Hepatitis C

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Outline

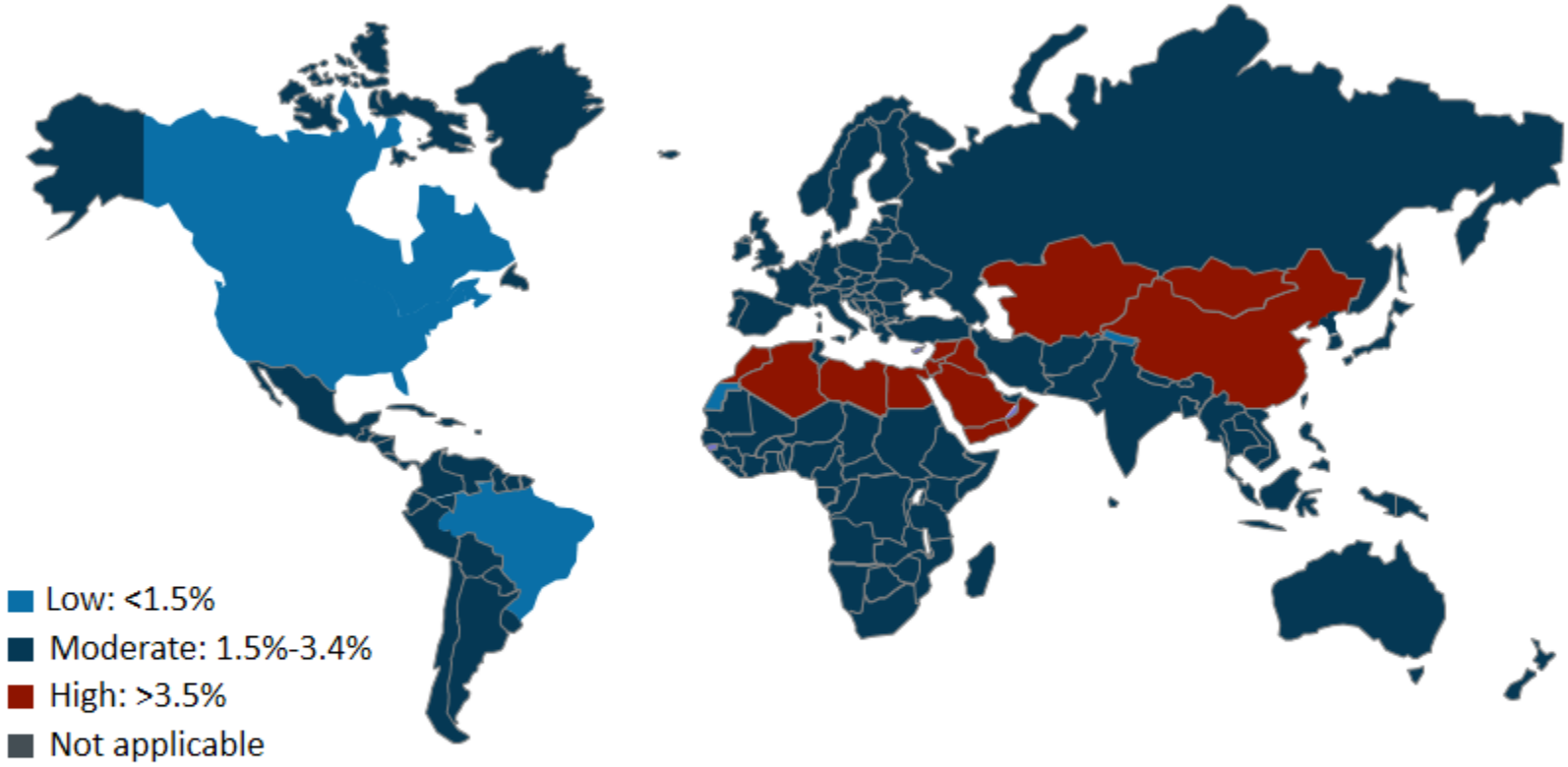
- Discussion

1. Epidemiology/ virology
2. Transmission
3. Clinical presentation

Introduction

- Hepatitis C virus was first discovered in 1989
- Globally, it is a major health problem with 71 million people that are viremic and an estimated 10.1 mil people chronically infected in sSA
- Prevalence varies as per region, with highest rates reported in Central and East Asia, North Africa and Middle East

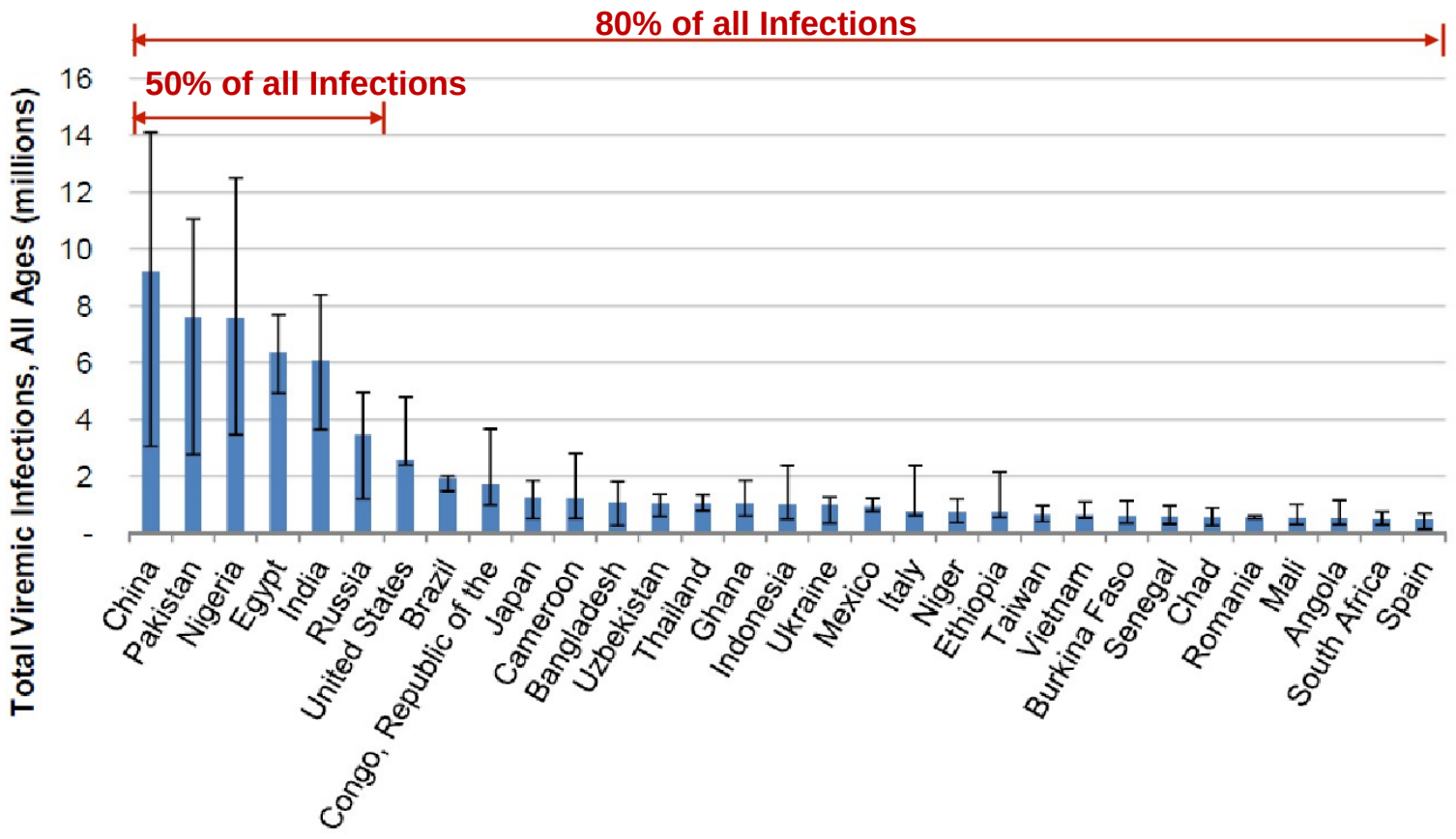
Estimated global hepatitis C prevalence – 140-185 million people



- Estimates are derived from a meta-analysis of data from 232 studies published between 1997 and 2007 and NHANES data up to 2010. Point prevalence estimates are calculated using regional population age weights.

Adapted from Hanafiah KM, et al. *Hepatology*. 2013;57:1333-1342.

Total Viremic HCV Infections - Countries Responsible for 80% of Global Infections



Gower, E., Estes C., Hindman, S., Razavi-Shearer, K., Razavi, H. Global epidemiology and genotype distribution of the hepatitis C virus. Journal of Hepatology 2014.

HCV Epidemiology : Africa

Regional prevalence & no of HCV-infected individuals in SSA (95% UI)

- ***East Africa***: 0.5% (0.4-0.7) : 2.1 M (1.6-2.9)
- ***Southern Africa:*** 0.7% (0.4-0.9) : 0.5 M (0.3-0.7)
- ***West Africa:*** 1.3% (1.1-1.4) : 5.1 M (4.3-5.7)
- ***Central Africa:*** 2.1% (0.1-6.9) : 2.4 M (0.1-8.0)

Data scarce on high-risk populations: MSM, PWID

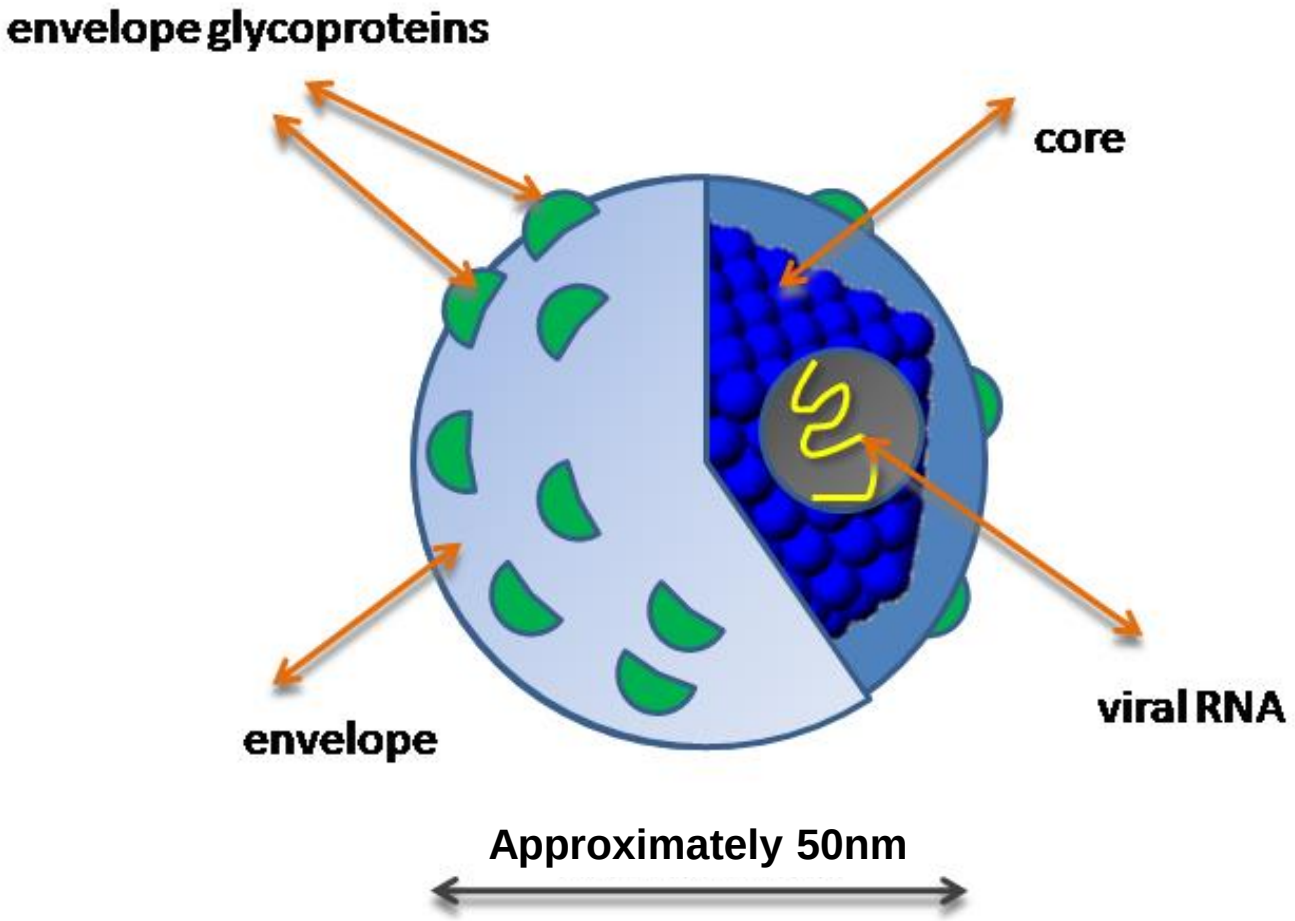
- Cultural biases or criminalization

MSM: Few accurate assessments of HCV seroprevalence

- ***Sudan:*** 0.1 to 1%
- ***South Africa:*** 3% in HIV negative MSM; 6% in HIV pos MSM in Cape Town

Lancet Gastroenterol Hepatol 2017;2:161; BMC Infect Dis 2016;16: 283; Lancet 2011; 378: 571; Int J Drug Policy 2013; 24: 78; J Int AIDS Soc 2015; 18: 19888; Sex Transm Infect 2013; 89 (suppl 3): iii17; S Afr Med J 2013; 103: 569 (abstr).

HCV viral structure



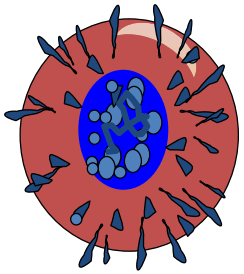
Hepatitis C virus

Single stranded, positive sense, RNA virus

- *Flaviviridae* family

No RNA polymerase proofreading ability

- forms heterogeneous viral populations or quasispecies



Half-life: ≈2.7 hours

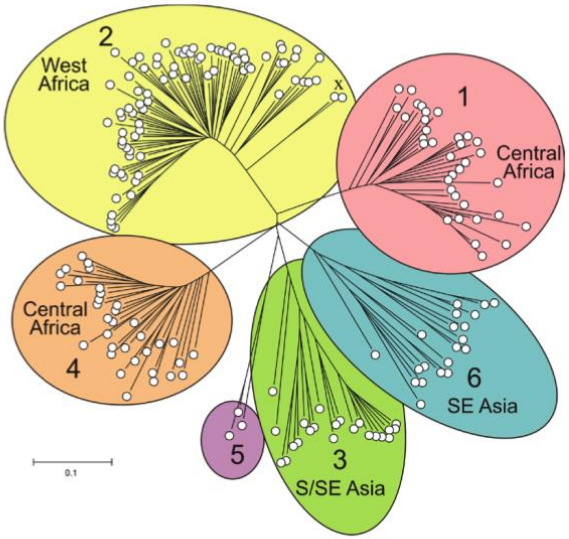
Daily production: 10^{12} virions

3000-amino acid polyprotein

Great genetic diversity

Six genotypes: 1,2,3,4,5,6

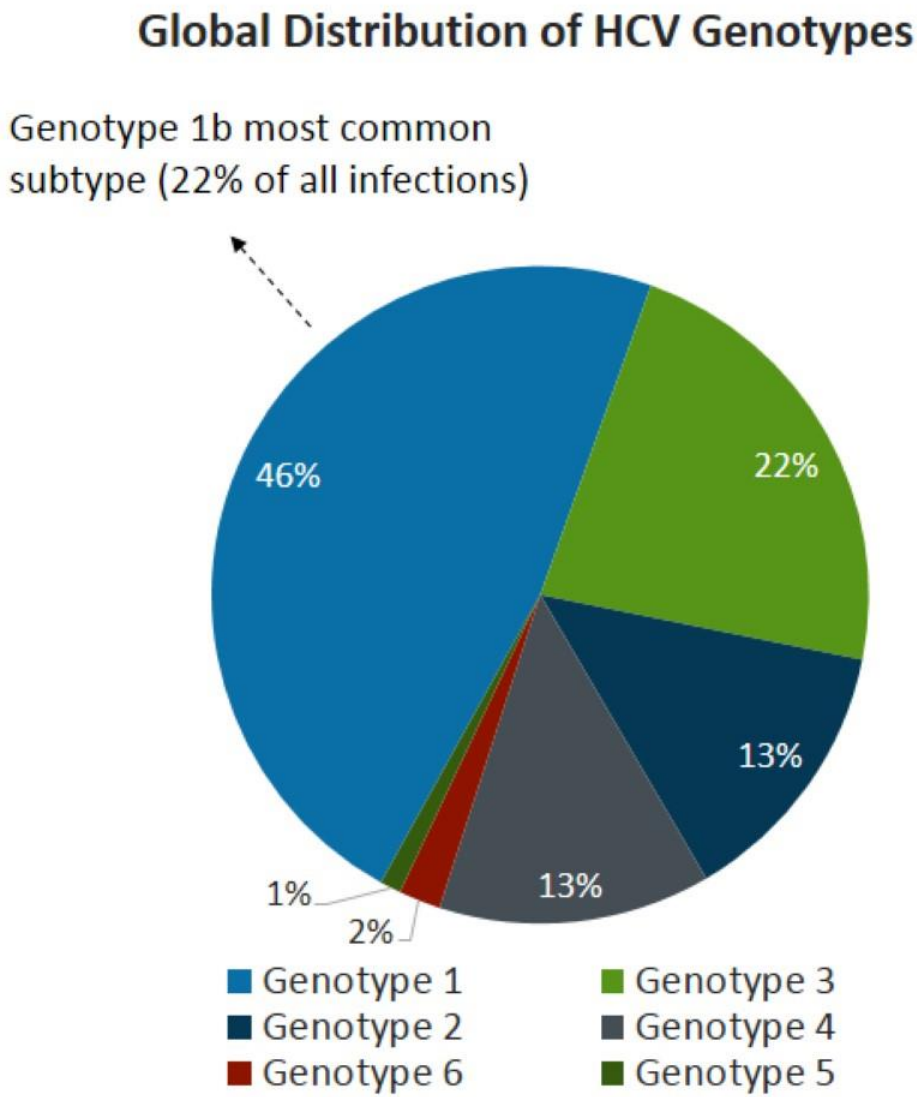
>80 subtypes: a, b, c, etc



Simmonds et al., Hepatology 2005, 42(4):962-73.

Choo QL, et al. Science. 1989;244:359-362.

HCV Genotypes

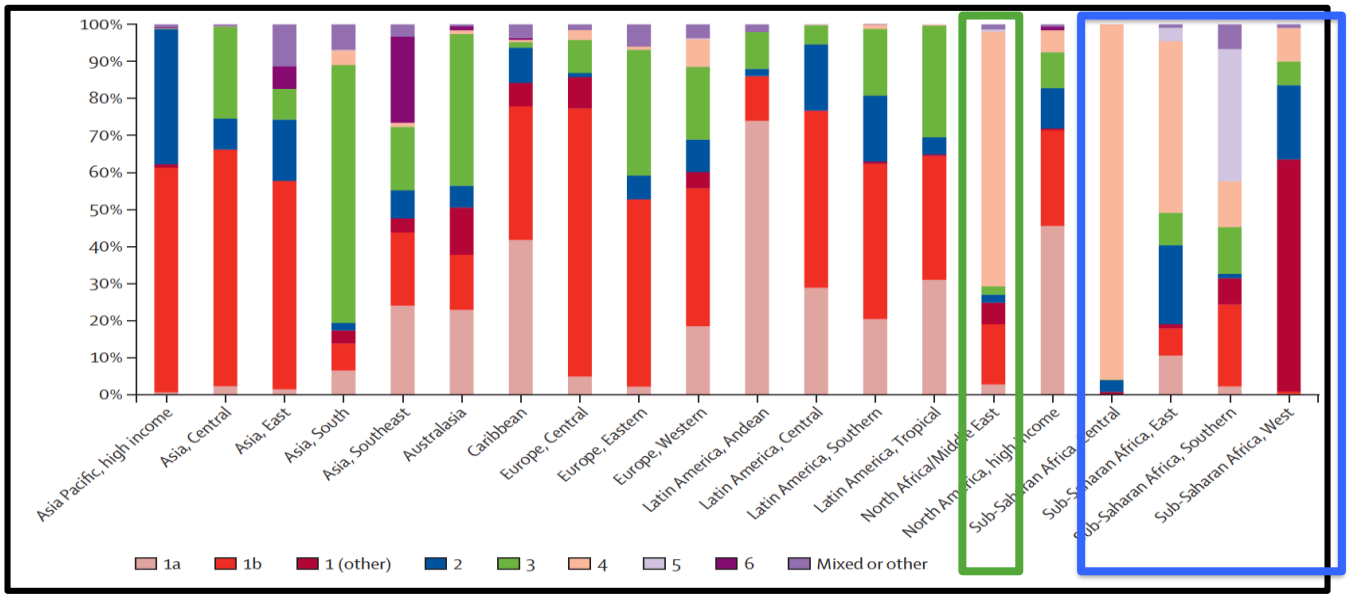


Different Genotypes Dominate in Different Regions

- Latin America, North America, Europe: genotype 1
- North Africa, Middle East: Genotype 4
- Asia: genotype 3 & 1
- Australasia: genotype 1 & 3

Gower E, et al. *J Hepatol.* 2014:61:S45-S57.

HCV Genotypes : Africa



Genotypes 1 and 4 predominate overall, but is pangenotypic (G1-5)

- ***Central Africa:*** G4 >80% - heterogenous: 4k, 4c, **4r** & 4f
- ***East Africa:*** G1-5 with G4 (50-68%) and G2 (33.3%) predominance
- ***Southern Africa:*** G1-5 with G5a predominance (35%), G1 (31%)
- ***West Africa:*** G1 (Nigeria 85%) and G2 (Ghana 87%)
- ***North Africa:*** GT4 predominates

Lancet Gastro Hepatol 2017;2: 161; J Viral Hepat 2016; 23: 881

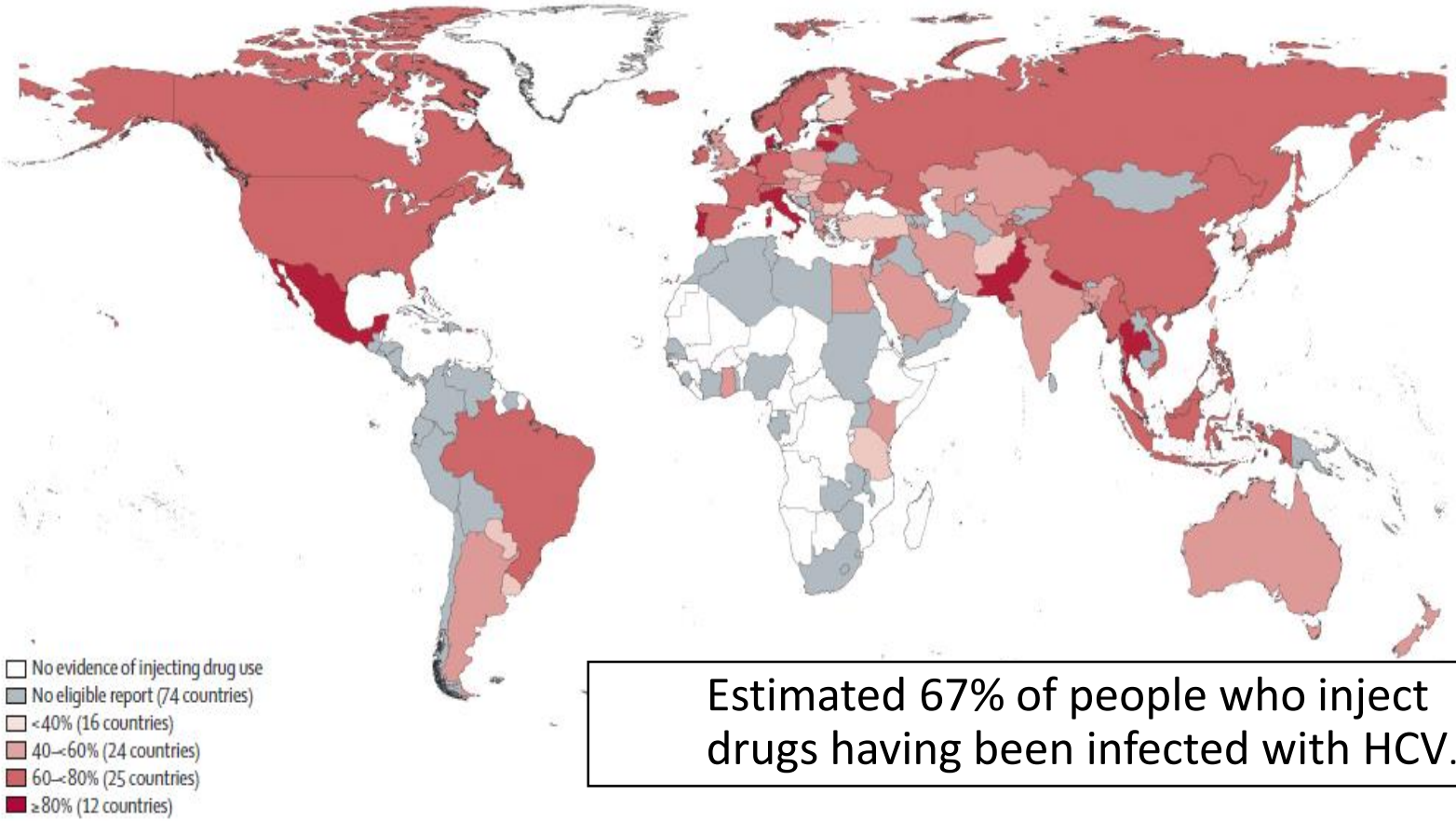
Risk factors for HCV infection

- Injecting drug use
- Blood/blood products < 1992 or where blood safety is inadequate
- Unsafe medical or dental interventions e.g. unsafe injection use
- Traditional practices
- Tattooing and body piercing using unsterilized equipment
- Needle stick injuries (healthcare workers)
- Perinatal/Mother to child
- Hemodialysis
- Sexual transmission (notably Men who have Sex with Men)

Risk Factors

Parenteral	Sexual	Perinatal
IDU	Multiple partners	High viral load
Nasal cocaine	Traumatic	HIV (+)
Transfusions	HIV (+)	
Needle stick injury	Use of a CSW	
Tattoos	Rectal contact	
Body piercing	MSM	
Manicures		
Household items		
Toothbrush, razor, nail clipper		
? Scarification		

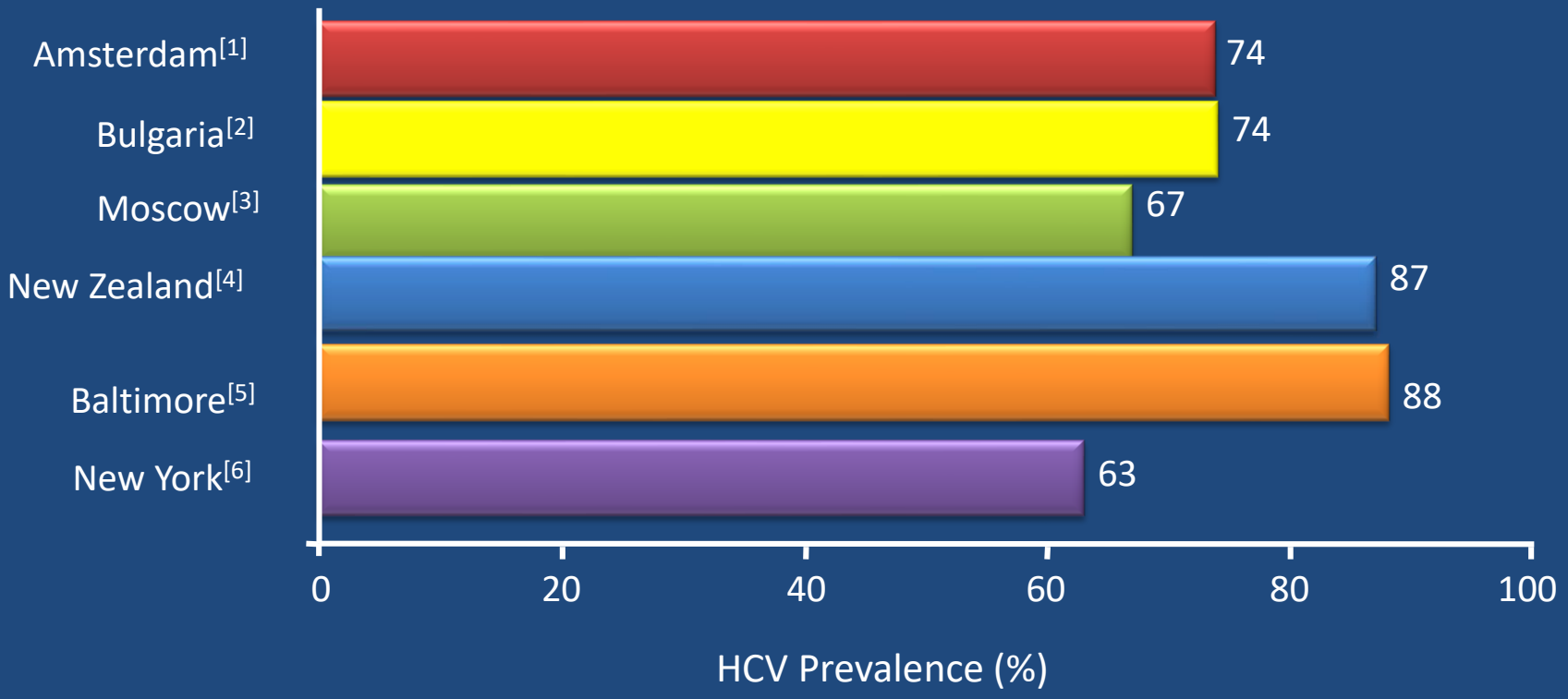
Prevalence of HCV among persons who inject drugs



Estimated 67% of people who inject drugs having been infected with HCV.

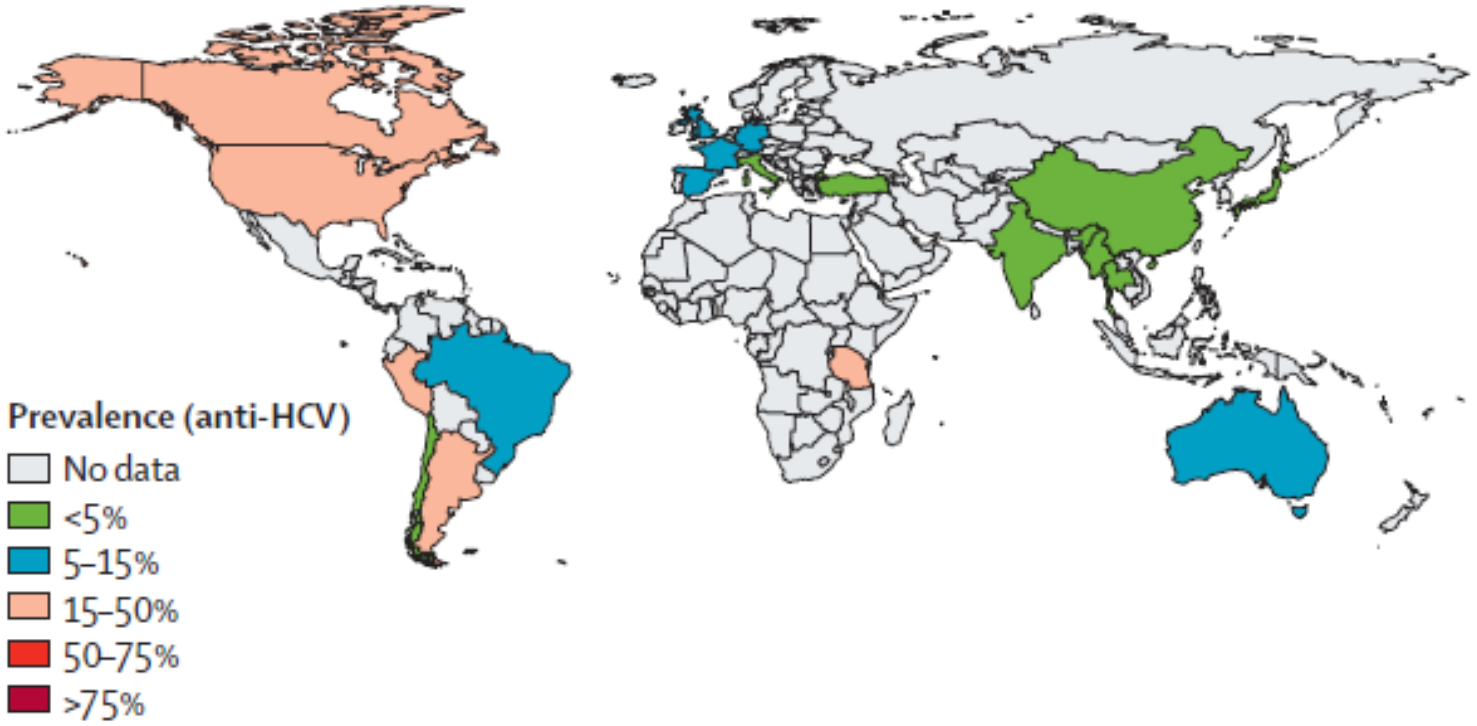
Nelson et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet, 378 (9791), 2011.

High Prevalence of HCV Among Injection Drug Users Worldwide



1. van den Hoek JA, et al. J Infect Dis. 1990;162:823-826. 2. Vassilev ZP, et al. Int J STD AIDS. 2006;17:621-626. 3. Rhodes T, et al. Addiction. 2006;101:252-266. 4. Kemp R, et al. N Z Med J. 1998;111:50-53. 5. Thomas DL, et al. Medicine. 1995;74:212-220. 6. Des Jarlais DC, et al. AIDS. 2005;19(suppl 3):S20-S25.

HCV/HIV coinfection - Men who have Sex with Men



Platt et al 2016

Hepatitis C prevalence in HIV + MSM in South Africa

Table 2. Hepatitis C infection prevalence

	Screened positive, *n*	Prevalence, % (95% CI)
All participants (*N*=500)	17	3.4 (2.1 - 5.4)
MSM (*N*=285)	16	5.6 (3.5 - 9.0)
Non-MSM (*N*=215)	1	0.5 (0.06 - 3.3)

CI = confidence interval; MSM = men who have sex with men.

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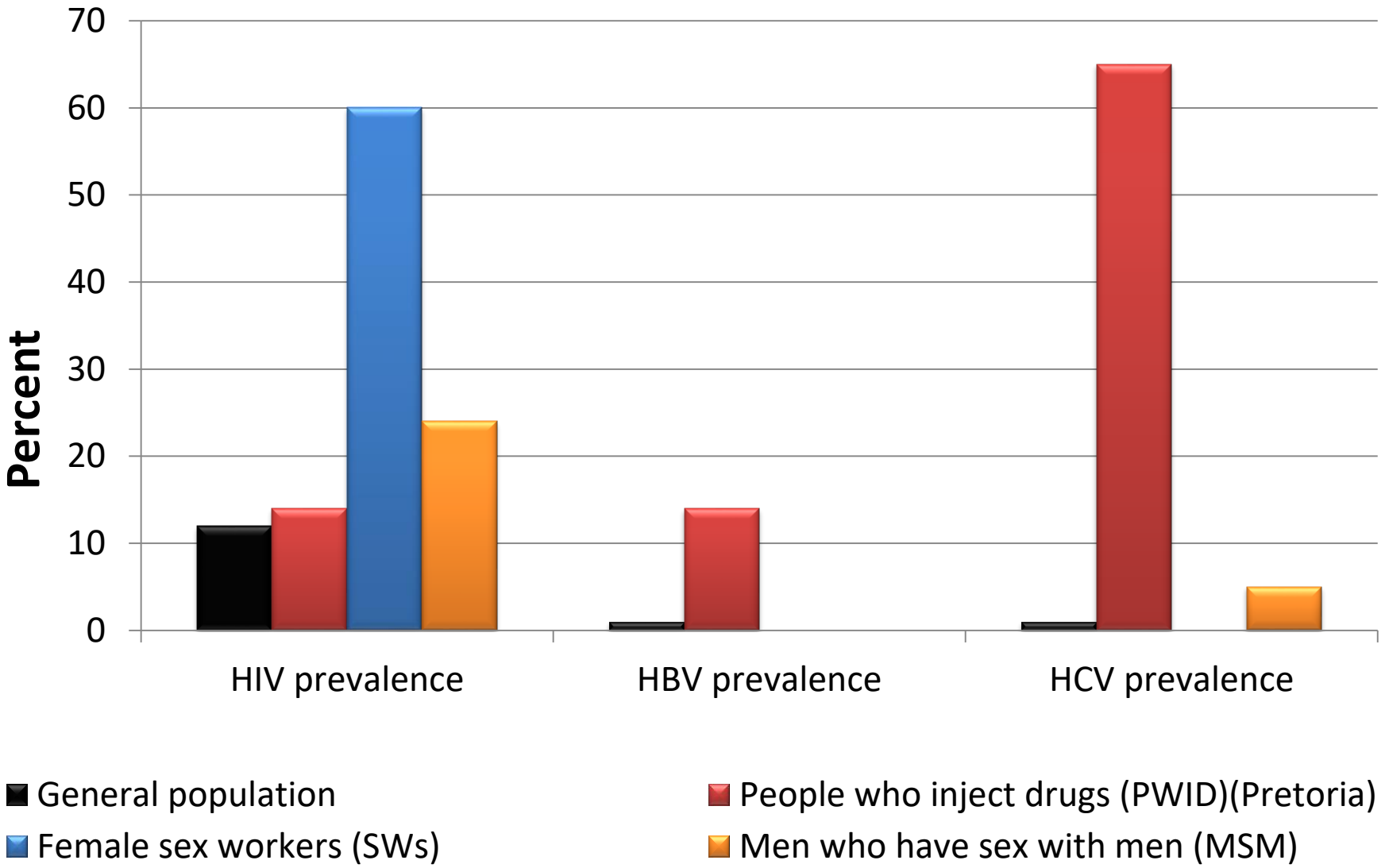
Viral hepatitis & HIV in South Africa



(Scheibe et. al 2016)

Low Risk of HCV Transmission Between Monogamous Sexual Partners

- 776 sero-discordant spouses followed for 10 yrs
  - Intercourse mean: 1.8/wk
  - No condom use, no anal sex
  - 3 new infections (incidence 0.37/1000 pt-yrs), but all 3 differed from partners strain
  - Net incidence of transmission: 0

Vandelli C, et al. Am J Gastroenterol. 2004;99:855-859

Viral Hepatitis awareness is poor

Mombassa (Kenya):

Out of 400 IDUs (59% anti-HCV+) **369 (92%)** did not know their HCV status as they had never been tested

(LEMOINE, personal communication)

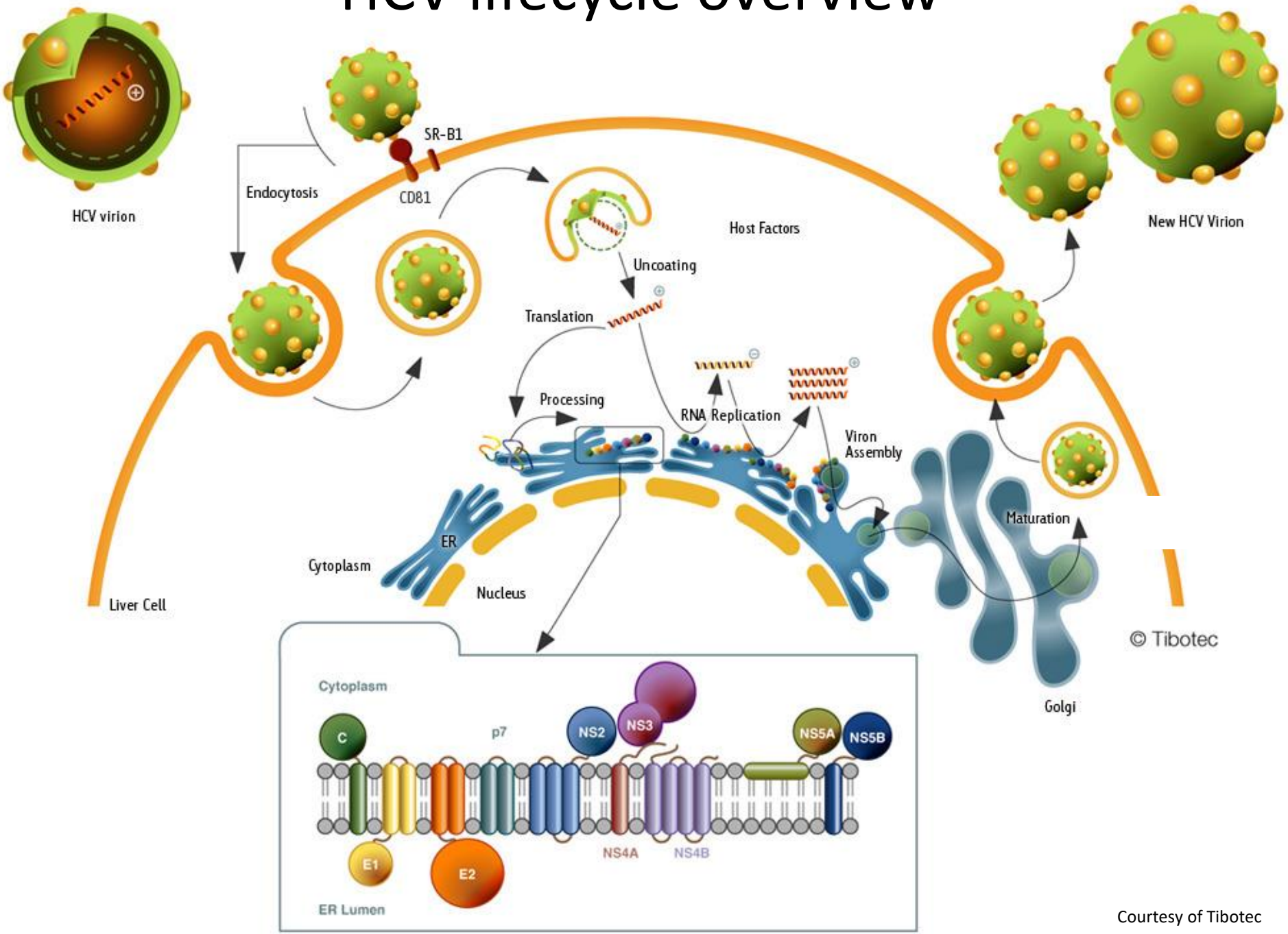
Gambia (West Africa):
Out of 489 participants screened in 2013 for HBV, **only two persons (0.4%)** had heard about HBV infection and had been tested for HBV in the past

None of the positive individuals were previously tested and knew their status

LEMOINE *et al,* Lancet Global Health 2016

Clinical Presentation

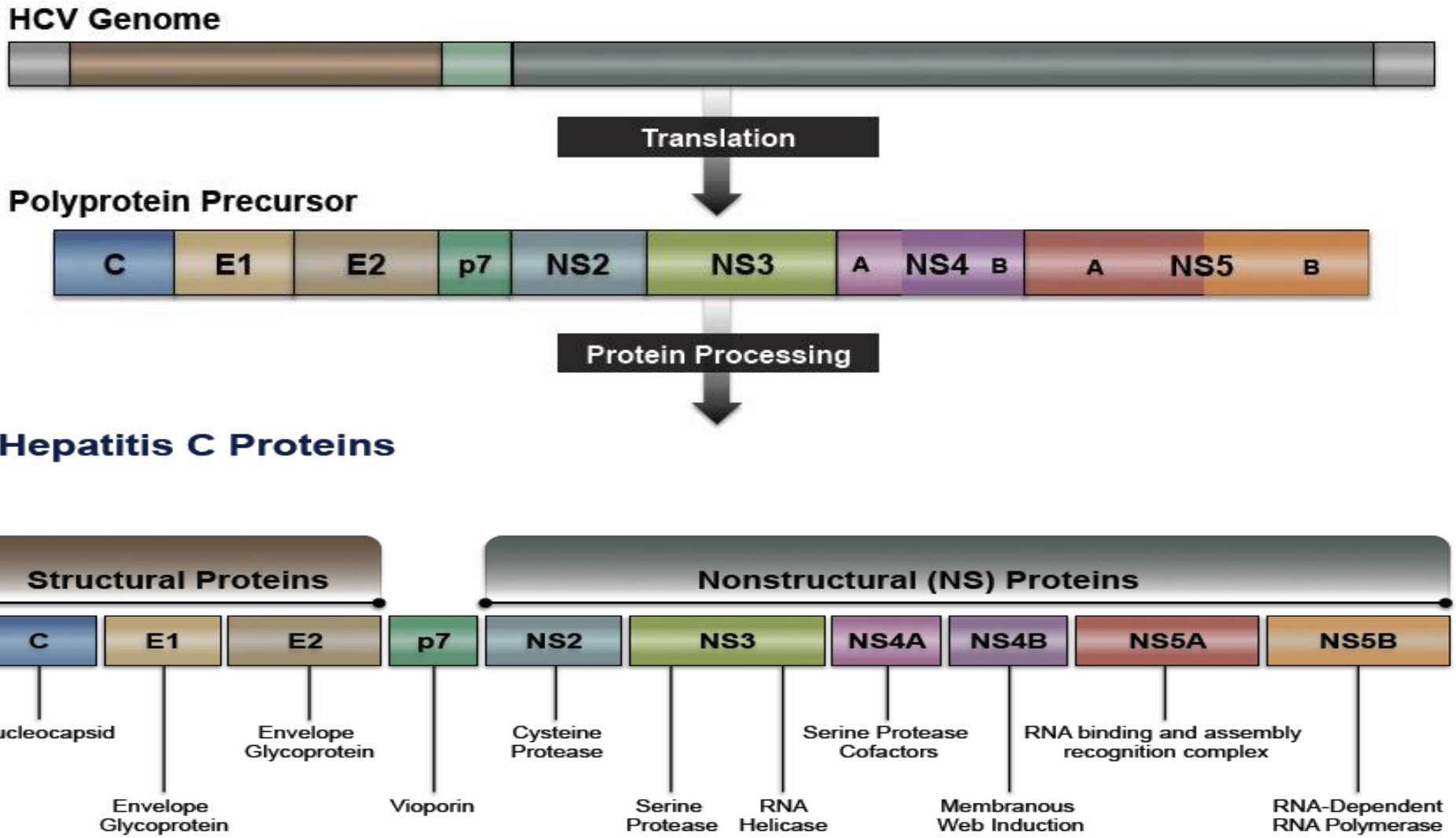
HCV lifecycle overview



Courtesy of Tibotec

Lifecycle : Viral poly-protein

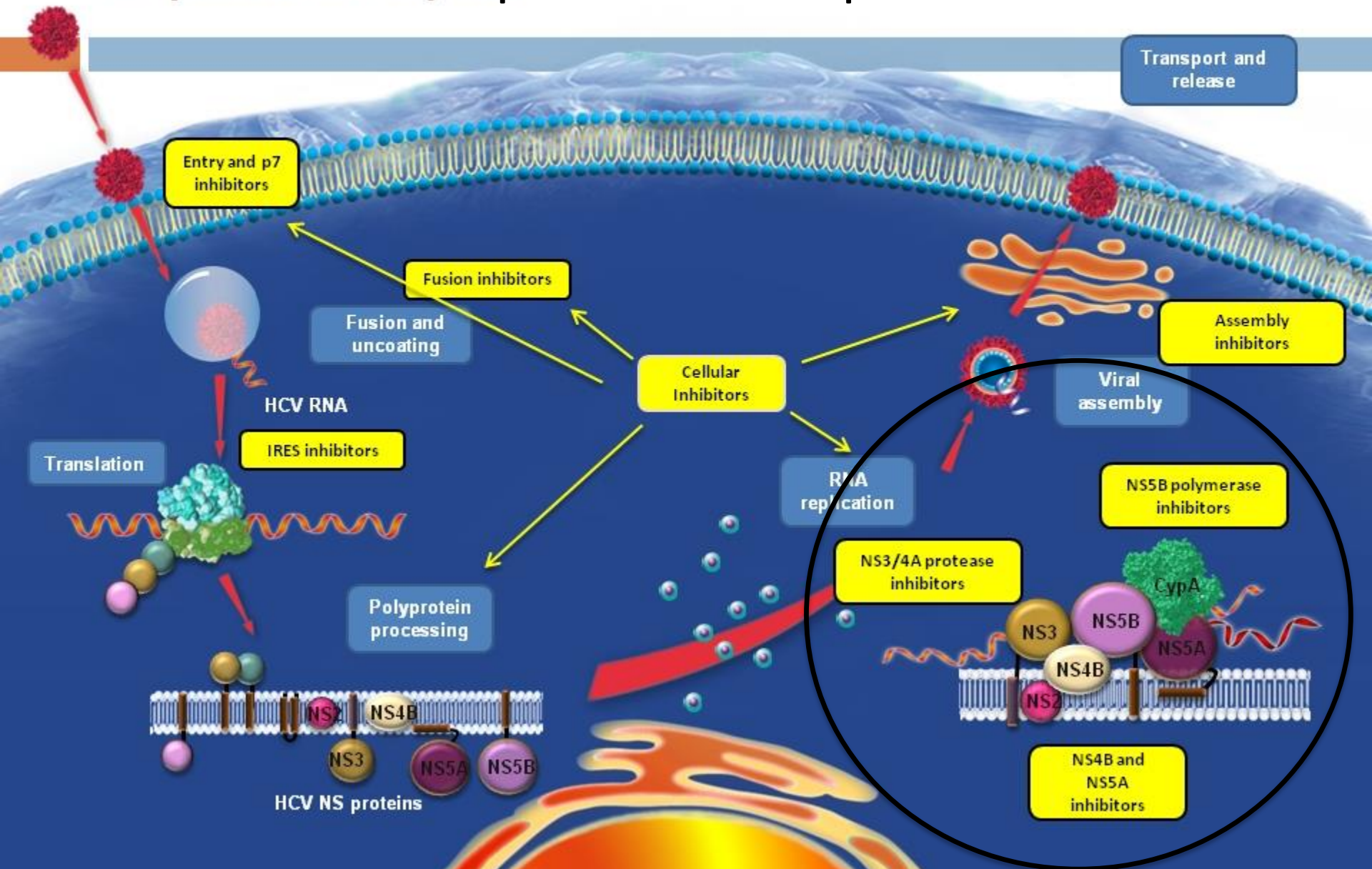
The viral RNA undergoes translation resulting in a single viral polyprotein



Viral enzymes

- **NS3/4A protease** assists in the downstream cleavage of viral peptides. It also has ability to cleave and inactivate host proteins that aid in antiviral activity (IRF-3)
- **NS5B RNA –dependent RNA polymerase** (RdRp) facilitate viral replication by copying a positive strand RNA into negative strand intermediate (a template for more viral RNA genomes)
- **NS5B RdRp** lacks proof reading capabilities and therefore mutations of HCV genome occurs at a rate of 10^{-4} per nucleotide
- **NS5A "replicase":** assists in viral replication and viral assembly.

Potential sites for therapeutic targets for hepatitis C therapies



Clinical features

Acute infection

- Acute infection is typically anicteric
- Less than 25% are clinically apparent
- Symptoms appear 2-6 weeks after exposure and may last 2-12 weeks
- HCV Ab may take upto 12 weeks to appear, a dx after suspected exposure is with PCR

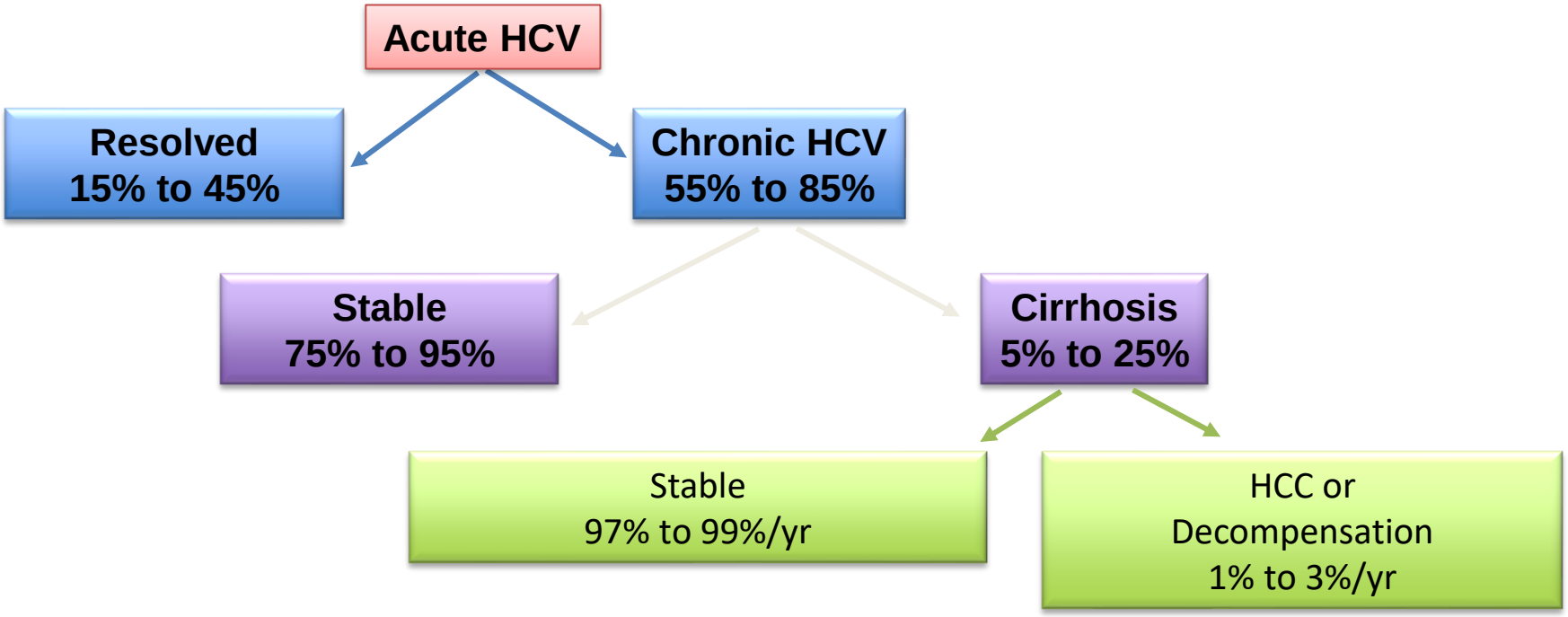
Acute infection

- Clearance is associated with favourable IFNL3(IL28B) genetic polymorphism, being female, jaundice, markedly elevated ALT and rapid decline of HCV RNA concentration
- Detectable RNA after 12 weeks implies chronic infection
- Treatment is associated with 100% SVR rates

Chronic infection

- Majority of patients exposed to HCV will progress to chronic infection
- 10-20% will develop liver related complications namely, liver cirrhosis, PHT and related complications and Hepatocellular carcinoma
- Factors associated with accelerated rates of progression include, older age at acquisition, male gender,obesity, alcohol consumption and HIV/HBV co-infection

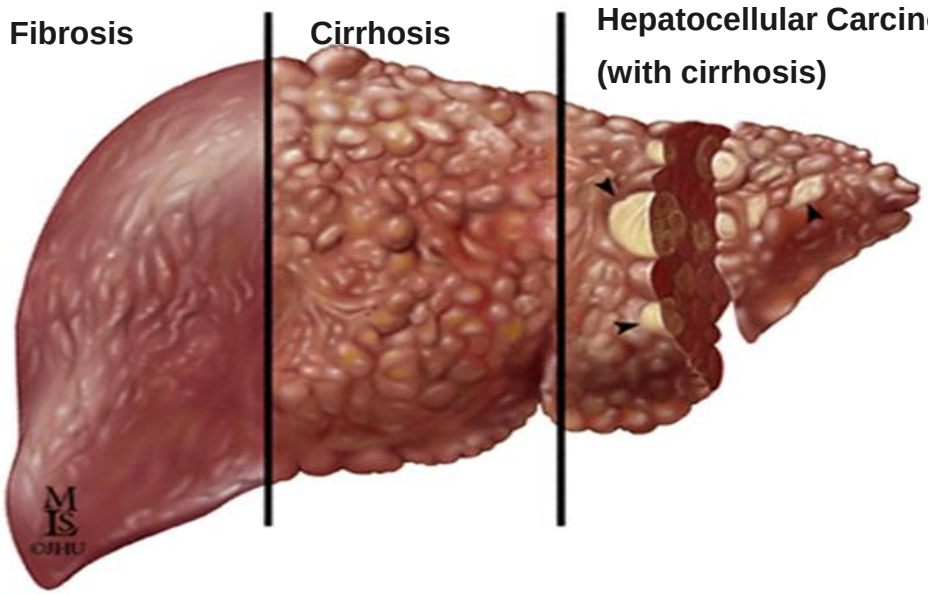
Natural History of HCV Infection



- Infection with HCV can also cause extrahepatic diseases including mixed cryoglobulinemia

Thomas DL, et al. Clin Liver Dis. 2005;9:383-398 Strader DB, et al. Eur J Gastroenterol Hepatol. 1996;8:324-328. Seeff LB, et al. Hepatology. 2002;36(suppl):S1-S2. Seeff LB, et al. Hepatology. 2002;36(suppl):S35-S46. Liang TJ, et al. Ann Intern Med. 2000;132:296-305. Fattovich G, et al. Gastroenterology. 1997;112:463-472.

Natural history of chronic HCV infection



Decompensated cirrhosis:

1. Ascites

2. Bleeding varices

3. Hepatic encephalopathy

4. Jaundice

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1. Highleyman L. Hepatitis C Support Project. http://www.hcvadvocate.org/hepatitis/factsheets_pdf/Fibrosis.pdf.

2. Bataller R et al. *J Clin Invest*. 2005;115:209-218;

3. Medline Plus. http://www.nlm.nih.gov/medlineplus/enxy.article/000280.htm.

4. Centers for Disease Control and Prevention. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm..

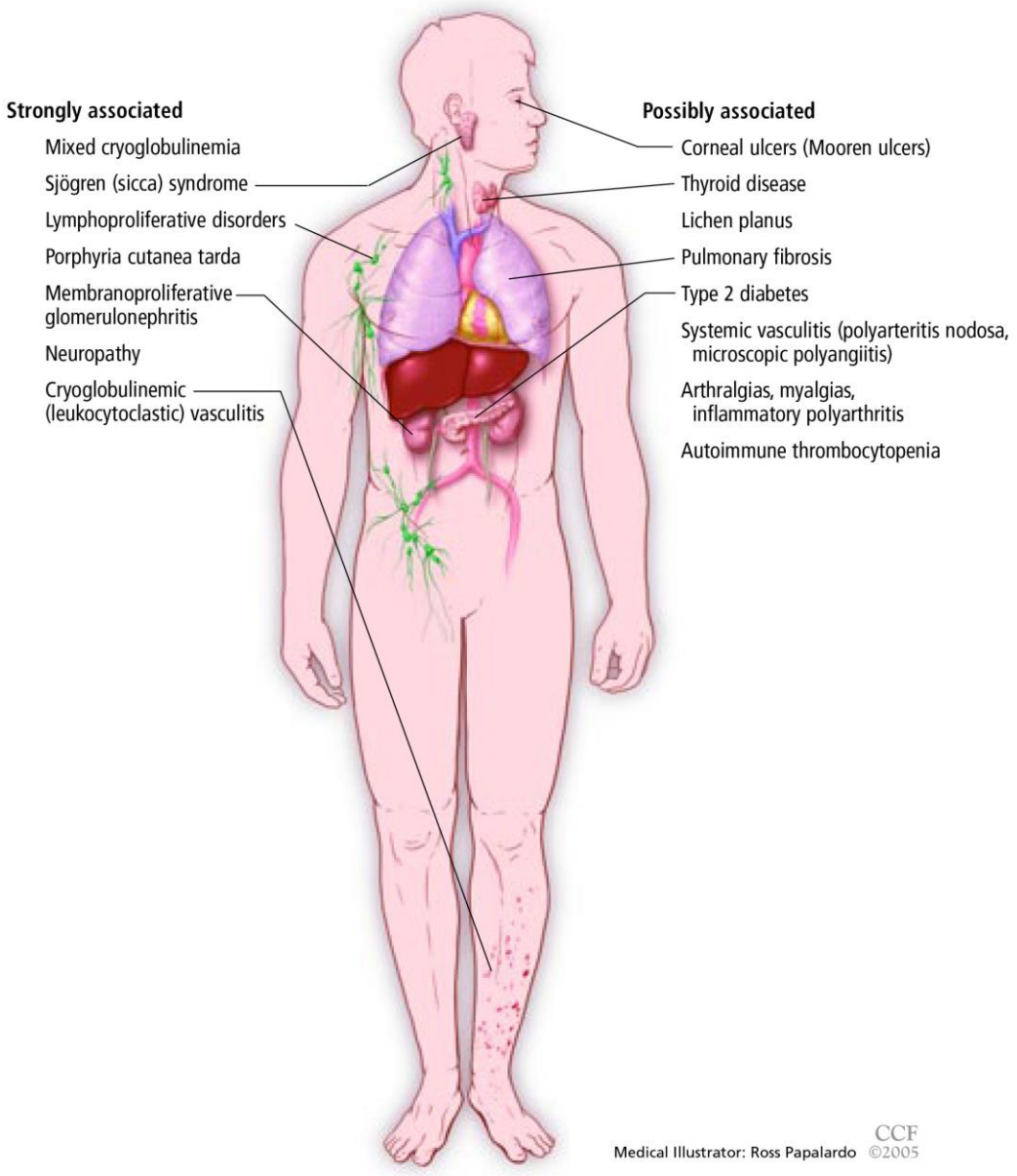
Other

Most common:

1. Mixed cryoglobulinemia vasculitis
2. Lymphoproliferative malignancies
3. RA - like polyarthritis
4. Diabetes mellitus
5. Antibody production (ANA, RF etc)

Associated

- Depression
- Cognitive impairment
- Fatigue



Conclusion

- HCV infection is a growing international concern with significant morbidity and mortality
- Globally, PWID and MSM constitute majority of those infected with HCV
- In Africa, traditional practices and iatrogenic transmission (unsafe blood transfusion and injection practices) are the main reasons for high prevalence
- However, alarming rates reported on small studies on high risks groups suggests that clinicians should be more vigilant on screening and educating those at high risk