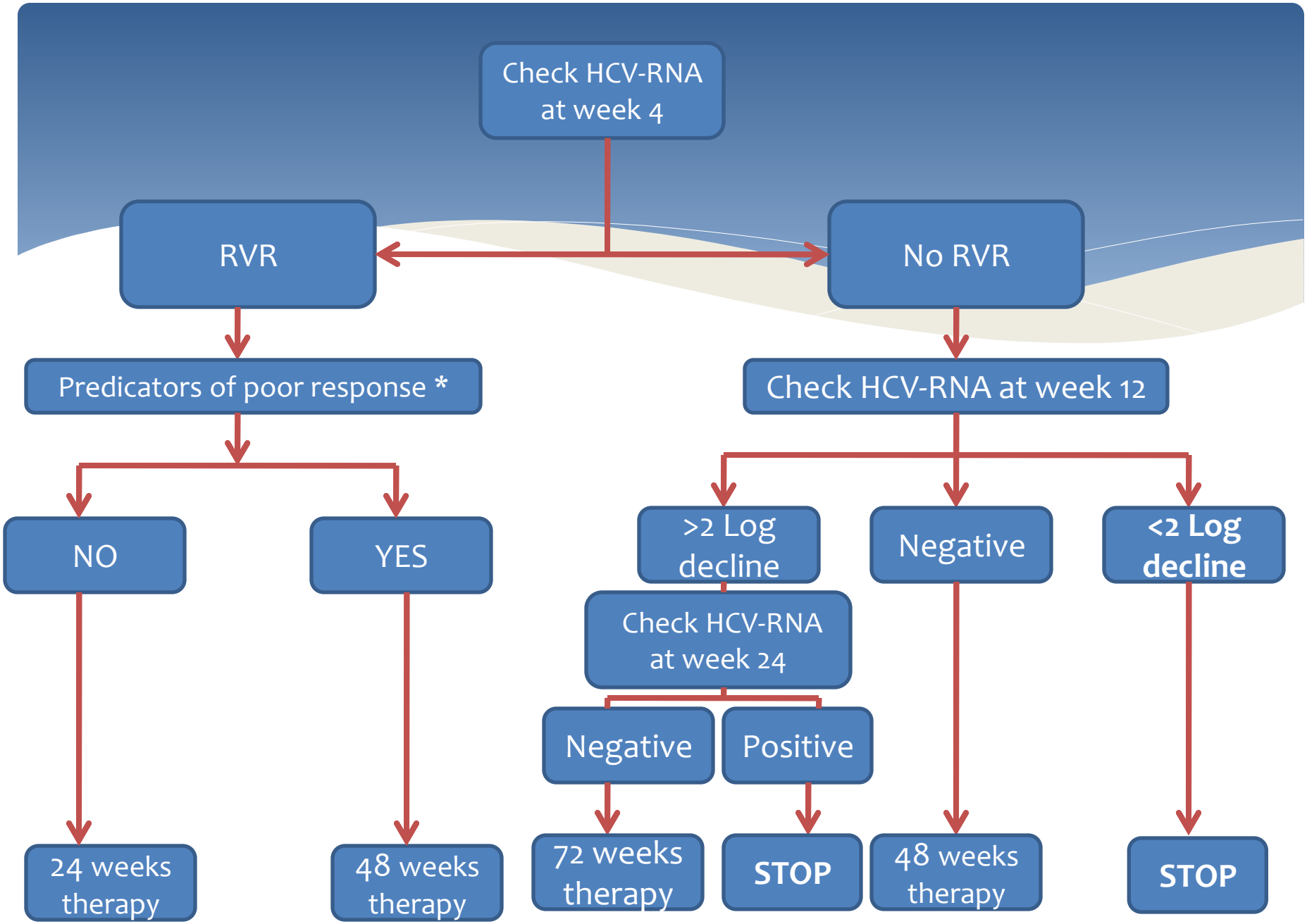
- SVR to peg IFN
- Duration of Treatment
- Predictors of Response
- Future Therapy

Sustained virologic response rates (SVR) in relation to HCV genotype



Optimizing Treatment for HCV Genotype 4

- SVR to peg IFN
- Duration of Treatment
- Predictors of Response
- Future Therapy

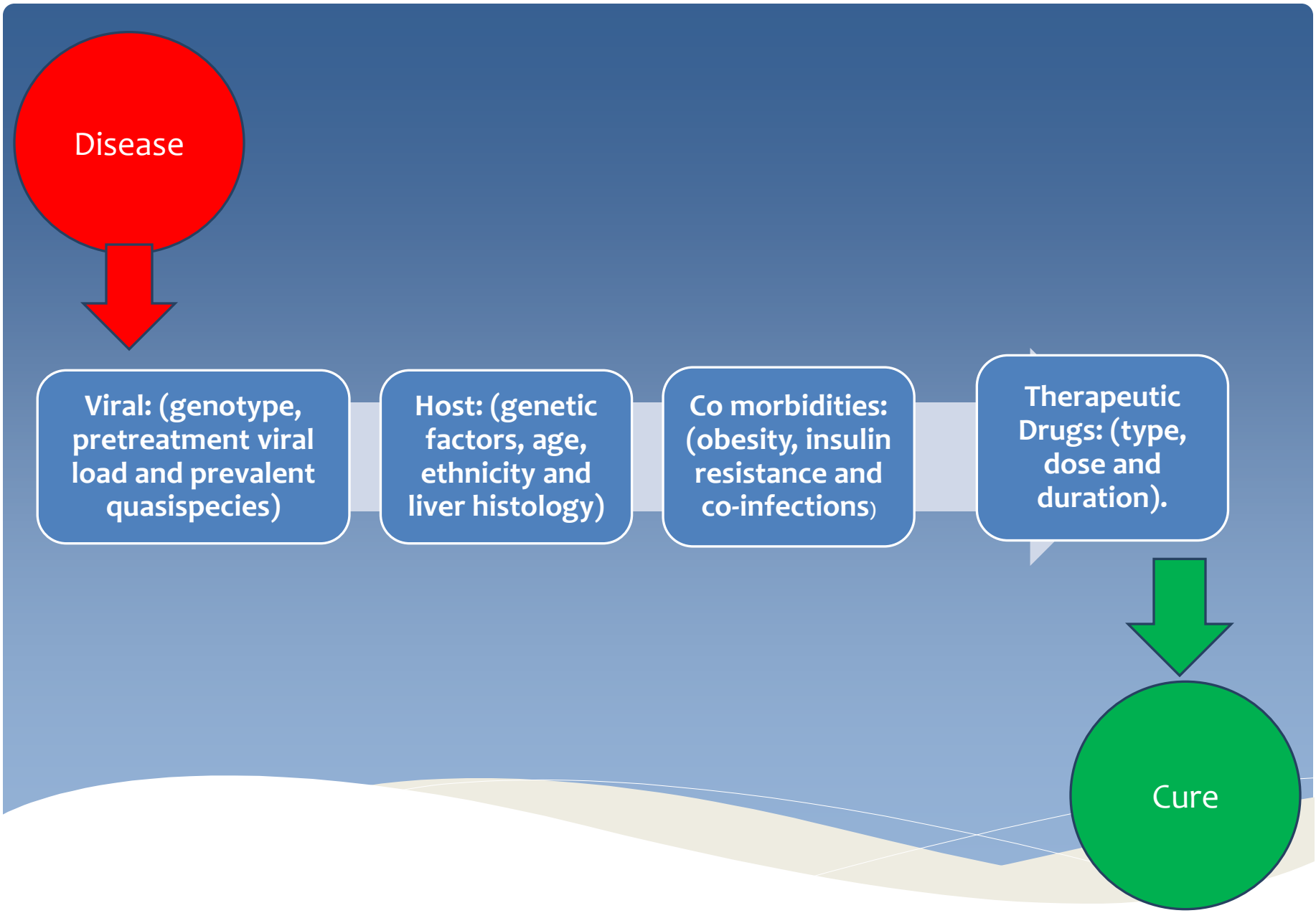


* High basal viral load (**≥800,000)/** Advancedf fibrosis (**F3,4)/ I**nsulin resistance (**HOMA-IR >2)**

. Khattab et al. J. Hepatology 2011

Optimizing Treatment for HCV Genotype 4

- SVR to peg IFN
- Duration of Treatment
- Predictors of Response
- Future Therapy

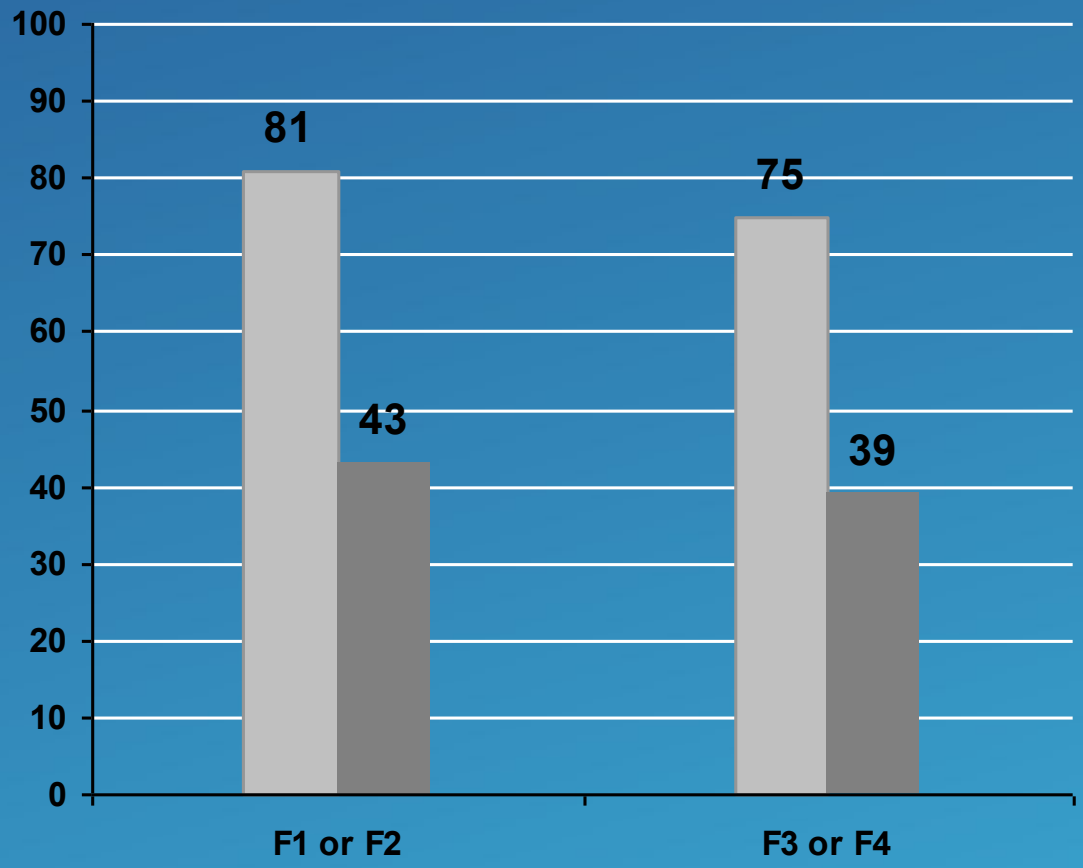

Disease
Viral: (genotype, pretreatment viral load and prevalent quasispecies)
Host: (genetic factors, age, ethnicity and liver histology)
Co morbidities: (obesity, insulin resistance and co-infections)
Therapeutic Drugs: (type, dose and duration).
Cure

Predictors of treatment failure in HCV 4

- In univariate analysis:
  - Weight > 80 kg
  - METAVIR score ≥ F3
  - Steatosis
  - AFP levels > median value
- In multivariate analysis:
  - AFP levels only

Males et al, Antiviral Therapy ,2007,12:797

SVR (%) according to the Metavir fibrosis score and median AFP values



Light grey:
AFP $\leq$ 4.5 ng/ml

Dark grey:
AFP > 4.5 ng/ml

Serum alpha-fetoprotein predicts treatment outcome in HCV patients regardless of genotype

Abdoul H, Mallet V, Pol S, Fontanet A

They examined the association between AFP level and SVR in 93 chronic hepatitis C patients. The SVR rate was much higher among patients with serum AFP levels below rather than above the median value (5.7 ng/ml) (58.7% and 19.2%, respectively; P<0.0001).
They concluded that AFP should be added to the list of factors predictive of treatment response in chronic HCV.

Plo S One,2008

IL28B polymorphism is associated with SVR in HCV genotype 4 patients.

The data showed a better treatment response rate of the C allele of the IL28B gene (p=0.0008). The response rates were 81.8%, 46.5%, and 29.4% for genotype CC, CT, and TT, respectively. No significant relationship was found between the polymorphism and the severity of the disease.

Asselah et al,J.Hepat,2011

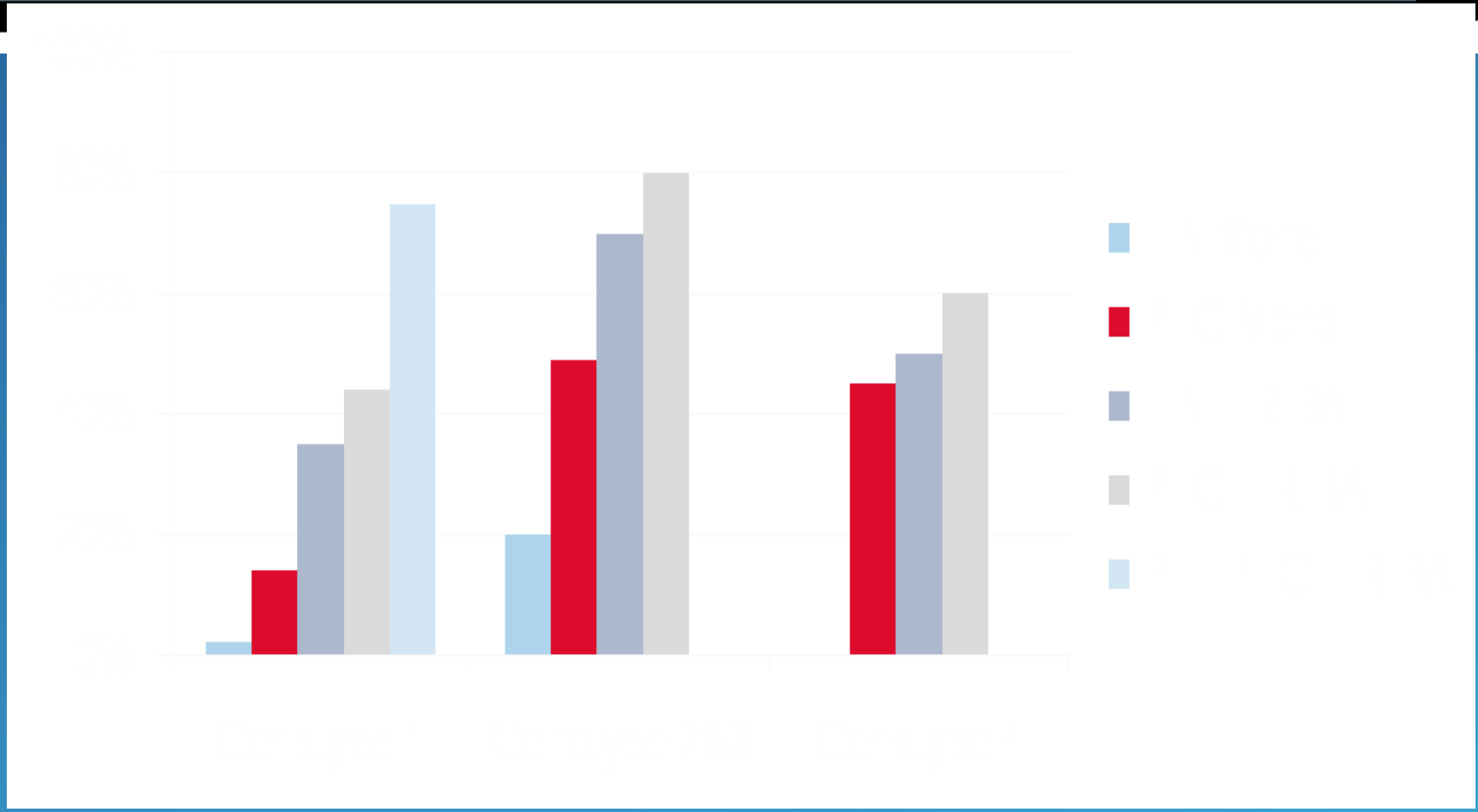
Optimizing Treatment for HCV Genotype 4

- SVR to peg IFN
- Duration of Treatment
- Predictors of Response
- Future Therapy

HCV Genotype 4

New direct acting antiviral drugs

Evolution of HCV Treatment



Protease inhibitors

- Most of these new antiviral drugs have only been developed and investigated for genotype-1 HCV
- The first two HCV protease inhibitors (telaprevir and boceprevir) were recently approved for genotype-1 HCV, in some countries.
- With genotypes 1 and 2 being most susceptible and genotypes 4 and 5 most resistant .

Multiple Classes of Direct Anti-Virals

NS3/4A Protease Inhibitors	NS5B Polymerase Inhibitors		NS5A Inhibitors	Cyclophilin A Inhibitors
	Nucleos(t)ide Analogue	Non-nucleos(t)ide		
▪ High efficacy ▪ Low genetic barrier to resistance ▪ Macrocyclic or linear ▪ Phase III: BI 201335, TMC435	▪ Mimic natural substrates of the polymerase ▪ Incorporated into RNA chain causing chain termination ▪ Broad genotypic coverage ▪ High genetic barrier to resistance ▪ Phase III: GI-7977	▪ Bind to several different allosteric enzyme sites; results in conformational change ▪ Resistance more frequent than nucs ▪ Several agents in phase II	▪ NS5A has role in assembly of replication complex ▪ Mechanism of inhibition under study ▪ Phase III: Daclatasvir (BMS-790052)	▪ Supports HCV-specific RNA replication, protein expression ▪ Interacts with NS2, NS5A, NS5B ▪ May regulate polypeptide processing, viral assembly ▪ Phase III: Alisporivir

Courtesy of Prof. M Thursz

NS5A Inhibitors

* The HCV nonstructural protein 5A (NS5A) is a multifunctional protein that is expressed in basally phosphorylated (p56) and hyperphosphorylated (p58) forms. NS5A phosphorylation has been shown to play a role in regulating numerous aspects of HCV replication. Classes of compounds that inhibit HCV RNA replication by targeting NS5A were recently discovered

ONLINE EXPERT POSTER REVIEW AND DISCUSSION

Advances in Chronic Hepatitis C Management and Treatment

Reporting From

THE 62ND AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES ANNUAL MEETING

(This coverage is not sanctioned by the conference organizers and is not an official part of the conference proceedings.)

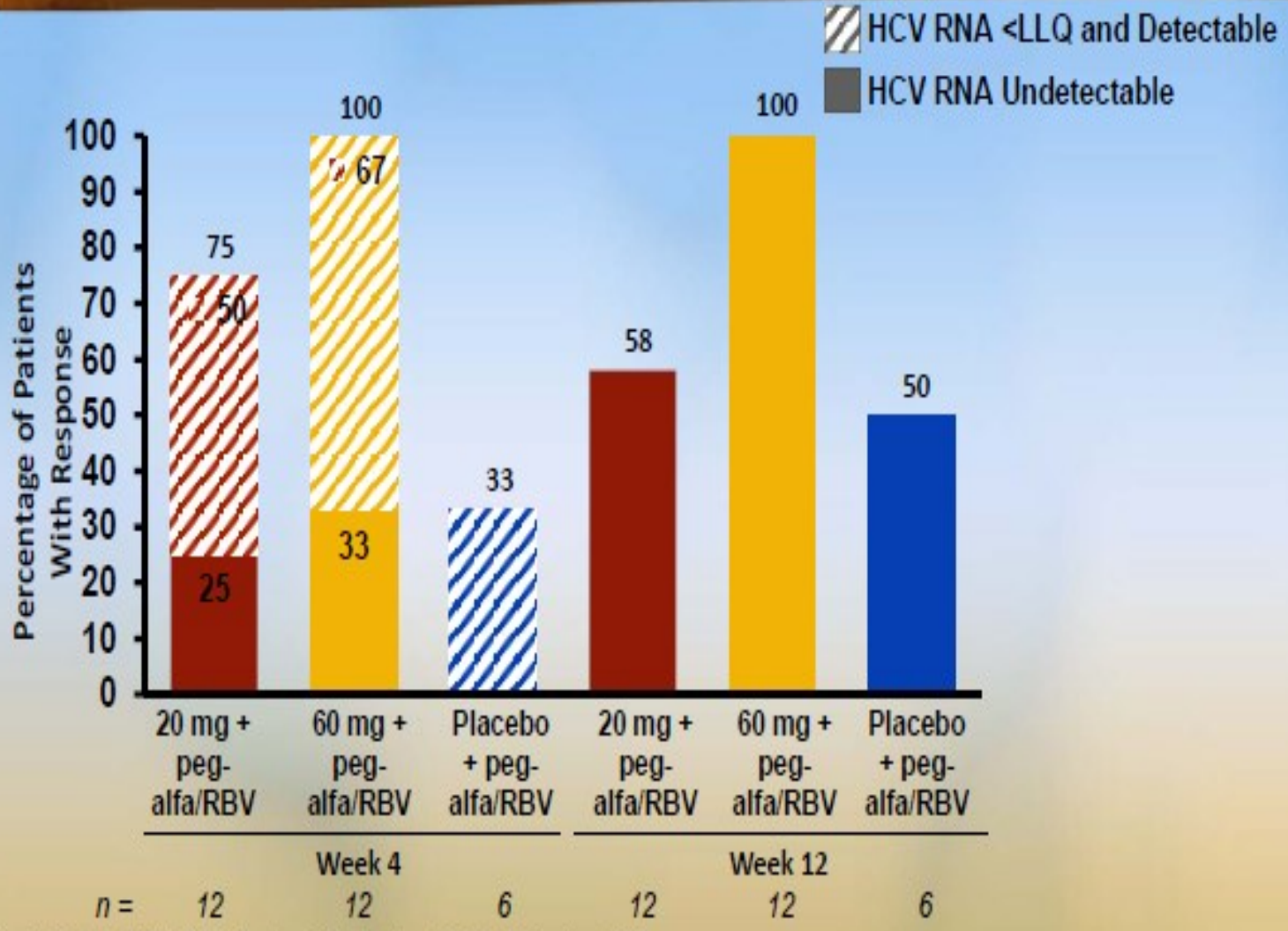
Jointly Sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

BMS-790052, A NS5A Replication Complex Inhibitor, Combined with Peginterferon-Alfa-2a and Ribavirin in Treatment-Naive HCV-Genotype 1 or 4 Subjects: Phase 2b AI444010 Study Interim Week 12 Results

C Hézode, GM Hirschfield, W Ghesquiere, W Sievert, M Rodriguez-Torres, S Shafran, PJ Thuluvath, HA Tatum, I Waked, G Esmat, EJ Lawitz, VK Rustgi, S Pol, N Weis, P Pockros, M Bourlière, L Serfaty, JM Vierling, MW Fried, O Weiland, MR Brunetto, GT Everson, S Zeuzem, PY Kwo, M Sulkowski, PD Yin, U Diva, EA Hughes, M Wind-Rotolo, S Schnittman

Abstract 227

Virologic Responses Through Week 12: HCV Genotype 4



Hézode C et al. 49TH IDSA; Boston, MA; October 20-23, 2011; Abst. 227.

Daclatasvir, an NS5A Replication Complex Inhibitor, Combined With Peginterferon Alfa-2a and Ribavirin in Treatment-Naive HCV-Genotype 1 or 4 Patients: Phase 2b COMMAND-1 SVR12 Results

AASLD 2012

* Among GT 4-infected patients, both 20 mg and 60 mg DCV + alfa/RBV achieved higher rates of SVR_{12} than alfa/RBV
  * 100% (12/12) of patients treated with 60 mg DCV achieved SVR_{12}
  * 67% (8/12) of patients treated with 20 mg DCV achieved SVR_{12}
  * 50% (3/6) of patients treated with alfa/rbv achieved SVR_{12}

Summary

* Epidemiological trials show that HCV-4 has spread beyond Africa and the Middle East to Western countries
* Recent clinical data provides new insights into HCV-4 infection and treatment strategies
* Baseline viremia, early viral kinetics, AFP and stage of liver disease are important to individualize therapy.
* Future therapy is promising with DAAs


Thank You
Gamal Esmat