Hepatitis C Infection Elimination until 2030 International Experiences and National Plan

Seyed Moayed Alavian
Professor of Gastroenterology and Hepatology
Editor in-chief of Hepatitis Monthly
E mail: editor@hepatmon.com

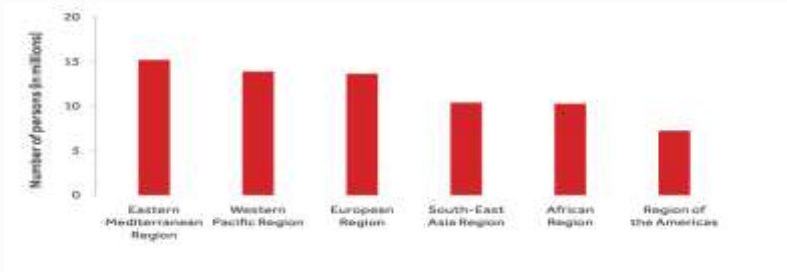
Introduction

- Hepatitis C is a major global health problem and the progression leads to life threatening complications.
- Most of the global HCV burden is in **low- to middle-income countries**.

Prevalence of HCV Infection by WHO Region

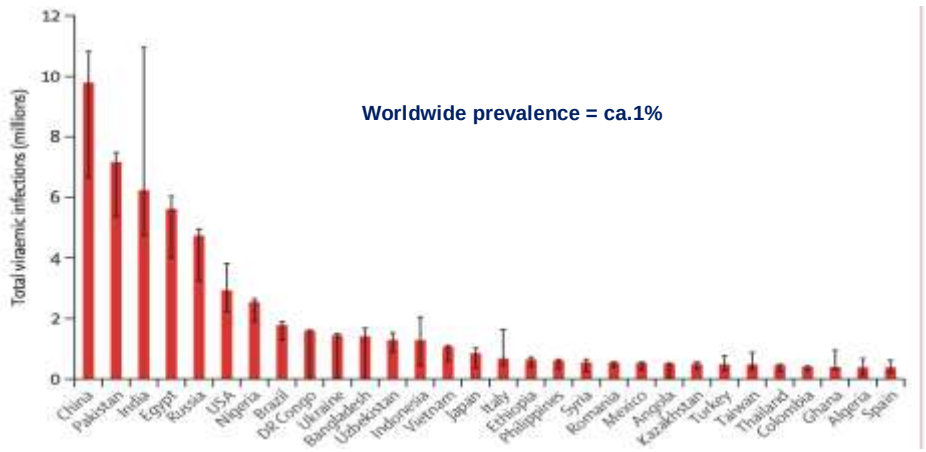
	Estimates of the prevalence of HCV infection (%)			Estimated number of persons living with HCV (millions)		
		Uncertainty interval			Uncertainty interval	
WHO region	Best	Lower	Higher	Best	Lower	Higher
African Region	1.0	0.7	1.6	11	7	15
Region of the Americas	0.7	0.6	0.8	7	6	8
Eastern Mediterranean Region	2.3	1.9	2.4	15	13	15
European Region	1.3	1.2	1.3	14	11	14
South-East Asia Region	0.3	0.2	0.3	10	8	10
Western Pacific Region	0.7	0.6	0.8	14	10	15
Total	1.0	0.8	1.1	71	61	78

Previously reported Worldwide Infection: Between 130-170 Million



WHO Global Hepatitis Report 2017

Global Prevalence of HCV by Country



Worldwide prevalence = ca.1%

Razavi H. Polaris Observatory HCV Lancet Gastroenterol Hepatol 2017

Map of Incidence of HCV Infection by WHO Region

WHO region	Map key	Incidence of HCV infection: Incidence rate (per 100 000): Best estimate	Uncertainty interval	Total number (000): Best estimate	Uncertainty interval
African Region		31.0	[illegible]	309	[illegible]
Region of the Americas		6.4	[illegible]	63	[illegible]
Eastern Mediterranean Region		62.5	[illegible]	409	[illegible]
European Region		61.8	[illegible]	[illegible]	[illegible]
South-East Asia Region		14.8	[illegible]	287	[illegible]
Western Pacific Region		6.0	[illegible]	111	[illegible]
Global		23.7	[illegible]	1 751	[illegible]

1,75 million new infections in 2015
Unsafe health care and injection drug use

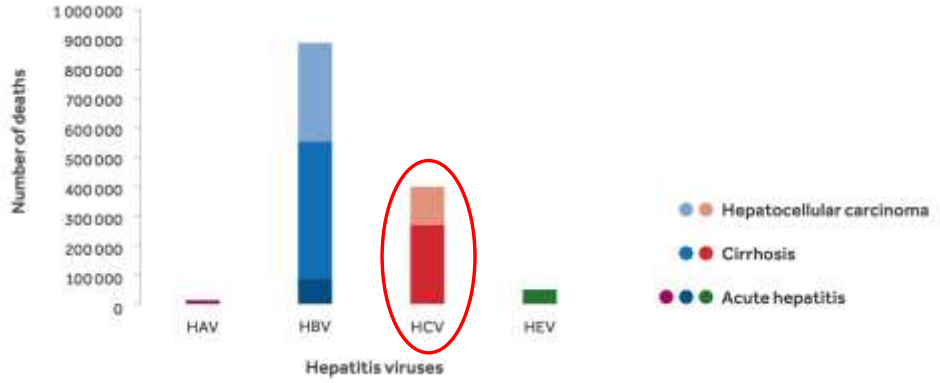
WHO Global Hepatitis Report 2017

The HCV Epidemiology Calculated in 2016 *vs* WHO Estimated Data for 2015

	WHO estimate (2015 data)	This analysis (2016 data)
New infections	1,700,000	1,597,812
Cures	843,000	1,512,759
HCV-related deaths	399,000	383,998
Epidemic size	**71,000,000**	**69,554,808**

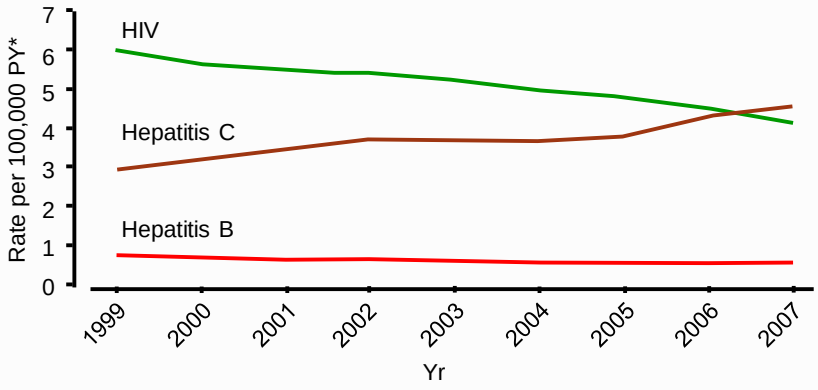
Hill A M et al. J Virus Eradication 2017; 3: 117–123

Mortality Rates Due to Viral Hepatitis in 2015



WHO Global Hepatitis Report

Mortality Rates Due to HIV, HCV, and HBV Infections in the US



Ly KN, et al. Ann Intern Med. 2012

Hepatitis C as a Neglected Disease

- NO Symptoms
- No effective treatment (before 2013!)
- Lack of knowledge (general population, healthcare workers and patients)

Hepatitis C in Iran

- Given the high coverage of HBV vaccination in infants and implementation of HBV vaccination programs among adolescent in Iran, HCV seems to emerge as the leading cause of viral hepatitis-related advanced liver disease and death in the near future.

- First report in Iran is related to Rezvan et al in 1994 in IBTO: 0.3% of blood donors in Tehran.

Rezvan et al. Vox Sang 1994

The Main Risk factors

Transfusion, undergoing endoscopy, extramarital sexual activities, non intravenous (i.v.) drug abuse, **i.v. drug abuse**, and receiving wounds at **war** were found to be independent risk factors of being HCV-positive.

No apparent risk factors could be demonstrated in **24.5%** of the positive cases.

Table 3 Logistic regression analysis of risk factors

Risk factor	Odds ratio	95% CI
Extramarital sexual activities	42.2*	5.3–335.7
Being wounded at war	5.2*	1.2–21.9
History of undergoing endoscopy	4.0*	1.3–12.5
i.v. drug abuse	52.8*	6.8–412.0
Needle-stick	8.9	0.8–93.9
Non-i.v. drug abuse	34.4*	4.2–278.2
Transfusion history	17.0*	7.0–41.0

*Odds ratio is statistically significant. CI, confidence interval; i.v., intravenous.

0.12% were HCV positive

Alavian SM, et al. Hepatitis C risk factors in Iranian volunteer blood donors: A case-control study. J Gastroenterol Hepatol. 2002

Epidemiologic profile and estimated disease burden of HCV in Iran in 2014

HCV epidemiology and burden	Frequency
Individuals living with chronic HCV infection	**186,500** individuals
HCV prevalence (viremic)	**0.24%** (0.17% - 0.31%)
HCV incidence (annual)	11 per 100,000
HCV diagnosis	**35%**
HCV treatment rate (annual)	**2.4% (n ~ 4,500)**
HCV genotype Less than 0.5% HCV seropositivity	Genotype 1: 64% Genotype 2: 2% Genotype 3: 33% Genotype 4: 1%
HCV-related decompensated cirrhosis	140 individuals
HCV-related HCC	160 individuals
HCV-related death	120 individuals

Hajarizadeh B, Razavi-Shearer D, Merat S, **Alavian SM**, Malekzadeh R, Razavi H. Liver disease burden of hepatitis C virus infection in Iran and the potential impact of various treatment strategies on the disease burden. Hepatitis Monthly. 2016;16(7):e37234

Burden of Hepatitis C, Iran and some countries in the region

	Iran	Pakistan
Country's Population (000)	71 000	167 000
Year	2006	2008
HCV Antibody Positive (000)		
Total Cases	275 (189 - 360)	8010 (5792 - 9920)
Prevalence	0.4% (0.3% - 0.5%)	4.8% (3.5% - 5.9%)
Year of Estimate	2006	2008
Viremic Infections (000)		
Total Viremic Cases	170 (117 - 223)	7001 (5062 - 8670)
Viremic Prevalence	0.2% (0.2% - 0.3%)	4.2% (3.0% - 5.2%)
Viremic Rate (%)	62%	87%
Year of Estimate	2006	2008
Genotypes (%)		
1a	40%	5%
1b	12%	1%
1 Other	1%	1%
1	53%	7%
2	1%	4%
3	28%	79%
4	1%	2%
5	-	0%
6	-	0%
Other	17%	8%
Year of Estimate	2004	1996 - 2011
Diagnosed (Viremic)		
Total Cases	60 000	1 050 000
Annual Newly Diagnosed	6000	100 000
Year of Estimate	2013	2010
Treated		
Annual Number Treated	4500	85 000
Year of Estimate	2011	2011
Liver Transplants		
Total Liver Transplants	590	300
HCV Liver Transplants	94	225
% due to HCV	16%	75%
Year of Estimate	2013	2012

Liakina V, Hamid S, Tanaka J, Olafsson S, Sharara AI, **Alavian SM**, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries .J Viral Hepat. 2015

15

Do not Forget the Missed Risk Factors

History of work as ampulla injectors especially traditional and low - educated

In a study in three prisons in three central provinces of Iran (Isfahan, Lorestan, Chaharmahal va Bakhtiari) in 2003 in male prisoners who were arrested because of their addiction

- 3.5% were HBs Ag positive and 35.8% were HCV antibody.
- According the age, the infection with HBV and HCV were more common in younger than 30 yrs. old.
- Isfahan , Lorestan and Chaharmahal va Bakhtiari: Addicted arrested respectively, 28.5%, 50% , 53.% HCV infected
- IUDs, Tattooing history, In jail more than 5 years were important
- **In Conclusion:** Potentiating of harm reduction program ,Education for dangerous behavior,

Javadi et al. Prevalence of HBV and HCV infections and associated risk factors in addict prisoners. Iran J Public Health. 2006

The Present and Future disease burden of hepatitis C virus infections with today's treatment paradigm

	Iran
Viremic HCV Infections	
2014 Est.	186
2030 Est.	213
Percent Change	14%
HCC Cases	
2014 Est.	110
2030 Est.	330
Percent Change	195%
Liver Related Mortality	
2014 Est.	140
2030 Est.	430
Percent Change	215%
Decompensated Cirrhosis	
2014 Est.	150
2030 Est.	660
Percent Change	350%
Compensated Cirrhosis	
2014 Est.	3500
2030 Est.	10 800
Percent Change	210%

In 2007, it was estimated that 75% of the infected population in Iran had been infected by IDU. Based on expert opinion, 4% of all HCV cases were infected via transfusion procedures. The majority of new cases are due to IDU, which is reflected in the young age distribution.

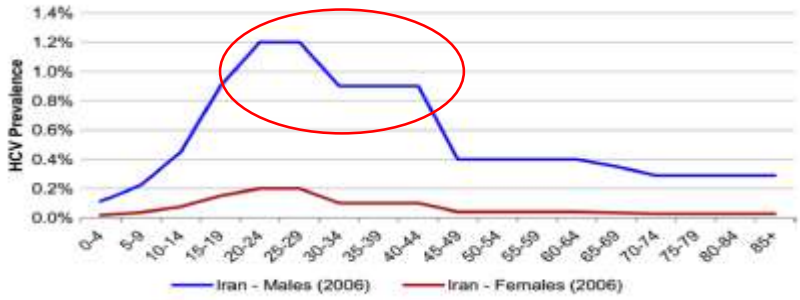
In 2014, there were an estimated 186 000 (123 000–250 000) viraemic individuals in Iran, increasing 14% to 213 000 individuals in 2030.

Sibley A, Han KH, Abourached A, Lesmana LA, Makara M, Jafri W, **Alavian SM** et al. The present and future disease burden of hepatitis C virus infections with today's treatment paradigm . J Viral Hepat. 2015

Younger HCV infected patients in Iran

Median age of 30 years and 70% between 20 and 44 years old

Iran has one of the lowest rates of HCV prevalence in the Middle East. Under the current treatment paradigm, HCV infections will increase in Iran.

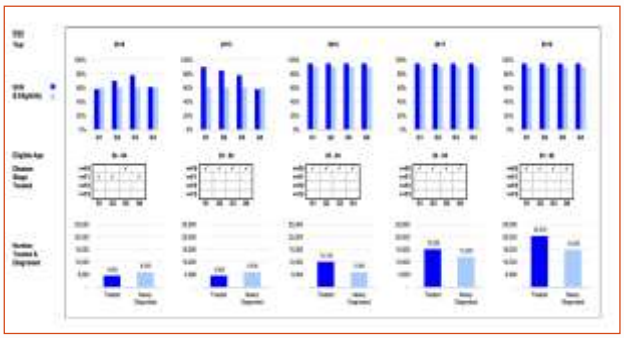


Less than 0.4% in general population

Liakina V, Hamid S, Tanaka J, Olafsson S, Sharara AI, **Alavian SM**, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries .J Viral Hepat. 2015

19

Elimination will be possible by 2030 in Iran



While increasing efficacy has moderate declines in all HCV-related indicators, an aggressive treatment strategy would eliminate HCV in Iran, bringing the viremic prevalence to approximately **0.02%** by **2030**.

Increase treatment by **5000** individuals every year starting in **2016** until reaching a maximum treatment of **20 500** in **2018**. By treating over **20 000** individuals annually for **5 years**, the treatment could then decrease to below current levels by 2030.

Due to the large numbers of individuals being treated, there would need to be an increase in diagnosis rate to keep pace with the treatment rate. Utilizing a risk factors approach could make diagnosis, treatment and thus **elimination, a real possibility in Iran.**

Alfaleh FZ, Nugrahini N, Maticic M, Tolmane I, Alzaabi M, Hajarizadeh B, **Alavian SM** et al. Strategies to manage hepatitis C virus infection disease burden - volume . J Viral Hepat. 2015

جدول ۲- توزیع فراوانی آلودگی به ویروس HCV به تفکیک سال در زندان‌های بررسی شده در کشور

سال بررسی	آلودگی به ویروس HCV		
	حجم نمونه	درصد آلودگی	95%CI
۱۳۷۹	۴۸۰	۲۴/۰	۲۰/۲-۲۷/۹
۱۳۸۰	۲۳۴۶	۳۴/۷	۳۲/۷-۳۶/۶
۱۳۸۱	۱۷۶۲	۴۴/۸	۴۲/۵-۴۷/۱
۱۳۸۲	۱۵۹۷	۴۶/۱	۴۴/۲-۴۹/۱
۱۳۸۳	۲۴۰۰	۳۲/۸	۳۰/۹-۳۴/۶
۱۳۸٤	۴۵	۴۲/۲	۲۸/۵-۵۶/۹
جمع	۸۶۳۰	۳۷/۸۵	۳۶/۸-۳۸/۹

Asgari F, Gooya MM, Mohammad K, Fotouhi A, Yousefi A. [Hepatitis C virus infection among Iranian prisoners and its relation with addiction, 2001-2005]. Hakim Research Journal. 2008

High risk group

30 December 2017 Zahedan

In 50 IDUs cases we had 9 cases with HCV positive and 2 cases with HIV

Undiagnosed cases

Hepatitis C Virus Infection and Its Prevalence in Iran

- Less than 0.5% of General population are HCV infected in Iran and the main risk factors are **history of blood transfusion before 1996** and **history of IDUs**
- The special group such as **Hemophilia** and **Thalassemia** and **Hemodialysis** patients selected for screening and treatment during recent 10 years and now..
- IDUs cases are the main high risk group now and harm reduction and other strategies should attenuated now.
- Treatment is a part of prevention for decrease the chance of transmission

Hepatitis C Elimination

Systematic Strategies Towards HCV Elimination

2011-2014

- Revolutionized treatment
- Direct Acting Antivirals (DAAs)
- No injections
- Once daily
- Minimum side effects
- Highly effective

Hepatitis Strategy, 2016: Elimination by 2030

	Interventions	2030 targets
1. Service coverage	1. Three dose hepatitis B vaccine	**90%**
	2. HBV PMTCT	**90%**
	3. Blood and injection safety	**100 % screened donations**
		90% reuse-prevention devices
	4. Harm reduction	**300 injection sets/PWID/yr**
	5. Treatment	**90% diagnosed**
		80% eligible treated
2. Impact	A. Incidence reduction	**90%**
	B. Mortality reduction	**65%**

PMTCT: Prevention of mother to child transmission **PWID**: Person who injects drugs

WHO 2016

Why Elimination of HCV is Feasible

HCV Meets All Established Criteria For Elimination

- No non-human reservoir
- Virus cannot amplify in the environment
- Simple and accurate diagnostic tools
- Practical interventions to interrupt transmission
- Infection is curable

Edlin BR, Winkelstein ER. Antivir Res 2014;110:79–93

Discussion

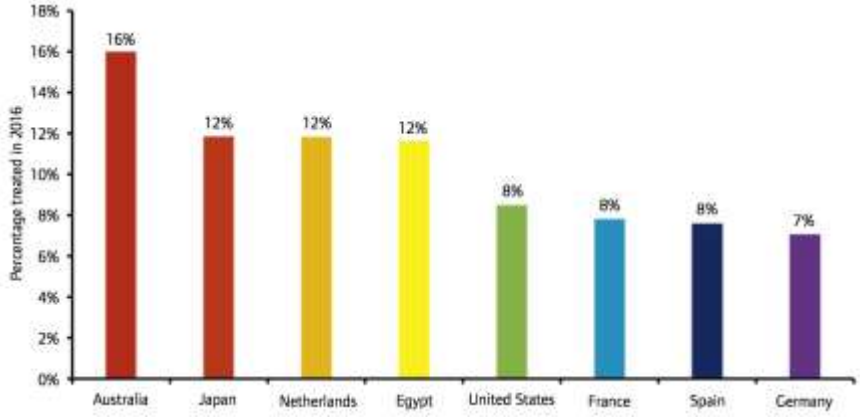
- Implications for health policy-makers and health service delivery with evidence of some doctors not following national HCV treatment guidelines .
- A shift is required from individual management of HCV to population management:
- –Improve screening, especially among those at high risk of HCV infection, through healthcare access points
- –Scale-up treatment including by broadening the HCV prescriber base
- Expand models of care to include screening, assessments, treatment, harm reduction and re-screening for those with continued high-risk behaviors
- •To achieve global HCV elimination, partnership is required between HCPs, policy-makers, patient organizations, and industry to develop and implement local strategies

Central elements for HCV elimination

- Generic DAA is a major step forward but there are still more requirements to ensure achieving WHO HCV elimination targets:
  - Affordable HCV diagnosis and treatment with access for all
  - Expanding prescribers
  - Integration of substance use care and HCV care
  - HCV awareness campaigns targeting the main population at risk
  - Peer-workers can facilitates linkage to care
  - Simplified diagnostics

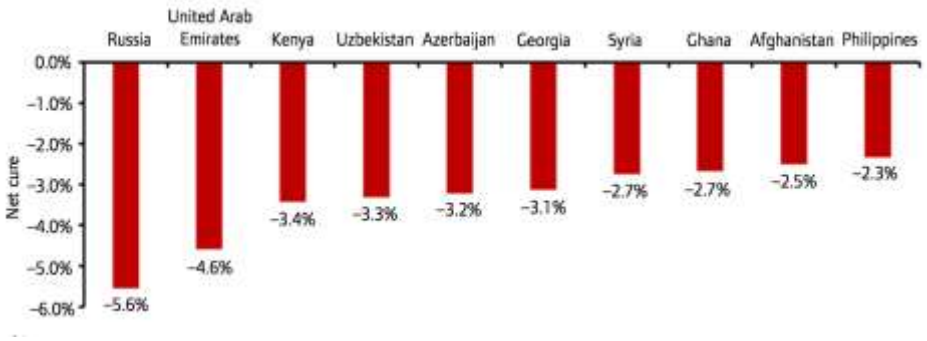
Alavian SM. Sharafi H. Elimination of Hepatitis C Virus Infection in Iran; strategies, and opportunities and limitations. Hepat Mon 2017.In press

The Eight Countries Treating the Most People by Percentage in 2016



Hill A M et al. J Virus Eradication 2017; 3: 117–123

The 10 Countries with the Lowest Net Cure in 2016

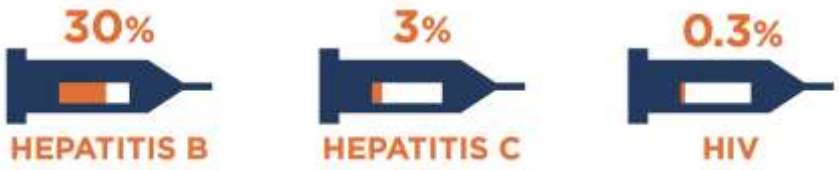


Hill A M et al. J Virus Eradication 2017; 3: 117–123

Estimated Risk of Getting Hepatitis or HIV from a Contaminated Syringe or Needle.

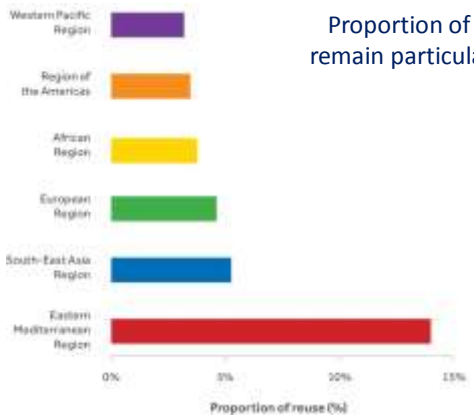
World Health Organization

An **unsafe injection** could **put you at risk** of getting a life-threatening infection such as:



www.who.int/infection-prevention

Blood and Injection Safety

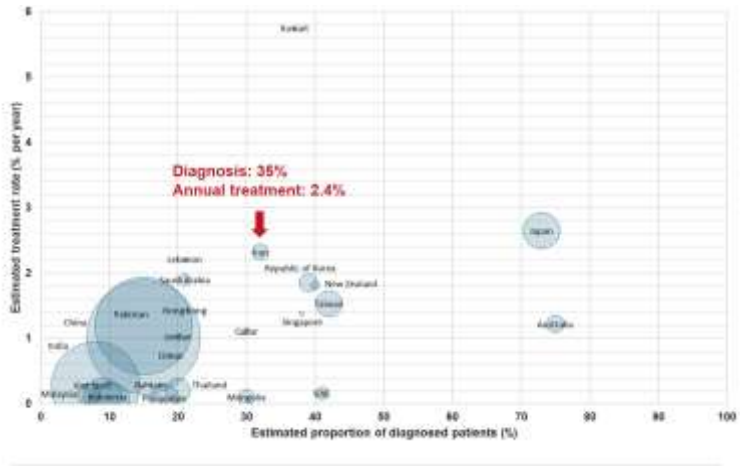


Proportion of unsafe injections by region, challenges remain particularly in the Eastern Mediterranean region

www.who.int/infection-prevention

Iranian Plan for Hepatitis C Elimination

Diagnosis rate



Hajarizadeh B, et al. Hepat Mon 2016; Razavi H, et al. JVH 2014; Hatzakis A, et al. JVH 2015; Sibley A, et al. JVH 2015

At Risk Populations

- People who inject drugs (PWID)
- Prisoners
- Thalassemia and Hemophilia patients
- Hemodialysis
- Transfusion history before 1375
- People with war and motor vehicle injuries
- Sex workers
- HIV infected people
- Sanitation workers
- First degree relatives of HCV infected people
- Medical and healthcare workers
- Organ transplant receivers
- Newborns of HCV infected mothers

37

Who are at high risk and we should focus on them now!

✓ Those who received blood and blood products before 1996

✓**So What is the role of government now for HCV elimination?**

38

Unexpected High Prevalence of Hepatitis C in Special Groups; Patients with Leprosy are Forgotten

In Baba-baghi village, Tabriz, more than 50% of patients with leprosy were found to have Anti-HCVAb. The patients had no known major risk factors of HCV transmission in Iran.

Maybe you are the one, who finds the next group

WHO Objectives and Iran

1. Prevention

A. Increasing information in general and priority populations

B. Improving blood safety

C. Harm reduction

2. Diagnosis

A. Strengthening the national laboratory system

B. Screening priority populations

C. Improving point of care diagnosis

3. Treatment

A. Expanding treatment

B. Implement appropriate models of care

C. Providing chronic care

4. Delivering for equity

A. Strengthening human resources

B. Ensuring access to good quality and affordable hepatitis medicines and diagnostics

C. Promoting an enabling environment

HCV Elimination Programs in Iran

- Prison-based programs
  - 10% HCV-seropositive
  - 35%-50% HCV-seropositive in inmates of addiction
- Community-based programs in high-risk groups
  - Including PWIDs, FSW and non-IV drug users
  - 10%-50% HCV-seropositive

HCV Elimination Programs in Iran

- Thalassemia and hemophilia
  - Less than 500 case need treatment
- Chronic kidney disease
  - Around 5% HCV-seropositive
- Other groups
  - People with history of blood transfusion before 1996
  - People with war injury
  - People with history of leprosy

HCV in Hemophilia and Thalassemia is on control in Iran now
How?

Iran Hepatitis Network

I hope for HCV elimination until 2020 in special patients

Treatment (A Brief History)

CLINICAL STUDIES

Peginterferon α-2a and ribavirin treatment of patients with haemophilia and hepatitis C virus infection: a single-centre study of 367 cases

Two hundred and twenty-five subjects **61%** achieved SVR, 66 patients relapsed and 30 subjects did not respond and nine patients developed breakthrough during treatment. Peg interferon alpha-2a in combination with weight-based ribavirin has SVR rate of **51%** for genotype 1 and **71%** for genotype non-1 infections in hemophilia patients.

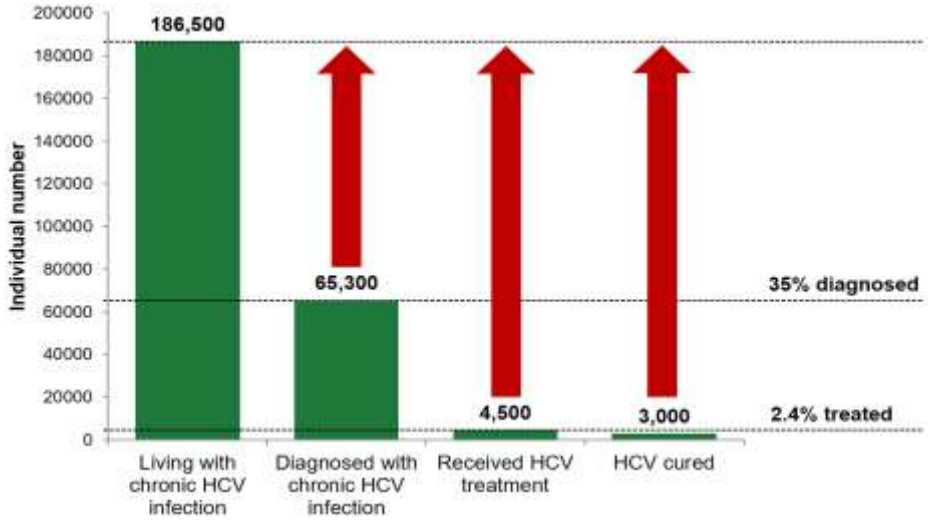
Alavian SM, et al. Peginterferon alpha-2a and ribavirin treatment of patients with haemophilia and hepatitis C virus infection: a single-centre study of 367 cases. Liver Int. 2010

44

Elimination of HCV in Hemophilia is a model for hemodialysis , but who is responsible!!

45

HCV care cascade in Iran (2014)



Hajarizadeh B, Razavi-Shearer D, Merat S, Alavian SM, Malekzadeh R, Razavi H. Liver disease burden of hepatitis C virus infection in Iran and the potential impact of various treatment strategies on the disease burden. Hepatitis Monthly.2016;16(7):e37234

Access or not access to DDAs

- In many countries, people don't have access to a course of brand-name direct-acting antiviral drugs due to their high cost -- as much as between $30,000 -$94,000 a patient.

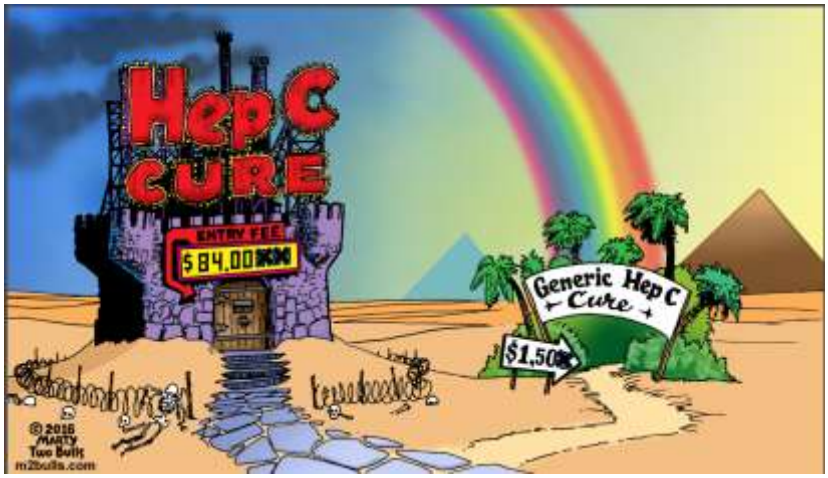
Expensive treatments for common conditions are unaffordable for most health system, even if they are cost effective.

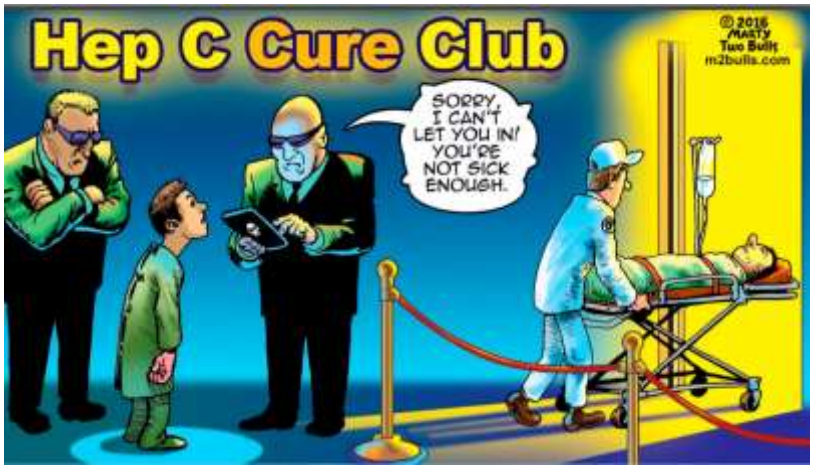
They are also very expensive.

Barcelona, EASL 2016

Generic medications may be a significant role in elimination

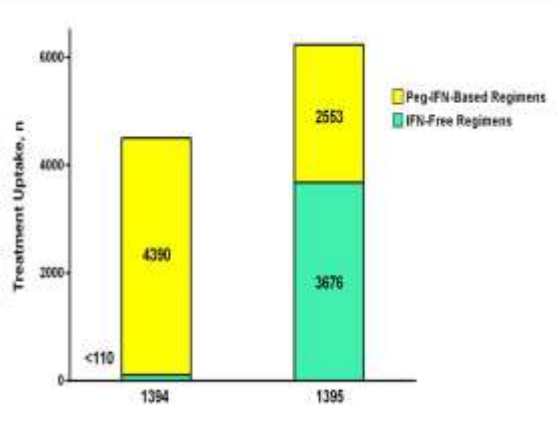
- Generic medications do **not** require the background research and development studies to support registration.
- There is a higher motivation to use the generic drugs in therapy of HCV infected patients in developing and developed countries.
- India, Egypt and Iran are pioneer in developing generic brands for therapy of HCV infection.


Hep C CURE
ENTRY FEE
$84,000
Generic Hep C Cure
$1,500
© 2016 MARTY Two Bulls
m2bulls.com


Hep C Cure Club
© 2016 MARTY Two Bulls
m2bulls.com
SORRY, I CAN'T LET YOU IN! YOU'RE NOT SICK ENOUGH.

Generic DAA is available in Iran

How many cases have treated with DDAs in Iran



- During two years from 2013-2014 : 230 cases have received the Harvoni, Brand of Sof-Led in Iran
- It was not affordable for all patients in Iran.
- Most of cases were treated with support of Disabled Organization
- The insurance companies did not accept to cover

But in one year (2015-2016): More cases with insurance coverage with generic type

- برای ریشه کنی هپاتیت سی تا سال 1410 نیاز است تا:
- 1) تشخیص سریع، ساده و ارزان در دسترس همگان قرار گیرد.
- 2) غربالگری وسیع، بخصوص در گروه های پرخطر (زندانیان، معتادین تزریقی، کودکان کار با رفتارهای جنسی پرخطر، افراد دارای سابقه دریافت خون و فرآورده های خونی قبل 1375و...) انجام شود.
- 3) موارد مثبت، شناسایی و درمان شوند.
- 4) داروهای ارزان در دسترس تمامی موارد شناسایی شده باشد.
- 5) به گایدلاین های بومی درمان هپاتیت سی توجه بیشتری شود.
- 6) گایدلاین های درمانی در اختیار متخصصین داخلی و حتی پزشکان عمومی قرار داده شود و پیگیری درمان بیماران، به سطوح پایین تر (پزشکان عمومی) سپرده شود.
- 7) هزینه درمان رایگان سالانه حداقل 20 هزار بیمار مبتلا به هپاتیت سی، توسط دولت تامین گردد.
- 8) آگاهی عمومی، نسبت به این بیماری افزایش یابد، تا از انتقال فرد به فرد جلوگیری شود.
- 9) راهکارهایی جهت کاهش ریسک ابتلا، در افراد گروه پرخطر در نظر گرفته شود.
- 10) جلوگیری از ابتلای مجدد پس از درمان هپاتیت سی، در گروه های پرخطر بخصوص معتادین تزریقی.
- 11) آگاهی پزشکان و همکاران دیگر گروه پزشکی نسبت به برنامه ی جهانی ریشه کنی هپاتیت های ویروسی ((Nohep افزایش یابد.
- 12) نظام جمع آوری اطلاعات دقیق ایجاد شود، تا تعداد موارد تشخیص داده شده و درمان شده در آن ثبت شود.
- ما پزشکان، پرستاران، ماماها، متخصصین علوم آزمایشگاهی و... تعهد می نماییم در راه رسیدن به این هدف بزرگ گام برداریم.

Strategies for control

- Community-wide education initiatives are needed for alerting people to the modes of transmission and facilitating a social climate at-risk people feel comfortable to seek testing and where harm-reduction strategies can be implemented.
- Active case finding according to main risk factors and therapy

5. Increase General Awareness About HCV

- ✓ Fifth, the media should be used to **increase general awareness about HCV infection** and help the process of identifying patients with HCV infection
- ✓ In Iran, we have established a nongovernmental organization, **Hope Health Club** to increase knowledge in the general population about viral hepatitis.
- ✓ www.hopehealthclub.com

باشگاه سلامتی امید
Hope Health Club

55

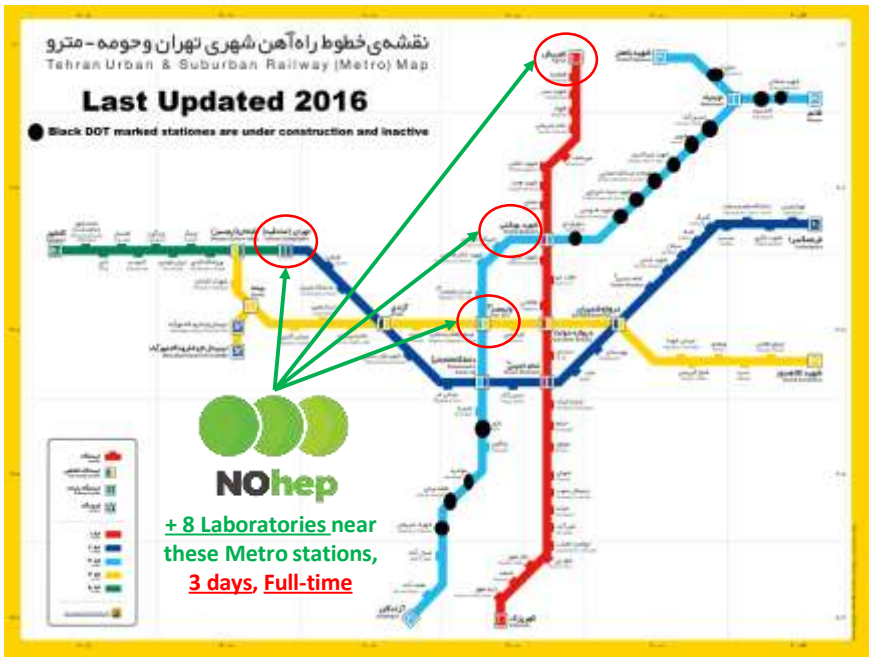
Distributing books and brochures

Face to Face Training

Health ambassadors

Animations

Iran Connected NOhep Program


نقشه‌ی خطوط راه‌آهن شهری تهران و حومه - مترو
Tehran Urban & Suburban Railway (Metro) Map
Last Updated 2016
Black DOT marked stationes are under construction and inactive
NOhep
+ 8 Laboratories near these Metro stations, 3 days, Full-time


Materials for 1st Iran Hepatitis Awareness Campaign
Iran Hepatitis Network, Tehran, Iran

Public awareness is important and effective in Australia
It can be more effective if it would be targeted to the right population

International Feedbacks

National Feedbacks

IHN, EASL and AASLD Collaborations

- ✓ Lastly, Iran Hepatitis Network, **European and American associations for the study of liver diseases** could increase their involvement in the Middle East by running **educational courses** about HCV management

AASLD

EASL
The Home of Hepatology

IRAN HEPATITIS NETWORK

69

Thalassemia

25

Elimination of HCV infection in Iran will be in 2030 but in thalassemia and hemophilia is possible in 2020!

Solution

Work together
More support for therapy
More attention to blood safety
More education the nurses in thalassemia centers Increase the thalassemia patients awareness regarding the issue.