Can We Cure HBV and HCV?

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Outline

- Natural history and current treatment of chronic HBV/HCV
- Impact of an HBV/HCV cure
- Barriers to an HBV cure
- Definitions and goals for an HBV/HCV cure
- Strategies for HBV/HCV cure

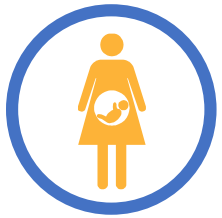
Eliminate viral hepatitis as a major public health threat by 2030

Prevention Measures

Improve blood safety and infection control

Vaccination

Extend harm reduction measures



Prevent MTCT

Diagnosis and Treatment

Expand testing and treatment for those already infected

Prevention targets

- **90%** of infants have HBV birth dose vaccination
- **100%** of blood donations screened
- **90%** have access to safe injections

Testing targets

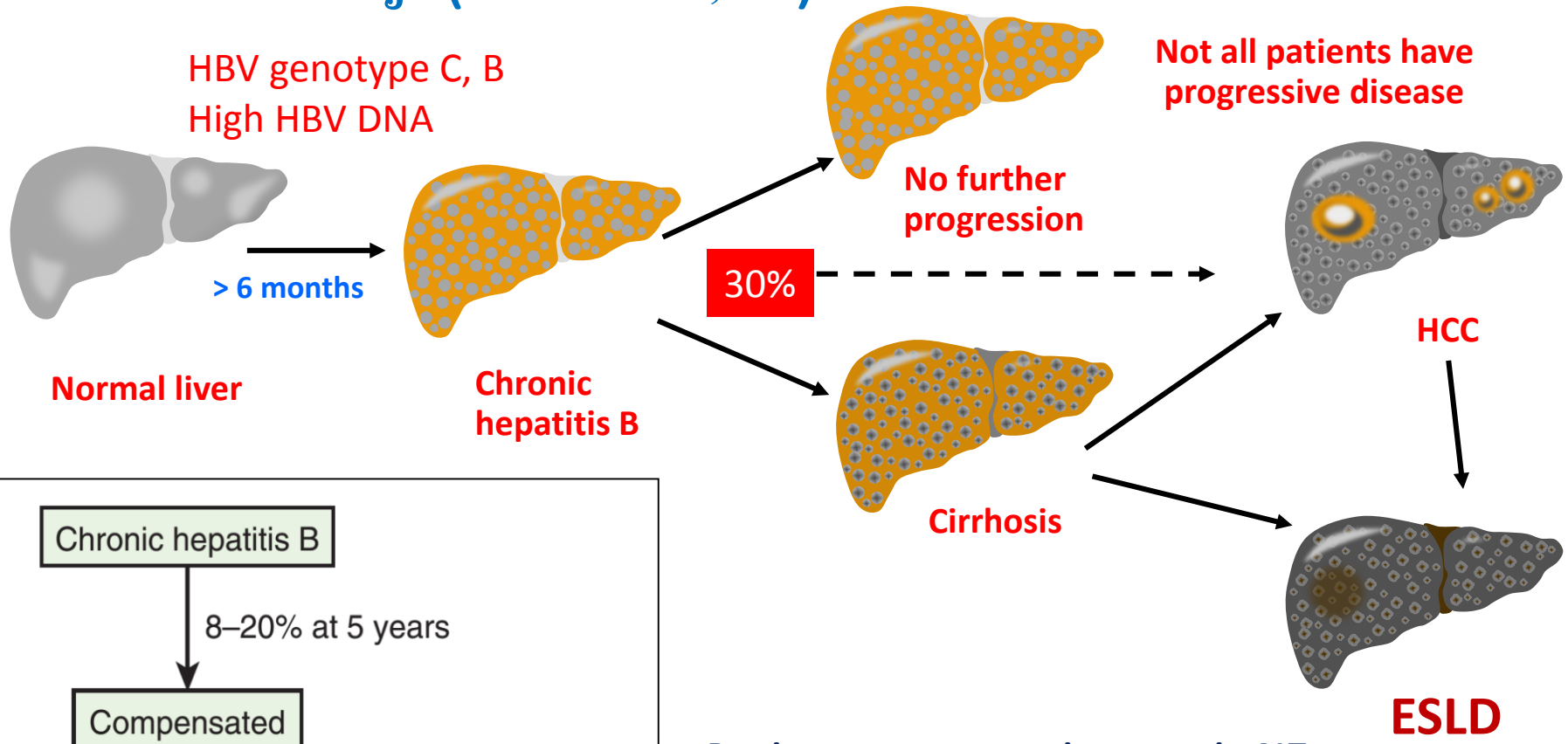
- **90%** of people aware of infection

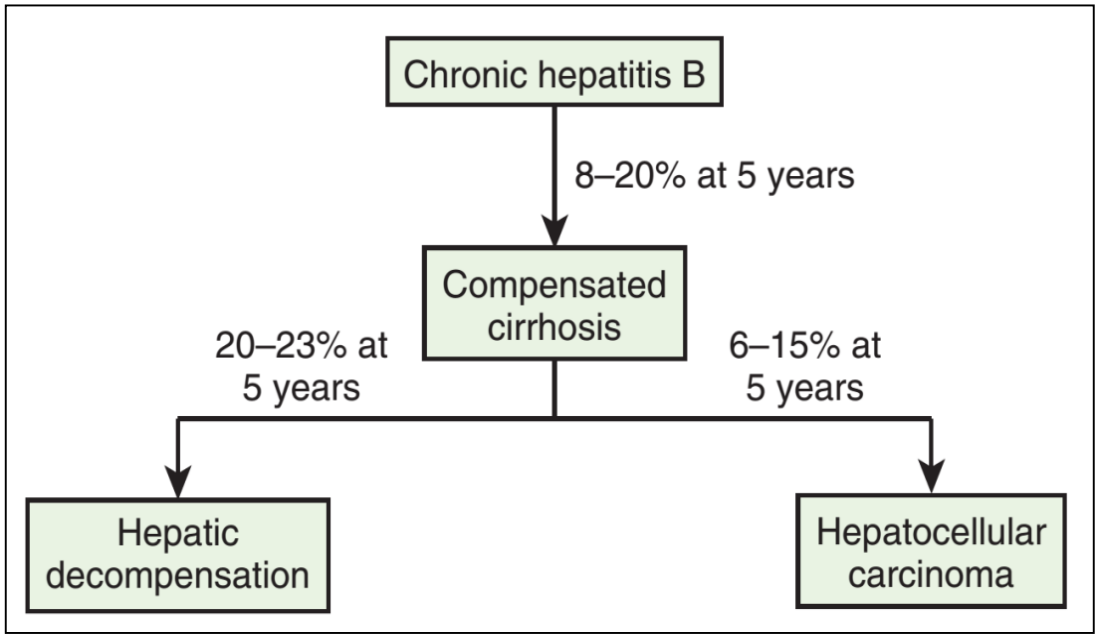
Treatment targets

- **80%** of eligible people treated

WHO. Global health sector strategy on viral hepatitis, 2016-2021.

มะเร็งตับและมะเร็งท่อน้ำดีสูงเป็นอันดับ 1 ในเพศชาย (33.4 ต่อ 100,000) อันดับ 3ในเพศหญิง (12.3 ต่อ 100,000)

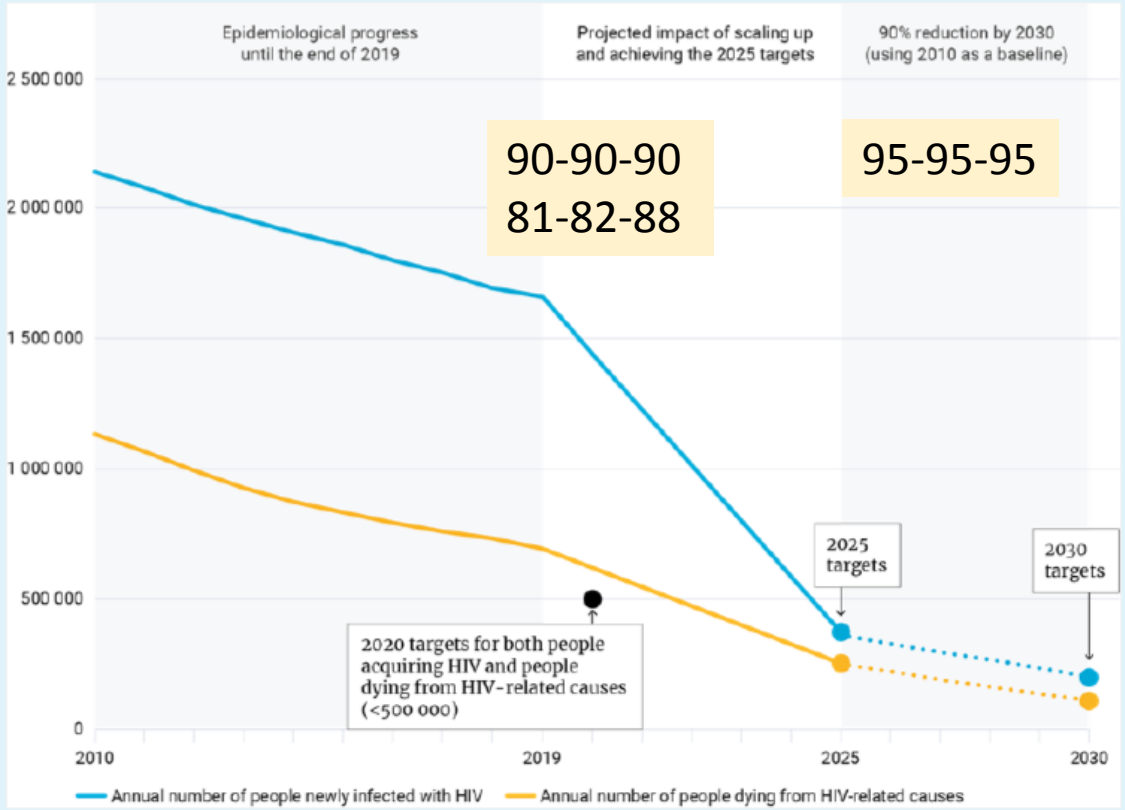




Persistent or recurrent increases in ALT or liver inflammation with unsuccessful immune clearance increase the risk of liver cirrhosis and HCC

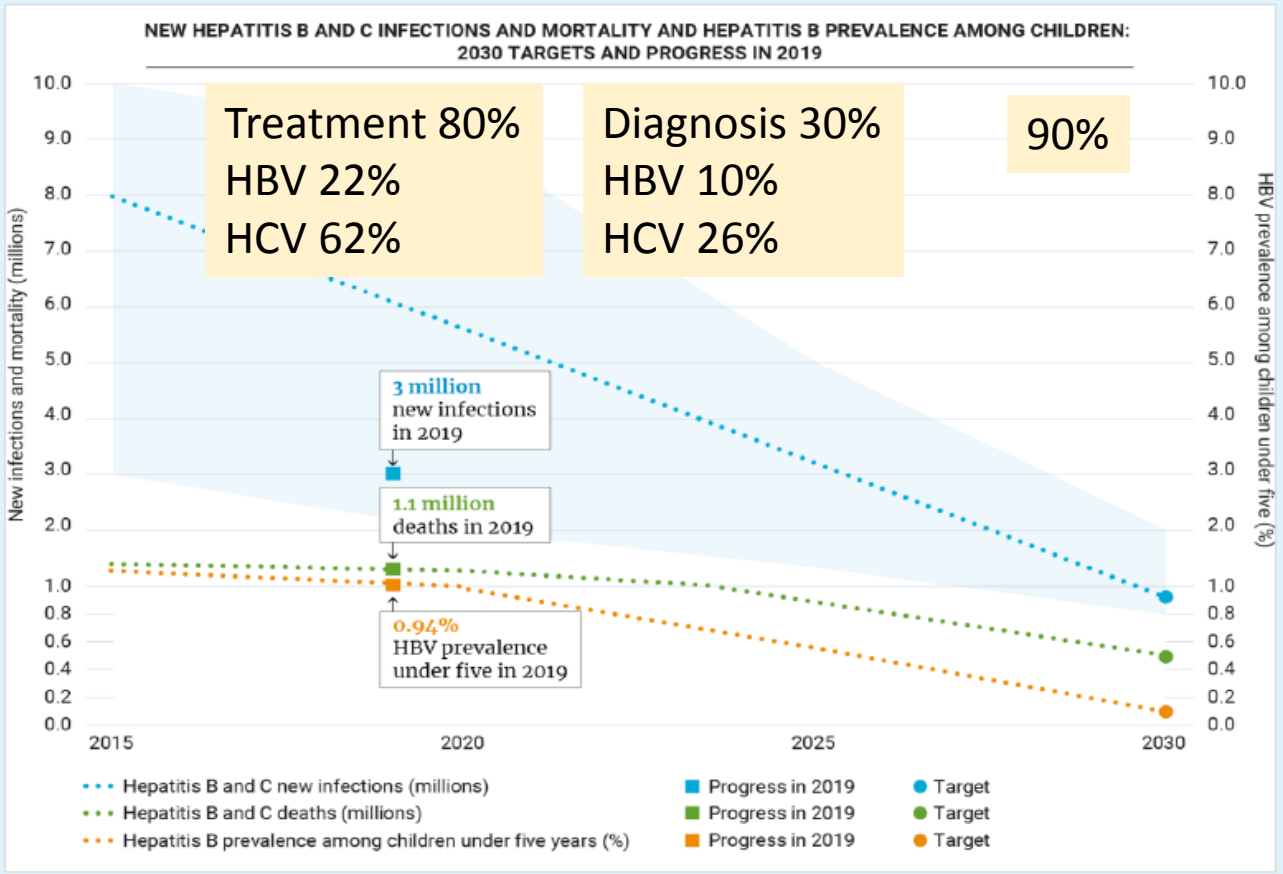
EASL. J Hepatol. 2012;57:167-185.

Global trends in people acquiring HIV and people dying from HIV-related causes, 1990–2019 and projections to 2030



Source: Avenir Health using 2025 targets and UNAIDS/WHO epidemiological estimates, 2020.

New hepatitis B and C infections and mortality, hepatitis B prevalence among children and estimated cancer deaths attributable to hepatitis B



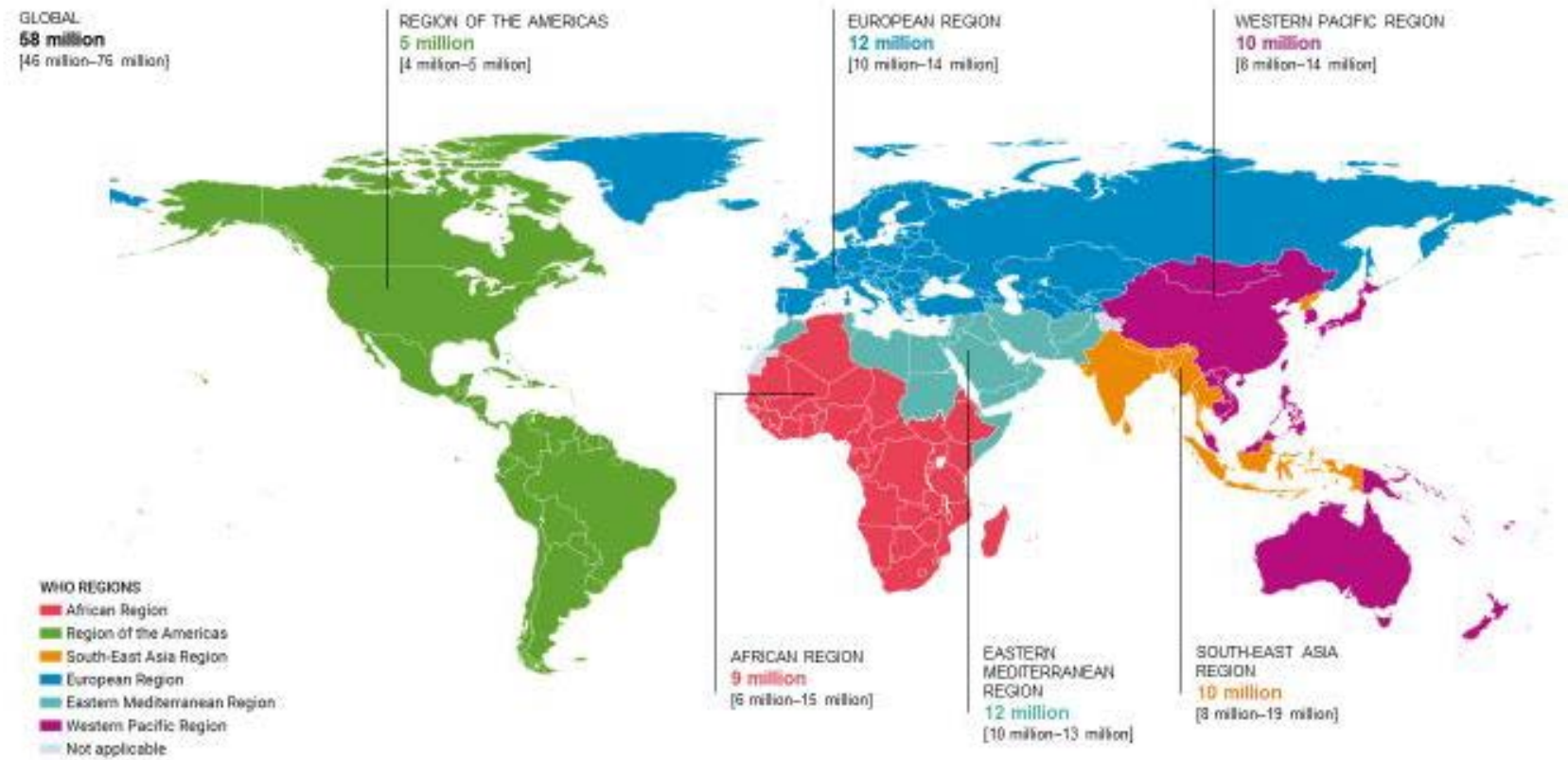
Global HBC 296 million, Southeast Asia 60 Million

Burden of chronic hepatitis B infection (HBsAg positivity) by WHO Region, 2019

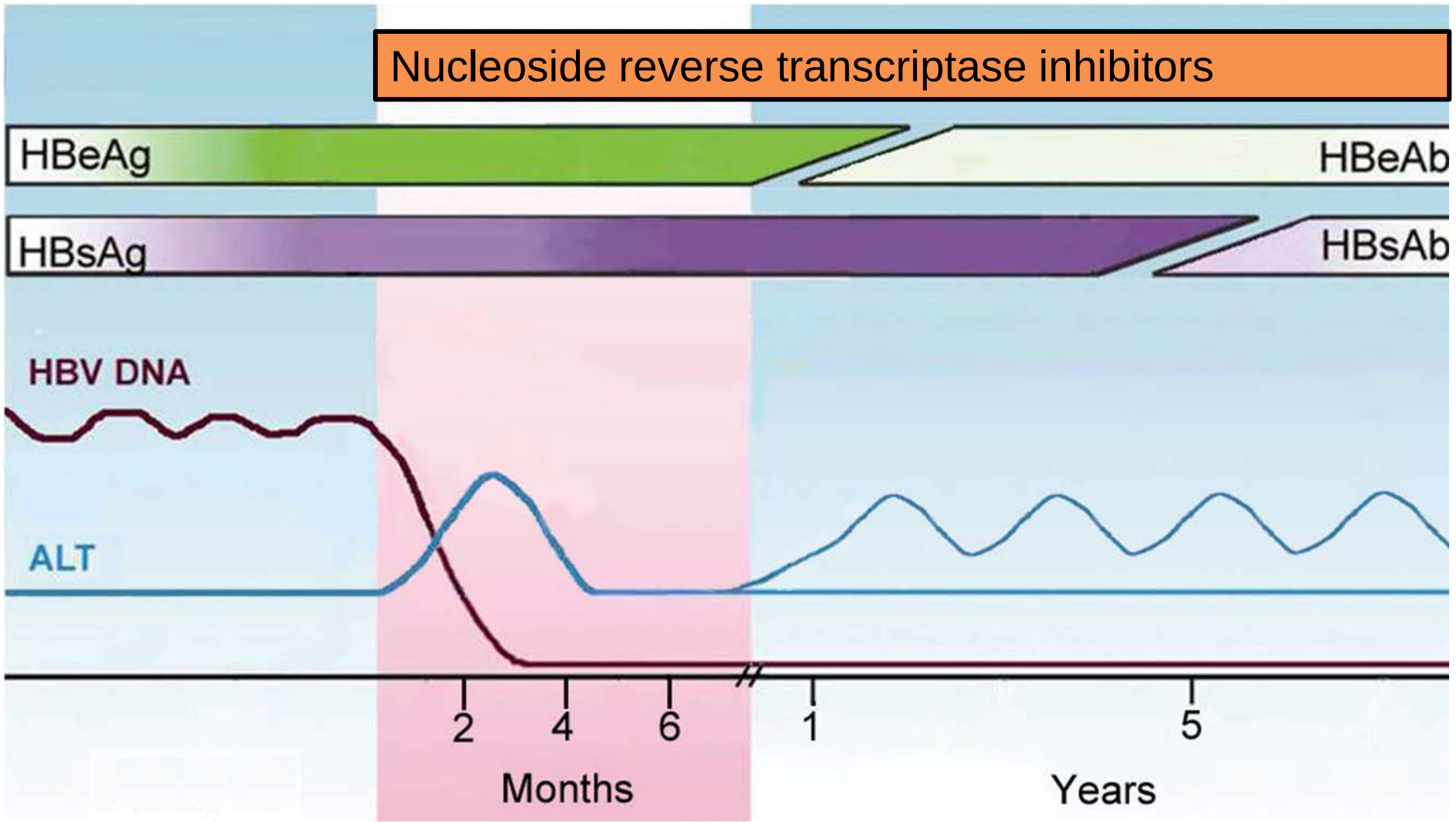
World Health Organization

Global HCV 58 million, Southeast Asia 10 Million

Burden of chronic hepatitis C viraemic infection by WHO Region, 2019



Natural history of chronic HBV infection post treatment



	HBV mono	HBV/HIV
HBeAb	5-10%	40-50%
HBsAb	<1%	10-15%

Heathcote et al *Gastroenterology* 2011; Marcellin et al., *Gastroenterology* 2016

Recommended therapy for Chronic Hepatitis B

Guidelines	Region	Recommendations
HBV monoinfection		
APASL[2016]	Asia	Entecavir, or Tenofovir
EASL [2017]	Europe	Entecavir, Tenofovir, or TAF
AASLD[2018]	US	Entecavir, Tenofovir, or TAF
HIV/ HBV co-infection		
DHHS/EACS	**All**	**TAF or TDF+ FTC or lamivudine**

TDF : tenofovir disoproxil fumarate; TAF: tenofovoir alafenamide, FTC: emtricitabine

HIV/HBV: treatment indefinite

Stop NUCs after long-term suppression if

- HBeAg pos CHB: ≥ 2 years post-HBeAg seroconversion *or*
- HBeAg neg CHB:indefinite; or ≥ 3 years normal ALT and DNA <LOD
- (mild disease)

Sarin SK, et al. Hepatol Int 2016; EASL. J Hepatol 2017; Terrault NA, et al. Hepatology 2018

ประเทศไทย : lamivudine

TAF: chronic hepatitis B infection ในผู้ใหญ่และเด็กอายุมากกว่าหรือเท่ากับ 12 ปีและมีน้ำหนัก≥ 35 kg

- Efficacy and safety of TAF have not been established for CHB in patients with decompensated cirrhosis, pregnant women, or children
  - Recommendations for these populations are subsequently limited

Patient Subgroup	AASLD Guidance
Decompensated cirrhosis	▪ ETV or TDF recommended ▪ If renal impairment and/or bone disease, ETV or TAF should be considered
Pregnancy	▪ Insufficient data to recommend in pregnancy
Children	▪ Insufficient data to recommend in children*

*Compared with TDF, which is approved for children 12 yrs of age and older, and ETV, which is approved for children 2 yrs of age and older.

- At risk for bone/renal disease: consider ETV or TAF
- decompensated cirrhosis: avoid TAF

Terrault. Hepatology. 2018;67:1560.

But ……lifelong treatment is far from ideal

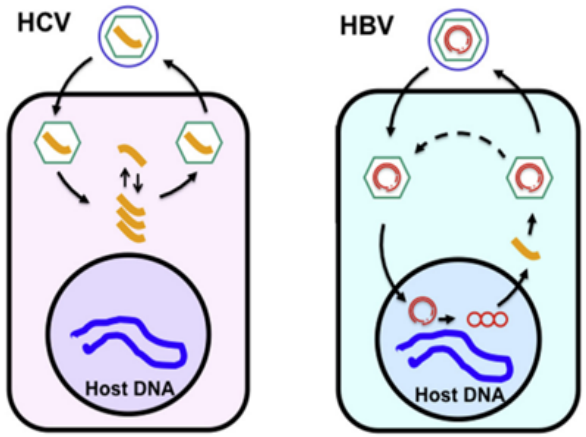
- Only 25-30% of HBsAg patients are **eligible for treatment**
- Reduce but not remove risk of liver cancer
  - Nucleos(t)ide therapy does not eliminate the risk of HCC

    No direct effect of NA on cccDNA
- **Life long treatment** is required
  - Cost
  - Risk of non adherence
  - Cumulative toxicity
  - Risk of resistance
- Stopping antivirals leads to viral rebound and risk of **transmission and severe flare**
- **Low rate of HBsAg loss/seroconversion (functional cure)**

Lin CL, et al. Aliment Pharmacol Ther 2016; 44: 213-22

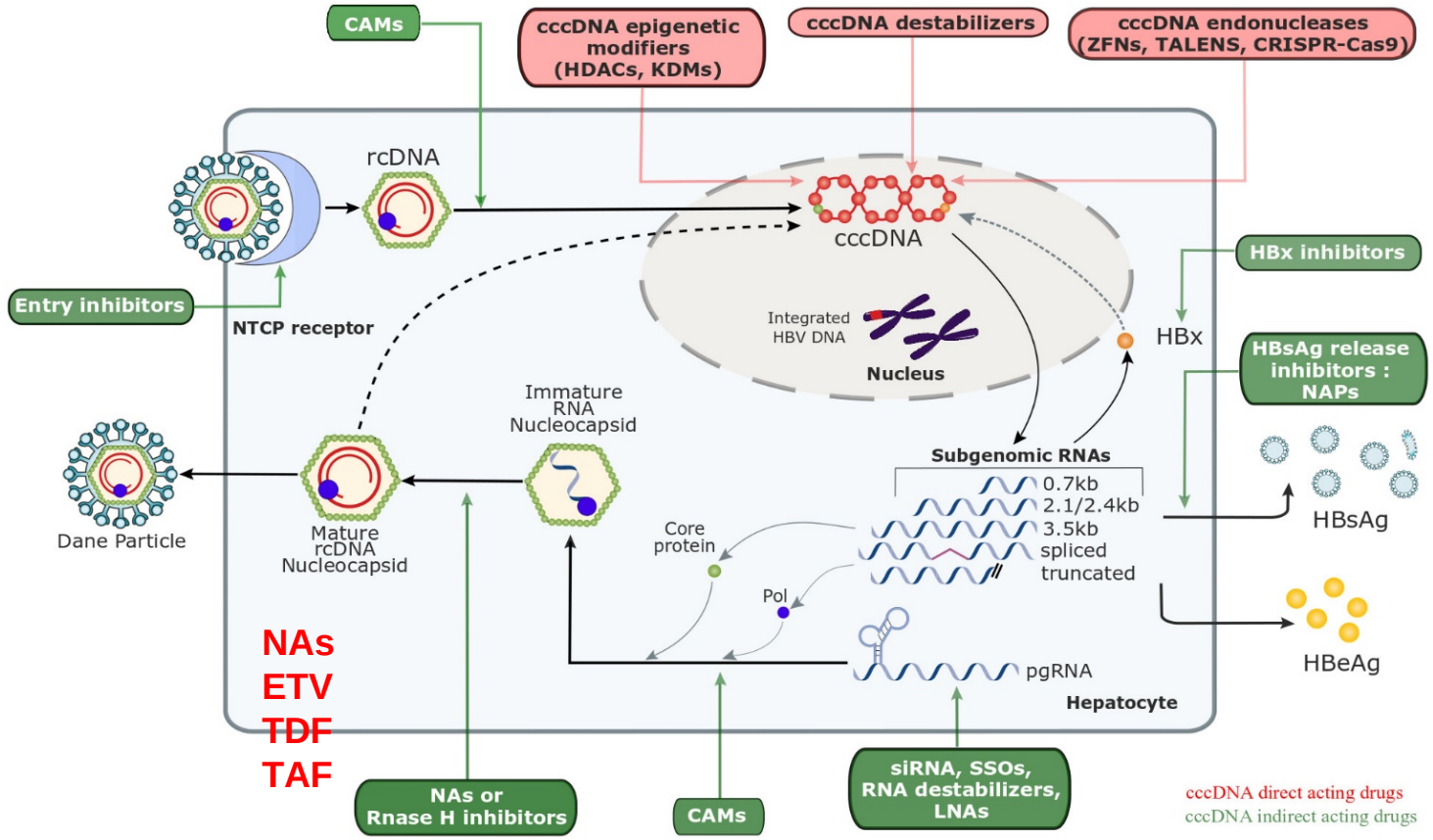
After HCV cure, HBV cure?

cccDNA is the major barrier to a cure for HBV



Barriers to HBV eradication

- **Covalently closed circular DNA (cccDNA)**
- **HBV DNA Integration**
- **Impaired host immune response**

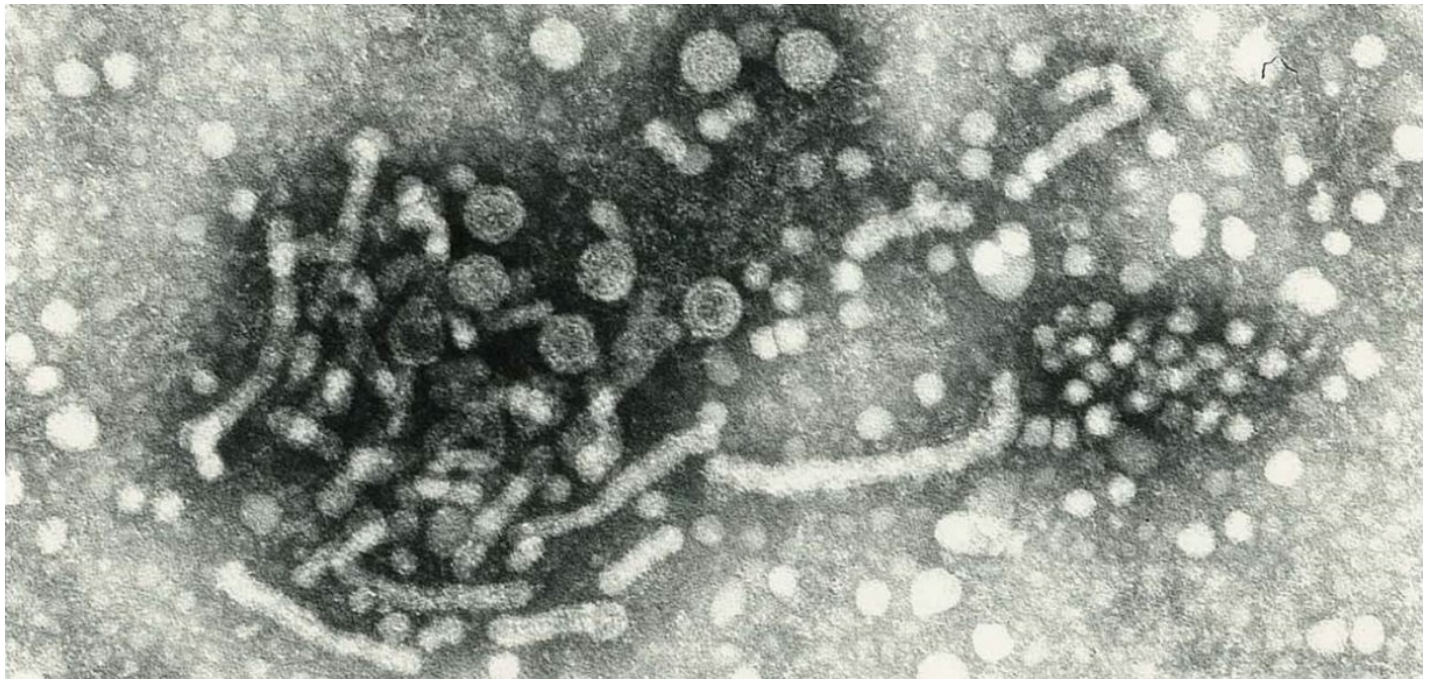


การที่ HBV สามารถรวมตัวเป็น cccDNA และintegrate เข้าไปใน host genome ทำให้โอกาสกำจัด HBV ให้หายไปทำได้ยาก

rcDNA=relaxed circular DNA; cccDNA=covalently closed circular DNA; pgRNA= pregenomic RNA;NRTI = nucleoside reverse transcriptase inhibitor

Zeisel MB, et al. Gut 2015; 64: 1314-26

HBsAg persists on treatment and inhibits immune function

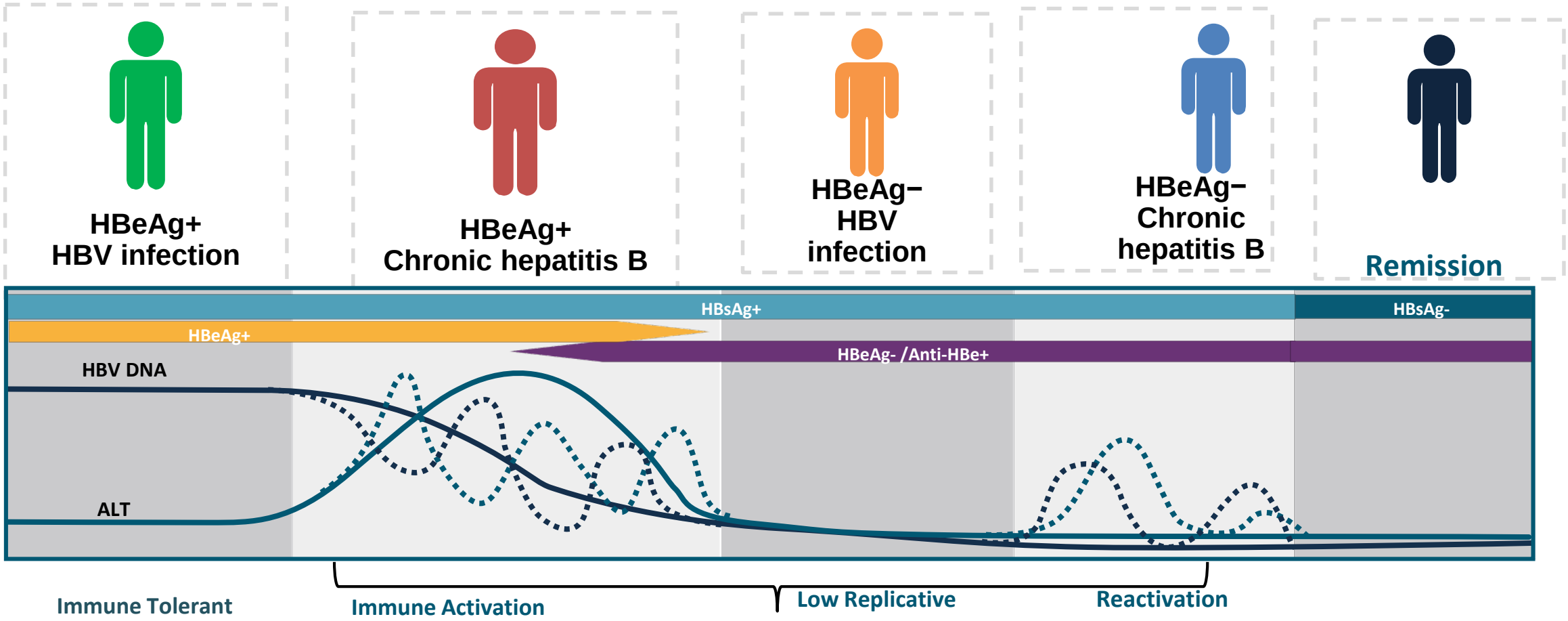


- HBsAg secreted in vast excess over virions (3-4 orders of magnitude) with limited change post NRTI
- HBsAg can suppress innate and adaptive immunity through inhibition of TLR2 and 9, interferon-alpha and myeloid dendritic cells

Wang, S J Immunol 2013.; Xu, Y. Mol Immunol 2009.; Op den Brouw, Immunology 2009.

คำนิยาม HBV cure

- A finite (1-2 year) therapy that will achieve **HBsAg loss**
- Effective across **ALL** phases of chronic HBV infection



Currently treated with antivirals

1. Tong. Dig Dis Sci. 2011;56:3143. 2. Yim. Hepatology. 2006;43:S173. 3. EASL. J Hepatol. 2017;67:370.

คำนิยาม HBV cure

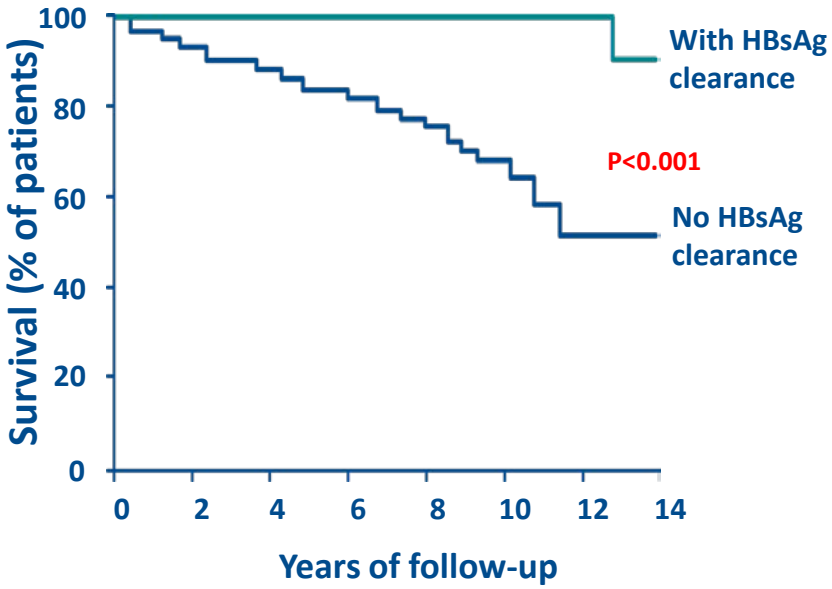
	Functional cure (remission)	Cure	Sterilising cure
HBsAg and HBV DNA	negative	negative	negative
Liver disease	no	no	no
cccDNA	positive	negative	negative
Integrated HBV DNA	positive	positive	negative
Risk of reactivation	yes	yes	no
risk of HCC and ongoing surveillance	yes	yes	no

cccDNA: covalently closed circular DNA

HBV Functional Cure

In practical, the end point of treatment is HBsAg clearance/seroconversion
—Functional (clinical) cure

- HBsAg clearance improves clinical outcomes (including decompensated cirrhosis/HCC) and survival



HBV mono

	Peg-IFN	Entecavir	Tenofovir
HBeAg positive			
HBsAg loss	5% (6 mo post-Tx) 11% (3 yrs post-Tx)	3% (1 yr) 5% (2 yrs)	3% (1 yr) 8% (3 yrs)
HBeAg negative			
HBsAg loss	4% (6 mos post-Tx) 6% (3 yrs post-Tx)	1% (1 yr)	0% (1 yr)

HIV/HBV

1. Thailand (N=92), HBsAg loss **15.3%** (5 yrs), HBeAg loss 44%
2. France (N=308) HBsAg loss 4.6% (3 yrs)
3. Zambia (N=284) HBsAg loss 10.2% (2 yrs)
4. Thailand (N=47), HBsAg loss 13%, HBeAg loss 48% (2 yrs)
5. Dutch cohort (N=104) HBeAg+ :HBsAg loss 8%, HBeAg-: HNsAg loss 8% (6 yrs)

Fattovich G et al. Am J Gastroenterol 1998; Zoulim F, et al. Current Opinion in Virology 2016, 18:109–116

1 Audsley J, A Avihingsanon, Lewin S JAIDS 2020. 2 Boyd A J cin Virol 2017
3 Chihota BV J Infect Dis 2020, 4 Matthews G Plos One 2013. Zoutendijk J Infct Dis 2012

Benefits after HBV Functional Cure

High liver-related mortality in HIV/HBV (> HBV 19times, > HIV mono(8 times)

HBV CURE

Public health benefit

- *Lower transmission rate*

Individual health benefit

- *Improve clinical benefit*

ART related hepatotoxicity

Overt infection

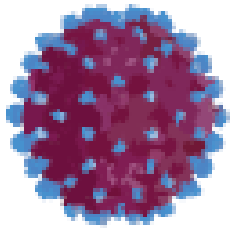
- *Cirrhosis*
- *Decompensation*
- *HCC development*
- *Transplantation*

Occult infection

- *Risk of HBV reactivation during DAA therapy for HCV or immune suppression*
- *HCC development*

Singh KP ,AIDS 2017

Clinical strategies for an HBV cure

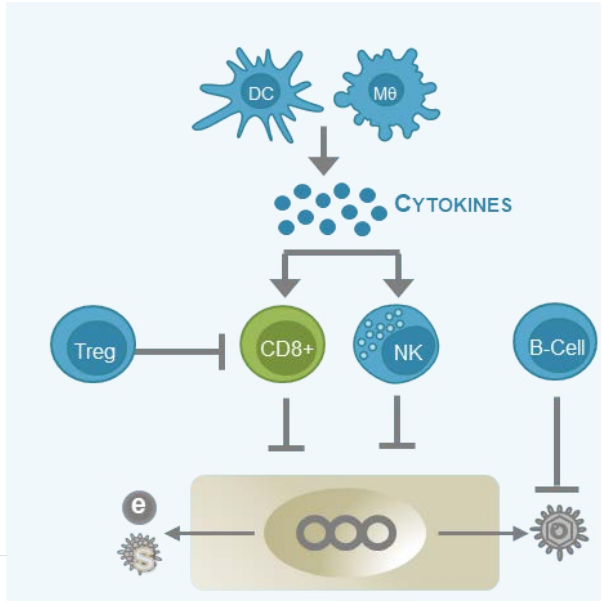


Reduce HBV

HBV DNA

HBsAg

cccDNA



PD-1

CD8+

enhance immune response

Weak immune response = **High viral burden**

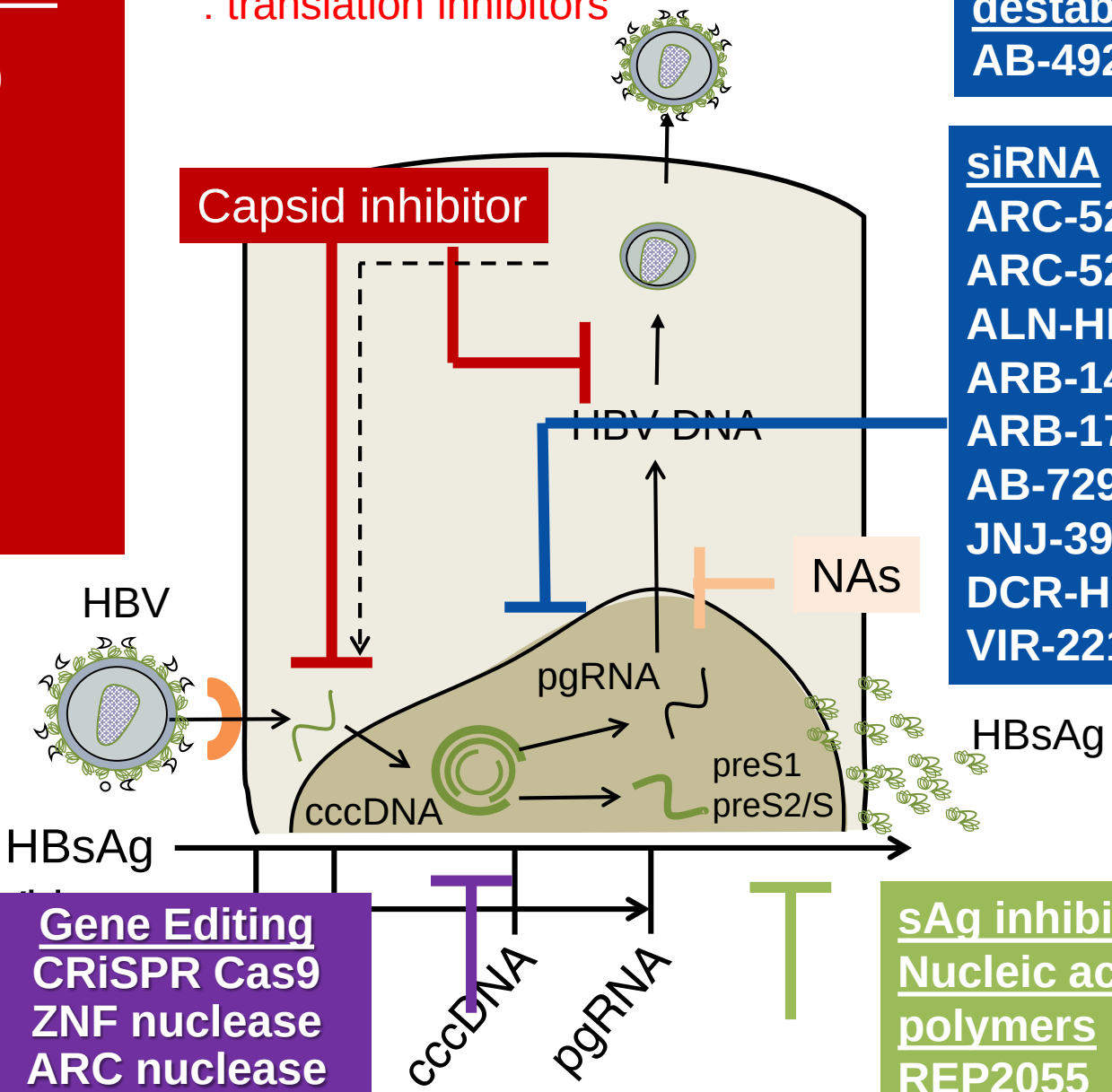
cccDNA Persistence

PD-1: programmed cell death-1

Capsid allosteric modulator

NVR 3-778
JNJ-379
JNJ-440
RO7049389
ABI-H0731
ABI-H2158
ABI-H3733
AT-130
BAY41-4109
HAP-12
GLS4JHS
HAP_R01
SBA_R01
AB-423
AB-506
RG-7907
EP-027367
EDP-514
ALG-001024
GLP-26

siRNA : Blocking HBsAg synthesis
: translation inhibitors



Entry inhibitor
Myrcludex B
Antibodies

Gene Editing
CRiSPR Cas9
ZNF nuclease
ARC nuclease
TALENS

sAg inhibitors:
Nucleic acid polymers
REP2055
REP2139

RNA destabilizers
AB-492

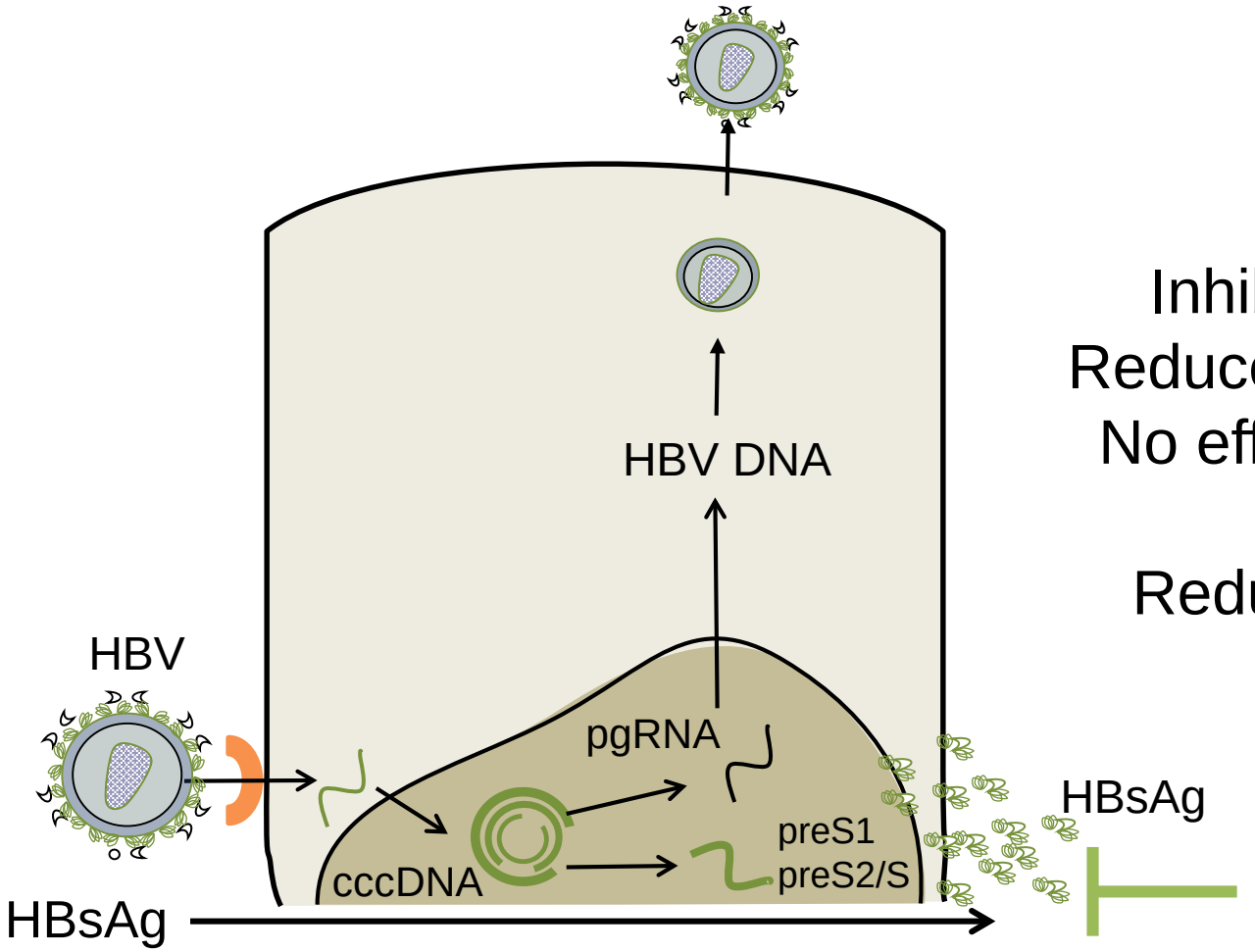
siRNA
ARC-520
ARC-521
ALN-HBV
ARB-1467
ARB-1740
AB-729
JNJ-3989
DCR-HBVS
VIR-2218

Transcription inhibitors
Demethylase inhibitor
PPAD5/7 inhibitor
HB X-inhibitors
FXR Agonists

ASO/LNA
RO70629311
GSK3228836
GSK3389404
ISIS 5053583

NAs
1.ETV
2.TDF
3.TAF

Blocking HBsAg synthesis: blocking subviral particles

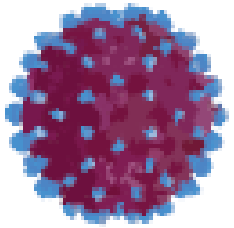


Inhibit HBsAg release
Reduce intracellular HBsAg
No effect on DNA/pgRNA

Reduce HBsAg in 41%

sAg inhibitors:
Nucleic acid polymers
REP2055
REP2139

Blanchet et al., Antiviral Res 2019; 164: 87-105; Vaillant A, et al. EASL 2019, Vienna, Austria. #FRI-210

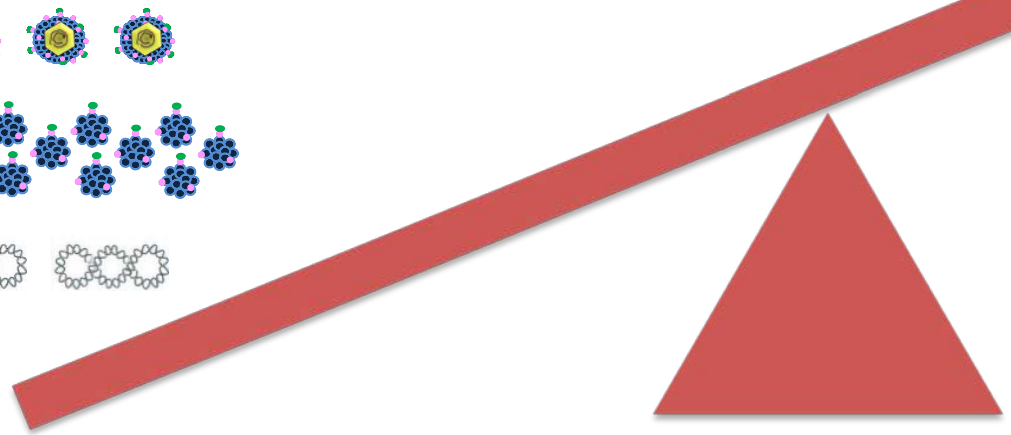


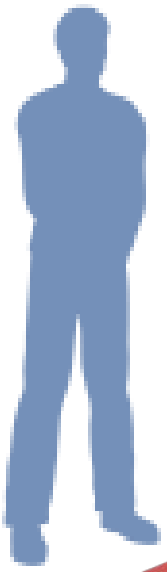
Reduce HBV

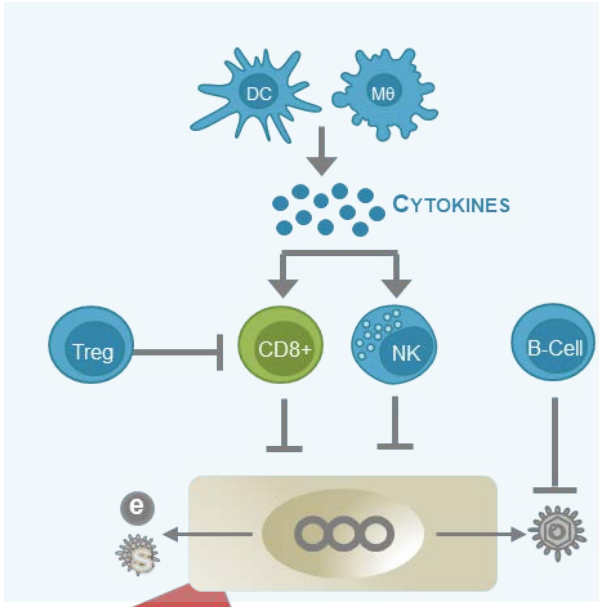
HBV DNA

HBsAg

cccDNA



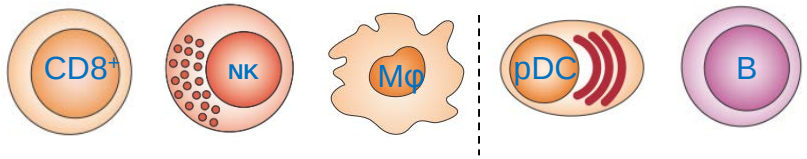




enhance immune response

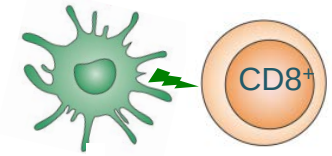
Ways to activate Antiviral Immunity against HBV

1. Stimulate Antiviral Effector Cells



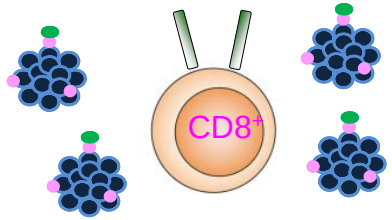
- TLR-7, TLR-8,
- CLRs, NLRs
- RIG-I (Inarigivir)

2. Generate New T cells



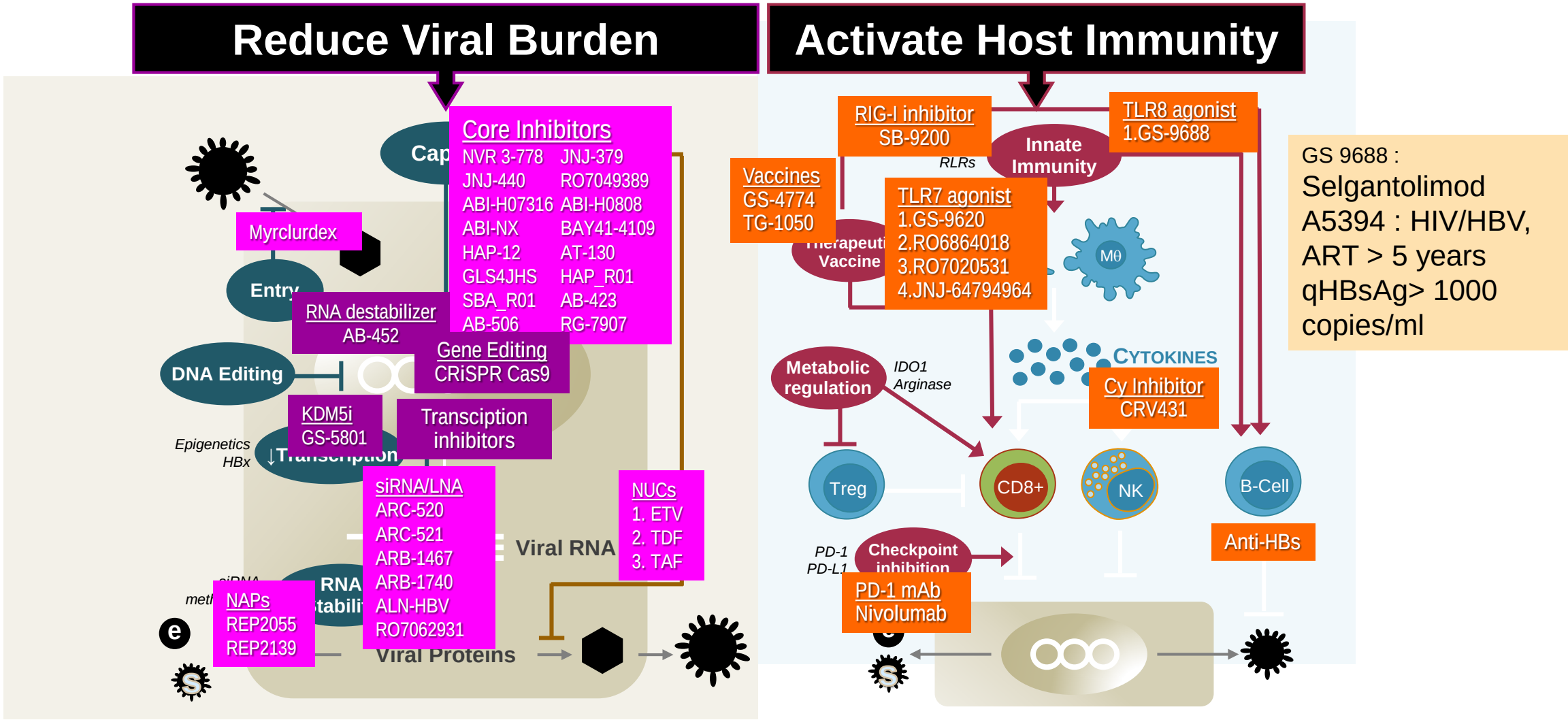
- Therapeutic vaccines

3. "Rescue" Exhausted T cells



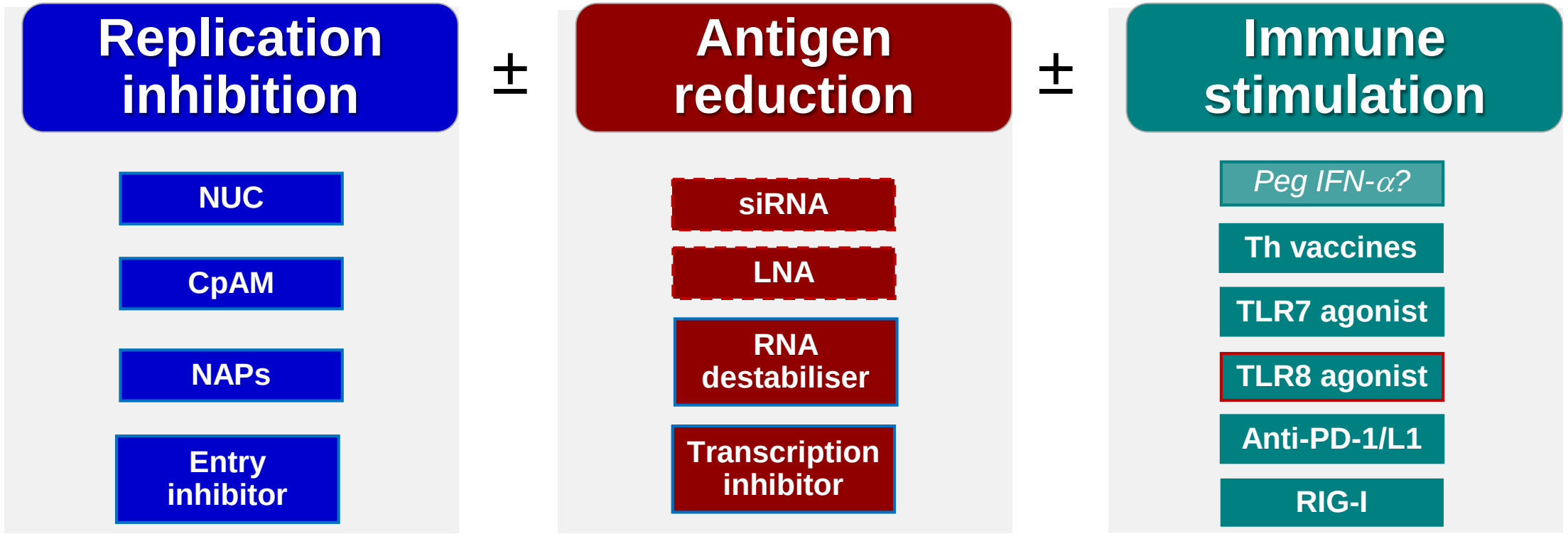
- Reduce viral antigens
- Modulate immune receptors (PD-1)
- Relieve suppression of T cells
- Inhibit T regs

HBV CURE Targets



GS 9688 :
Selgantolimod
A5394 : HIV/HBV,
ART > 5 years
qHBsAg> 1000
copies/ml

Combination interventions for HBV cure: similarly to HIV

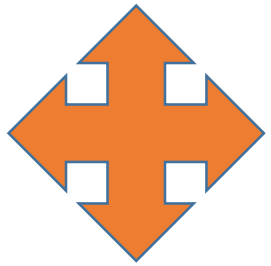


- Combine same class drugs to increase activity & prevent resistance
- May need 2, 3, 4 drug combinations in different patient populations

Summary and implications

- **เพื่อให้ถึงเป้าหมาย ending hepatitis ต้องเพิ่มการตรวจคัดกรอง และlink เข้าถึงการรักษา (HIV model)**
- **การรักษาด้วยยา NA อย่างเดียวไม่สามารถทำให้เกิด HBV cure ได้** เพราะยาไม่ได้มีผลต่อ **cccDNA**
- เพื่อให้เกิด HBV cure ต้องใช้ยาสำหรับ target มากกว่า1ตำแหน่ง และอาจร่วมกับยา/วัคซีน (therapeutic vaccine)ที่ไปมีผลเพิ่ม host immunity
- ปัจจุบันมีโครงการวิจัยสำหรับ HBV cure จำนวนมาก ซึ่งทุกโครงการจะเป็น combination therapy
- HIV/HBV ที่ได้ tenofovir based ART พบ HBeAg seroconversion และ HBsAg seroconversion สูงกว่า HBV อย่างเดียวส่วนหนึ่งเป็นจากภาวะ immune recovery syndrome
- **biomarker for a cure น่าจะมีประโยชน์ เพื่อจะดูว่า cccDNA ลดลงหรือหายไป**

Hepatitis C



HIV

Burden, acute HCV, STI

Disease progression

Drug-drug interaction

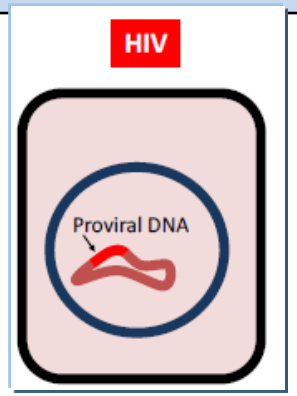
Re-infection

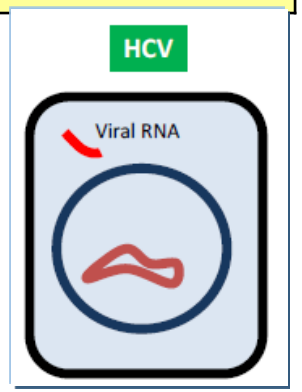
Treatment : HCV = HIV/HCV

HCV มีโอกาสรักษาหายขาด>95% ดังนั้น HIV และคนที่มีความเสี่ยงทุกคนควรจะได้รับการตรวจคัดกรองและเข้าสู่การรักษา

Test & Treat

Virus	HIV	HCV
Genome	RNA	RNA
การกลายพันธุ์	สูงมาก	สูงมาก
ไวรัสตัวใหม่ที่ผลิตได้ต่อวัน	10^{10}	10^{12}
Viral Genetic Archiving	YES	NO
Drug Targets	Multiple	Multiple
โอกาสรักษาหายขาดด้วยยา?	NO (integrated viral DNA)	**YES**
จุดมุ่งหมายของการรักษา	Lifelong suppression	**CURE:** clearance from plasma and liver





58M HCV
34 M HIV
7 M HIV/HCV

Pawlotsky JM. *J Hepatol* 2006;44:S10-S13;
Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004;54:6-9;
3. Lucas GM. *J Antimicrob Chemother* 2005;55:413-416, Soriano V JAC 2008: 62:1-4

HIV/HCV co-infection burden

- ↑ incidence :IDU, MSM_HIV+[1–3]
- Compared to non HIV, HIV/HCV
  - ↑viraemia (8-20x faster)[1,4]

Thailand : prevalence 8-10% among HIV[9] , 0.94% among general population[11]

  - High percentage of HCV RNA in semen than HCV mono (37.8% vs 18.4%) [5]
  - ↑ Maternal HCV transmission(20% vs 6%) and sexual transmission(3% vs <1%)[1,6]
  - ↓ HCV seroclearance, ↑ viral persistence (95% vs62%)[7] esp CD4<200 cells/uL (5%) vs CD4>500ells/uL (8.3%) vs HIV-(13.8%) [1,4,8]
    - ↑ chronic HCv infection 90% in HIV + vs 70-80 % HIV-
  - Prior DAA era : ↑ hepatic fibrosis (2–5-fold greater), cirrhosis (2-3 fold), liver failure (16 fold) decompensation, hepatocellular carcinoma (6 fold) and liver-related mortality[1,6]

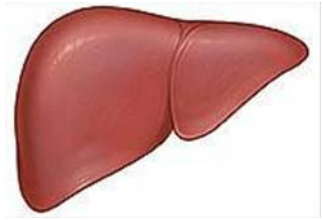
1. World Health Organization. Protocol 6. Management of hepatitis C and HIV coinfection. WHO Regional Office for Europe 2007;
2. Wiessing L, et al. Euro Surveill 2011;16:pii:20031; 3. Taylor LE, et al. Clin Infect Dis 2012;55(S1):S33–42; 4. Sherman KE, et al. Gastroenterology 2005;128:313–27;5. Briat A., AIDS 2005;19:1827–35. 6. Vallet-Pichard A, Pol S. J Hepatol 2006;44(S1):S28–34. 7. Danta M, . J Infect Dis 2008;197:1558–66 8.Thomas DL. JAMA 2000; 284:450-456. 9.Durongpongkasem PJ Med Assoc Thai 2018; 101 (4):72 10. Wasitthankasem R et al. Plos One 2016; 11(2): e0149362

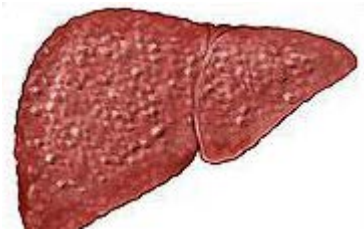
Effect of HIV on HCV

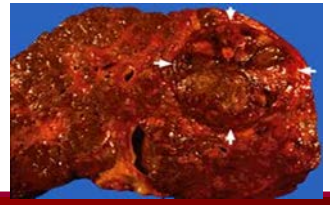
20-25 years

25-30 years

*20%-30% of individuals are symptomatic







Acute Infection*

Chronic Infection 75%-85%

Cirrhosis 10%-20% over 20 years

Hepatocellular Carcinoma (HCC) 1%-4% per year

Decompensated Cirrhosis (DCC) 5-yr survival rate 50%

Clearance of HCV RNA
20-40% : HCV mono
5-10% HIV/HCV

Extrahepatic Manifestations

25% of CHC ➡ cirrhosis in 10 yrs
53% of cirrhosis ➡ HCC in 10 yrs

GT3 >GT1

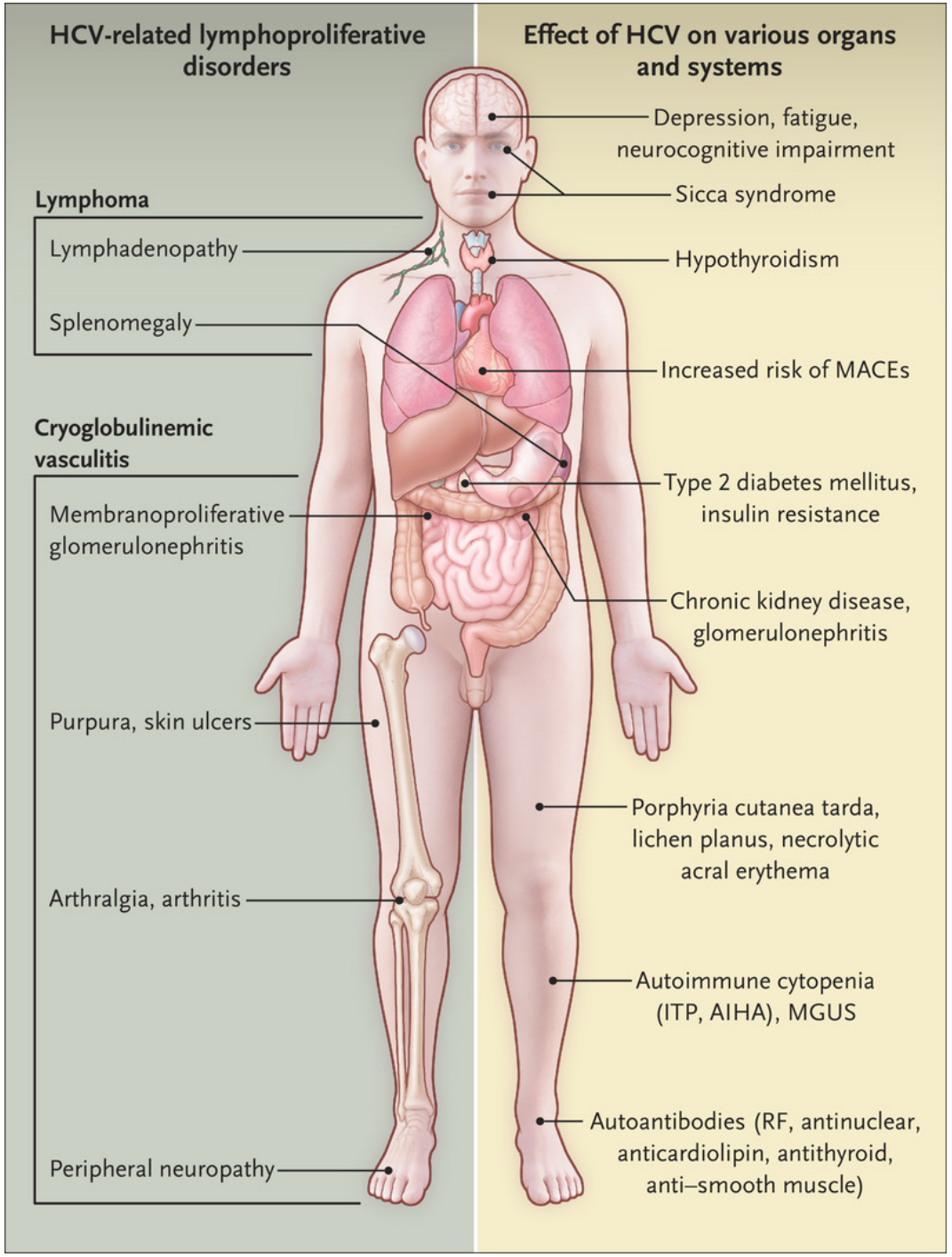
↑ viral persistence (95% vs62%) esp CD4<200

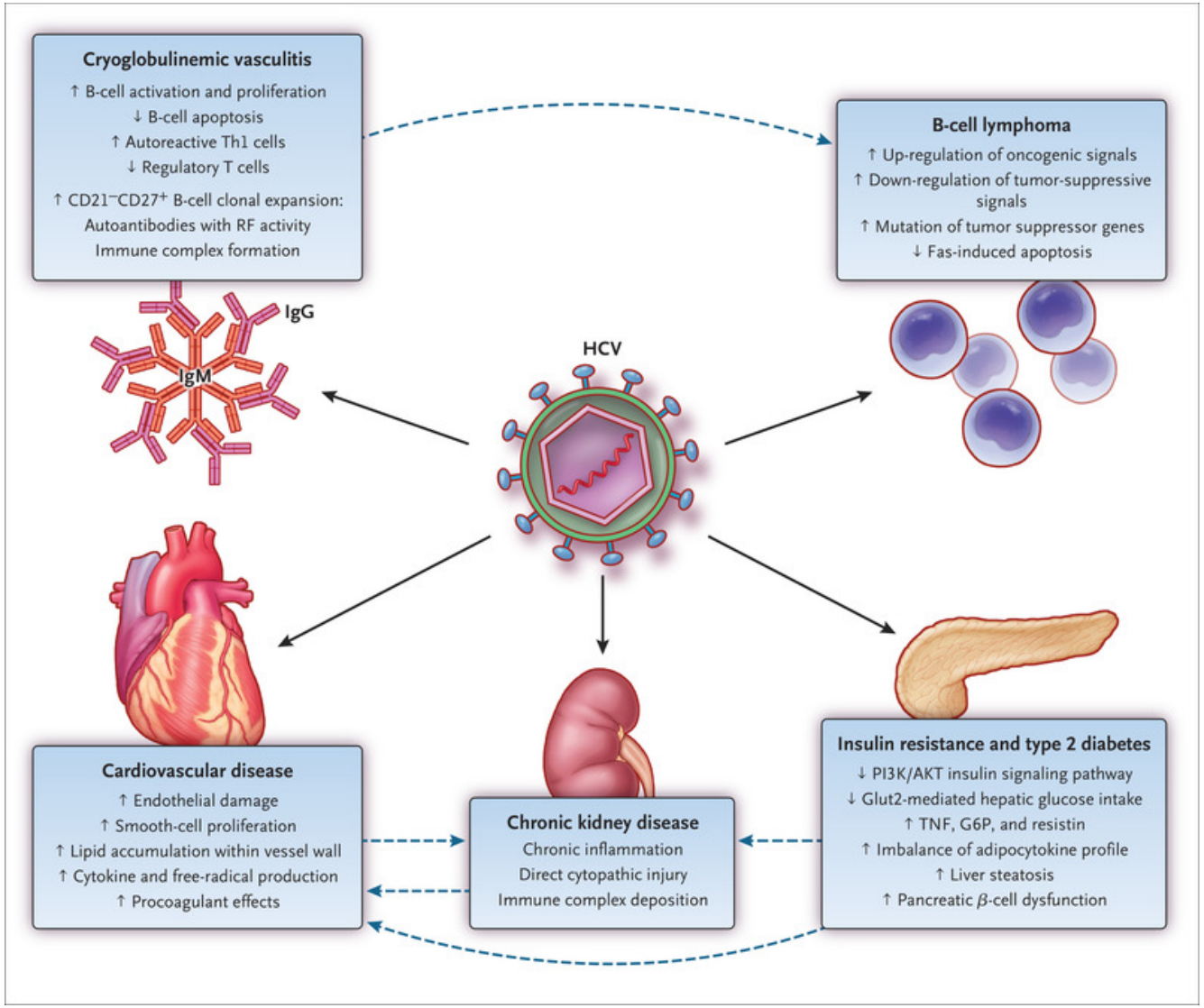
15–25% of HIV/HCV develop cirrhosis and liver failure within 15 years

Adapted from Chen SL, Morgan TR.
Int J Med Sci. 2006;3:47-52.
Clinical and Molecular Hepatology Review 2014;20:89-136
Schlabe S SExpert Opinion on Pharmacotherapy 2018

Rapid fibrosis progression : **Age > 40 yr** , heavy alcohol use, **coinfection with HIV or HBV**, steatosis and insulin resistance

Extrahepatic Manifestations of Chronic HCV Infection (HIV/HCV พบ 40-70%)

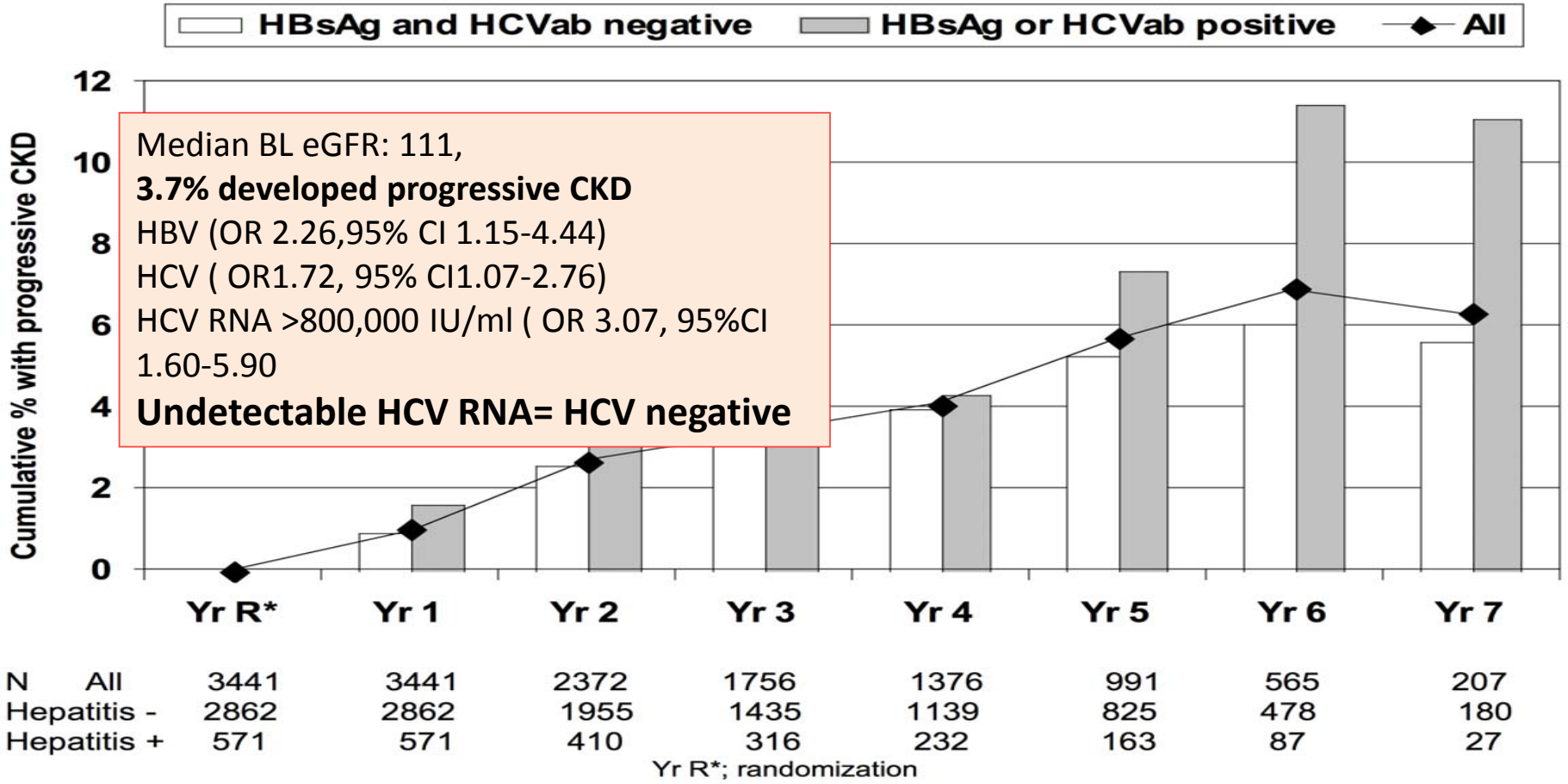




N Engl J Med 2021; 384:1038-1052

Active HCV Is associated with Chronic kidney disease

N=-3441 (HBV 3.3%, HCV 13.8%) ; SMART and ESPRIT; eGFR (median times=3)
Progressive CKD : ESRD, renal death, eGFR decline :>25%to eGFR< 60 or 25% decline with BL eGFR <60



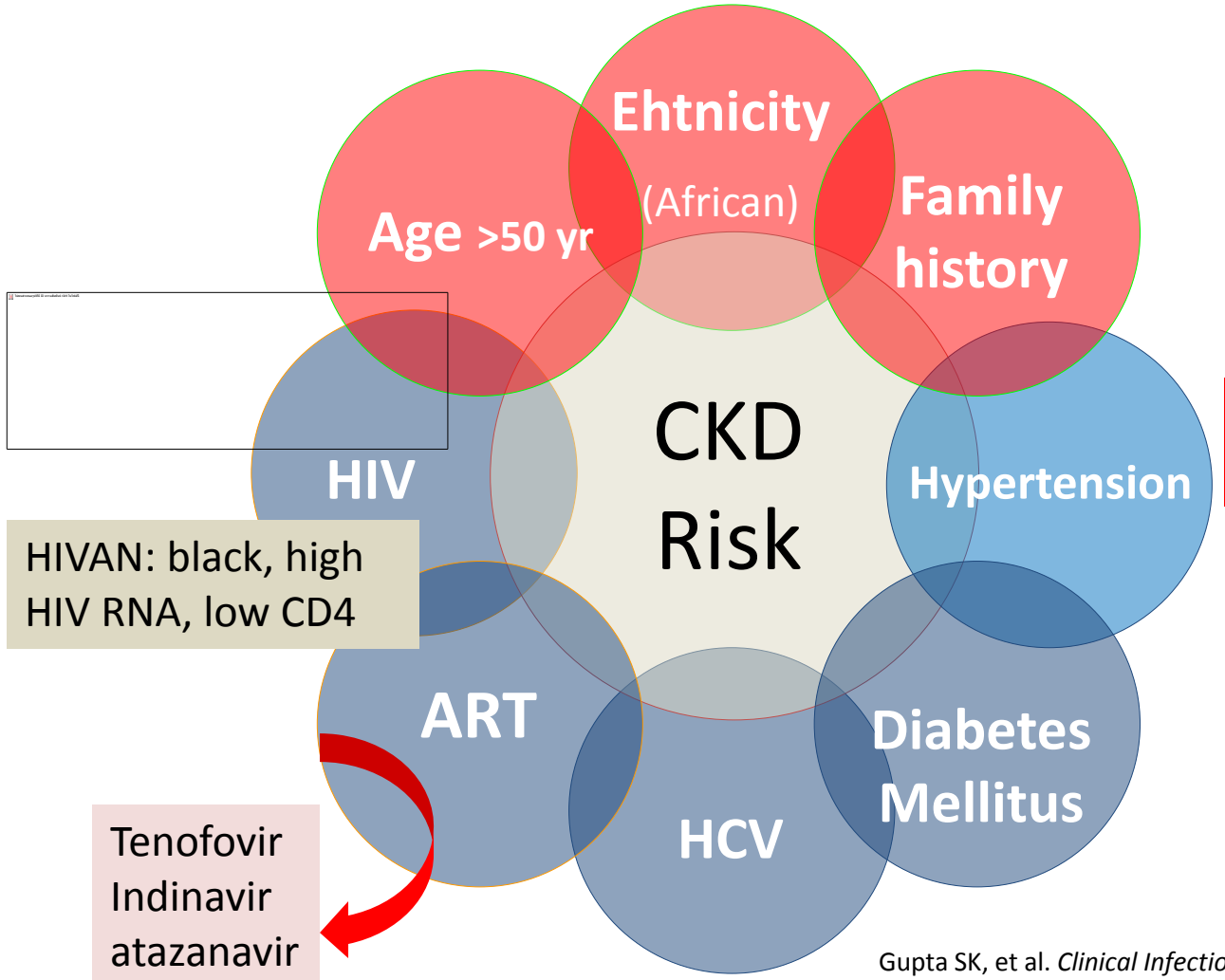
Median BL eGFR: 111,
3.7% developed progressive CKD
HBV (OR 2.26,95% CI 1.15-4.44)
HCV (OR1.72, 95% CI1.07-2.76)
HCV RNA >800,000 IU/ml (OR 3.07, 95%CI 1.60-5.90
Undetectable HCV RNA= HCV negative

Mocroft et al., Plos One 2012; 7 :e40245

HCV viremia increases the incidence of CKD, advanced CKD in HIV
Peters L AIDS 2012, Lucas GM, J Infect Dis 2013
HCV infection was associated with CKD, proteinuria in Taiwan (non HIV, N=54966) : Lee JJ Am J Kidney Dis 2010

Meta analysis : HCV increases the risk of CKD
- among HIV : Fabrizi F J Med Virol 2015
- Non HIV : Fabrizi F Dig Dis Sci 2015

HCV RNA increased risk of CKD



= modifiable

= non modifiable

Nephrotoxic drug
: NSAID, amphotericin

HIVAN: black, high HIV RNA, low CD4

Tenofovir
Indinavir
atazanavir

Gupta SK, et al. *Clinical Infectious Disease.* 2005; 40:1559-1585.

Screening****

Rapid diagnostic antibody tests

OraQuick® HCV Test

Anti HCV Ab positive

enzyme immunoassay antibody tests

Confirmation

HCV RNA

HCV RNA > 6 months : chronic HCV

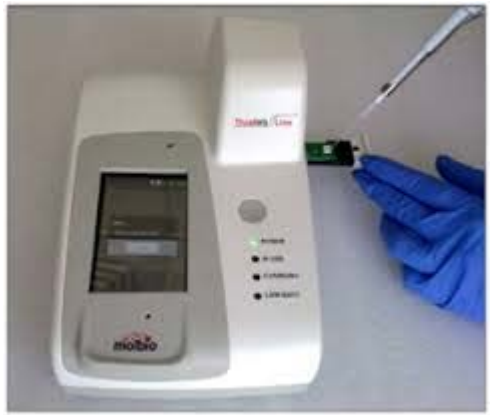
- **Positive: active HCV infection**
  - **Further evaluation**
    - Genotype, cirrhosis, comorbidities (HBV, HIV, DM, renal disease)
  - **Refer for treatment**
- **negative**
  - **Spontaneous HCV clearance**
    - **No Treatment**
    - Repeat HCV RNA at 6 months

สปสช 2021
Rapid anti HCV Ab =70 บาท
Anti HCV Ab =300 บาท
Fibroscan/fibro test 2000บาท

Point of care testing

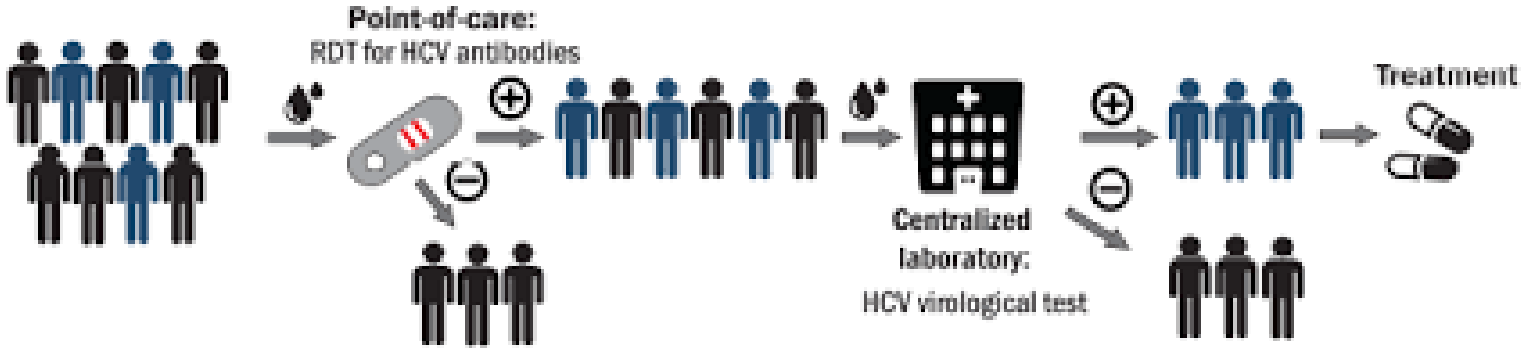
genedrive

GeneXpert



Truenat

HCV RNA 10-10,000,000 IU/ml



HCV RNA Point of Care testing :Xpert HCV Viral load

Xpert HCV Viral load : all HCV genotypes,
range of 10 to 100,000,000 IU/mL
<1 minute hands-on time , Run daily or on-demand

ใช้เวลาตรวจ 105 นาที พิมพ์ผลตรวจได้เลย

Xpert machine =125 เครื่อง, 77 จังหวัด

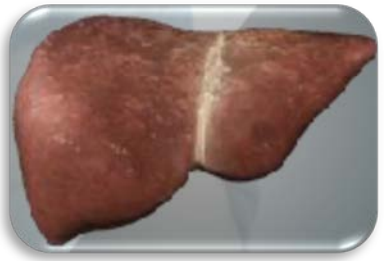
Anti HCV Ab: false negatives

Common Causes of False Negative Test Results

*ถ้าCD4 <100 cells/uL ผล anti-HCV อาจให้ผลลบลวงได้ ถ้ามีความเสี่ยงต้องตรวจ HCV RNA หรือตรวจ anti-HCV ใหม่ เมื่อตอบสนองต่อยาต้านดีแล้ว (CD4 สูงขึ้น)

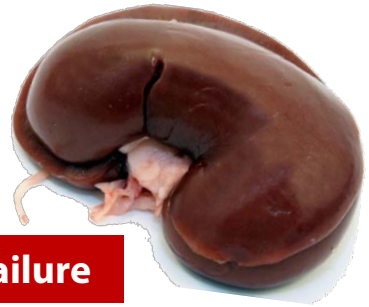
Immunosuppressed Individuals

~6% of HIV-positive patients don't produce HCV antibodies



Patients With Acute HCV

May take up to six months for antibodies to develop

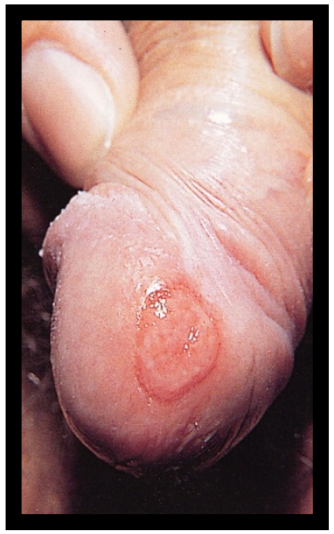


Renal Failure

HCV-Associated Mixed Cryoglobulinemia

Acute HCV : MSM_HIV+

Acute HCV:1. Positive HCV RNA test, anti HCV Ab negative 2. positive anti HCV Ab (seroconversion) within 12 months



sexual HCV transmission

Sex
- MSM
- Group sex

2 : risk 9 fold

≥ 3: risk23 fold
- Sildenafil
- STI : **syphilis**

substance abuse
- Crystal methamphetamine

HIV :- high HCV in bllod and semen
Low CD4 at GI mucosa

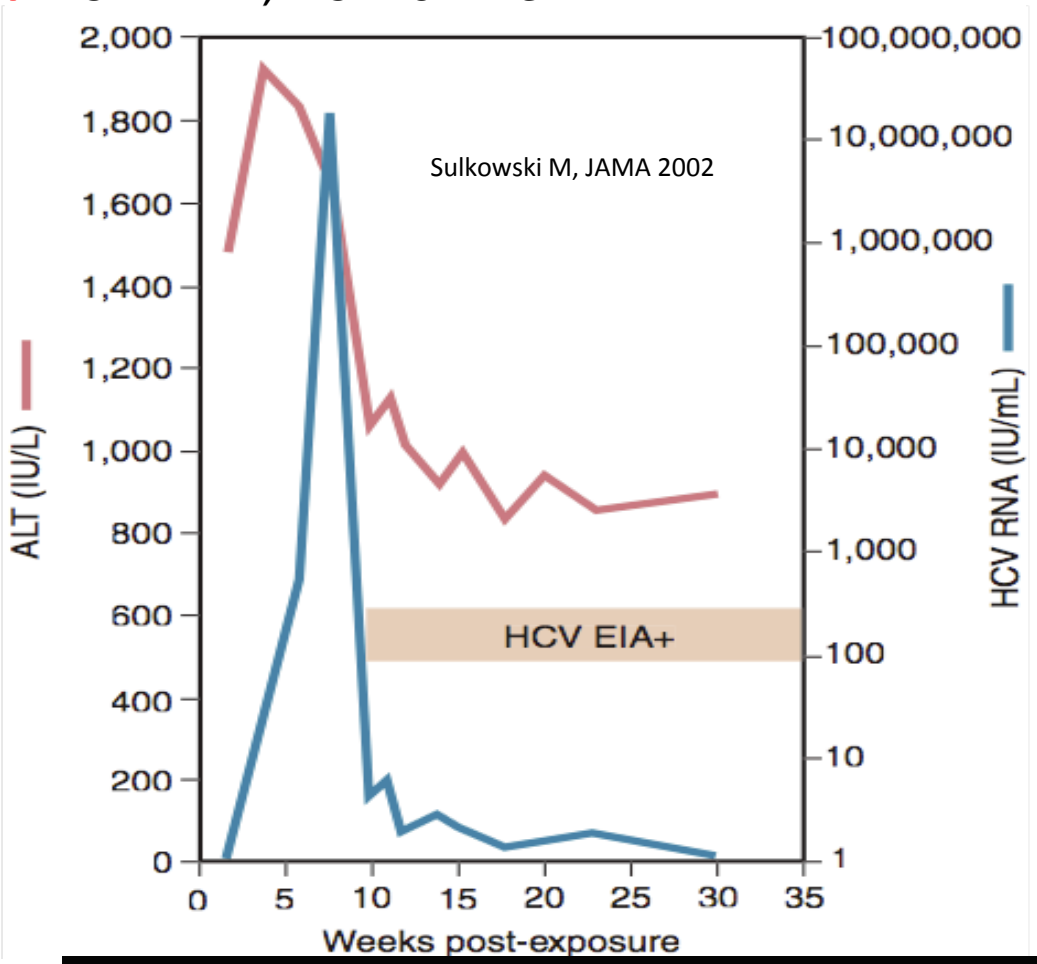
MSM/HIV +

↑ **viraemia (8-20x faster)**
High HCV RNA in semen than HCV mono (37.8% vs 18.4%)

Danta et al, AIDS 2007, Witt MD et al Clin Infect Dis 2013, Larsen C PLoS ONE 2011Chan D 2016:49: 47–58

Acute HCV Infection: MSM-HIV+, MSM-on PreP

- viremia detectable within 7 to 10 days (1-3 wk after exposure)
- ALT elevation 2 to 8 weeks post-infection (4-12 wk post exposure)
- antibody seroconversion 8 to 10 weeks
- HCV VL fluctuations



- **Anti HCV Ab is negative during first 6 week**
- **High HCV RNA during first 8-10 weeks**
- **80 % asymptomatic cases**

Risk of transmission

- **MSM-HIV+**
- **MSM-HIV-, on PreP**

Annual HCV testing for sexually MSM/HIV+, PreP users

Thailand
- HCV screening for all HIV
- Repeat HCV if –unexplained ALT/AST elevation
  -MSM with multiple partner, syphilis
-all PreP users

AASLD/IDSA HCV Screening Recommendations

Recommendations for One-Time HCV Testing	Rating
One-time, routine, opt-out testing recommended for all persons 18 yrs of age or older	I, B
One-time testing recommended for all persons younger than 18 yrs of age with exposures, activities, or conditions/circumstances associated with increase HCV infection risk	I, B
Prenatal testing as part of routine prenatal care recommended for each pregnancy	I, B
Periodic repeat testing should be offered to all individuals with exposures, activities, or conditions/circumstances associated with increased HCV exposure risk	IIa, C
Annual testing recommended for: all individuals who inject drugs; men with HIV infection who have unprotected sex with men; men who have sex with men and are taking HIV pre-exposure prophylaxis	IIa, C

MSM c PrEP, MSM/HIV

AASLD/IDSA HCV guidance. https://www.hcvguidelines.org/evaluate/testing-and-linkage.

Hepatitis C is an STI in HIV-infected MSM in Asia!

ORIGINAL ARTICLE

WILEY Liver INTERNATIONAL

Molecular epidemiology of acute HCV infection in HIV–positive patients from Hong Kong, Taipei, Tokyo

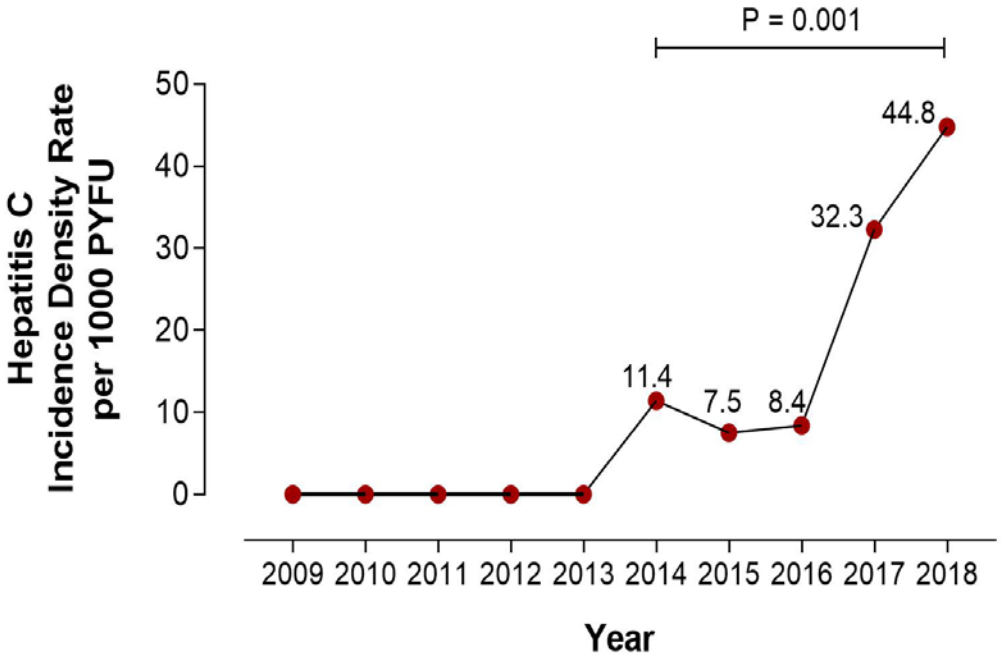
N=234 PLHIV
Year 2010-2016

	Hong Kong	Taipei	Tokyo	*P* value
Patient number, N	58	138	38	
Age at the diagnosis of acute HCV infection, mean (SD), y	36.0 (8.2)	34.7 (7.6)	40.5 (6.9)	<0.001
Male, % (n)	100 (58)	100 (138)	100 (38)	
HIV transmission route, % (n)				
Male-to-male sex	98.3 (57)	92.0 (127)	94.7 (36)	0.295
Heterosexual	1.7 (1)	2.2 (3)	2.6 (1)	
Injecting drug use	0 (0)	0.7 (1)	2.6 (1)	
Unknown	0 (0)	5.1 (7)	0 (0)	

Sun HY Liver Int 2019,39(6):1044-1051

Hepatitis C in Acute HIV cohort in Bangkok

Outbreak of acute HCV infection in a cohort of 573 HIV+ MSM in Bangkok, Thailand

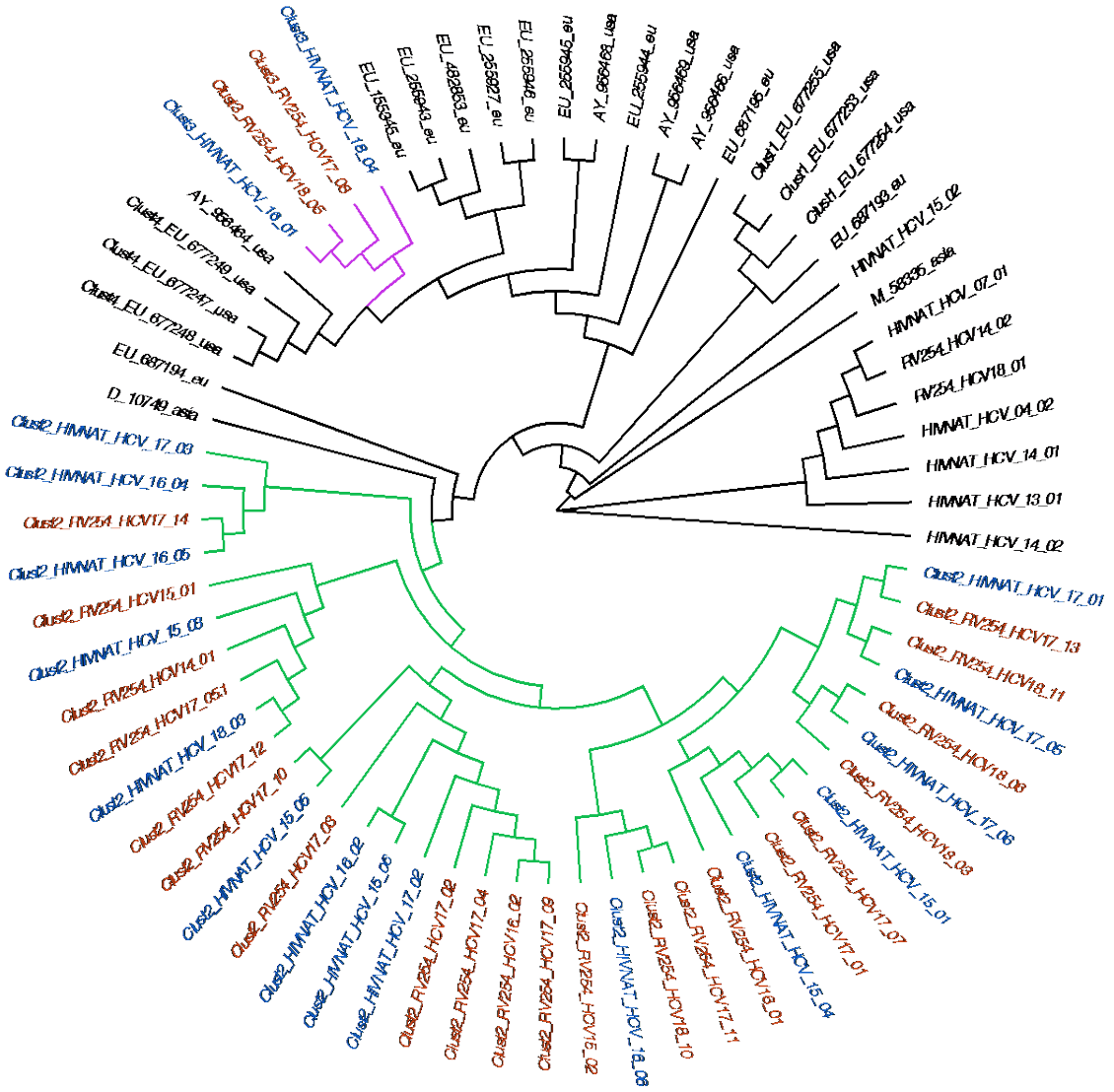


Risk factors for Acute HCV incidence among HIV+ MSM in Bangkok, Thailand (n=39 acute HCV cases)

Risk factor	aHR	95% CI	P-value
methamphetamine use	2.33	1.13 to 4.8	0.022
Group sex	2.54	1.26-5.12	0.009
syphilis	2.43	1.22-4.85	0.012

Wansom T Acquir Immune Defic Syndr. 2020 Aug 1;84(4):331-335

Hepatitis C is a rapidly emerging STI in Bangkok



Phylogram of n=48 acute HCV cases among HIV+ MSM in Bangkok 2014-2018

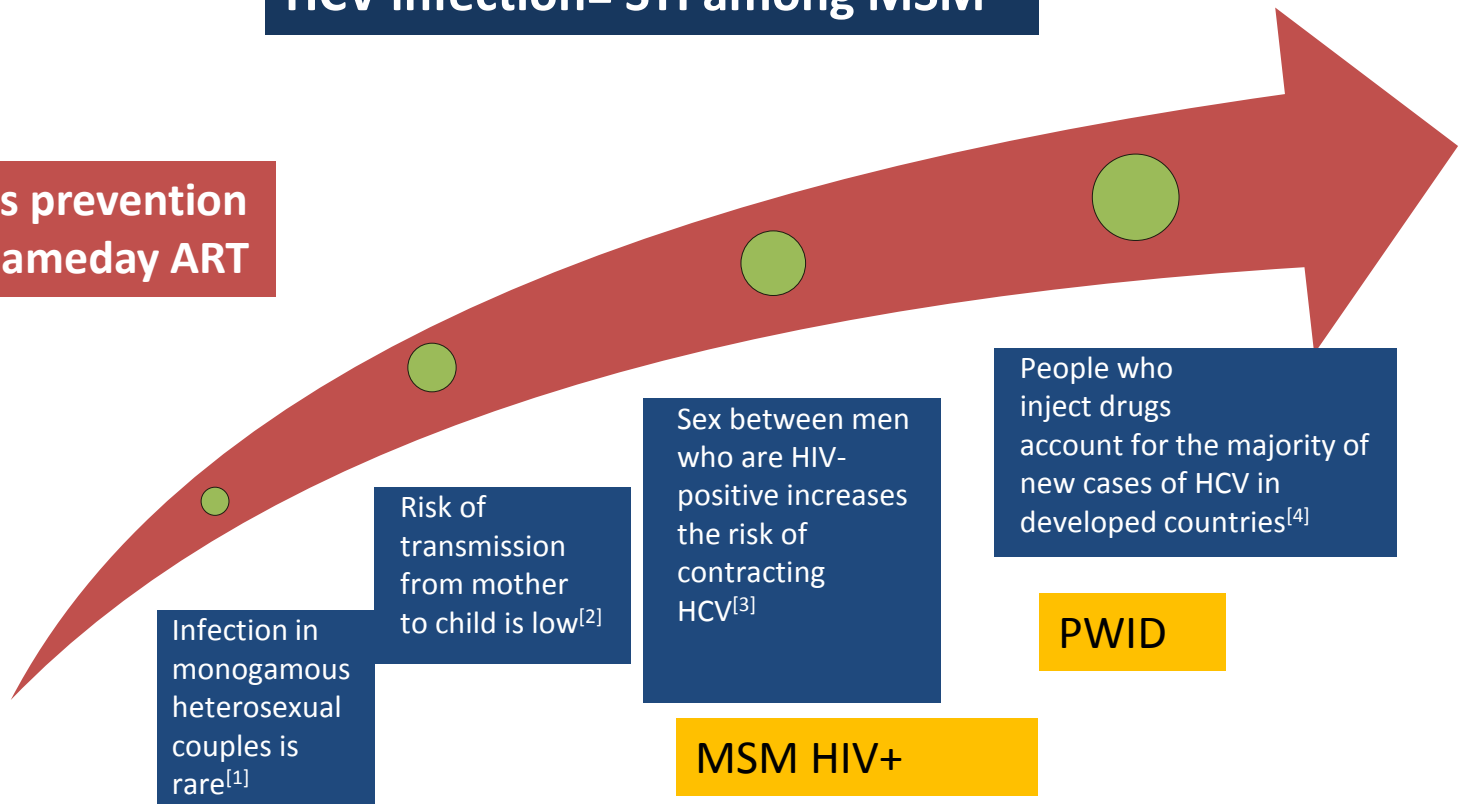
- 85% are clustered in one large (n=36) and one small (n-4) clusters
- 90% HCV genotype1

Han, CROI, 2020

Hepatitis C Is an INFECTIOUS Virus: Treatment as Prevention

HCV infection= STI among MSM[6]

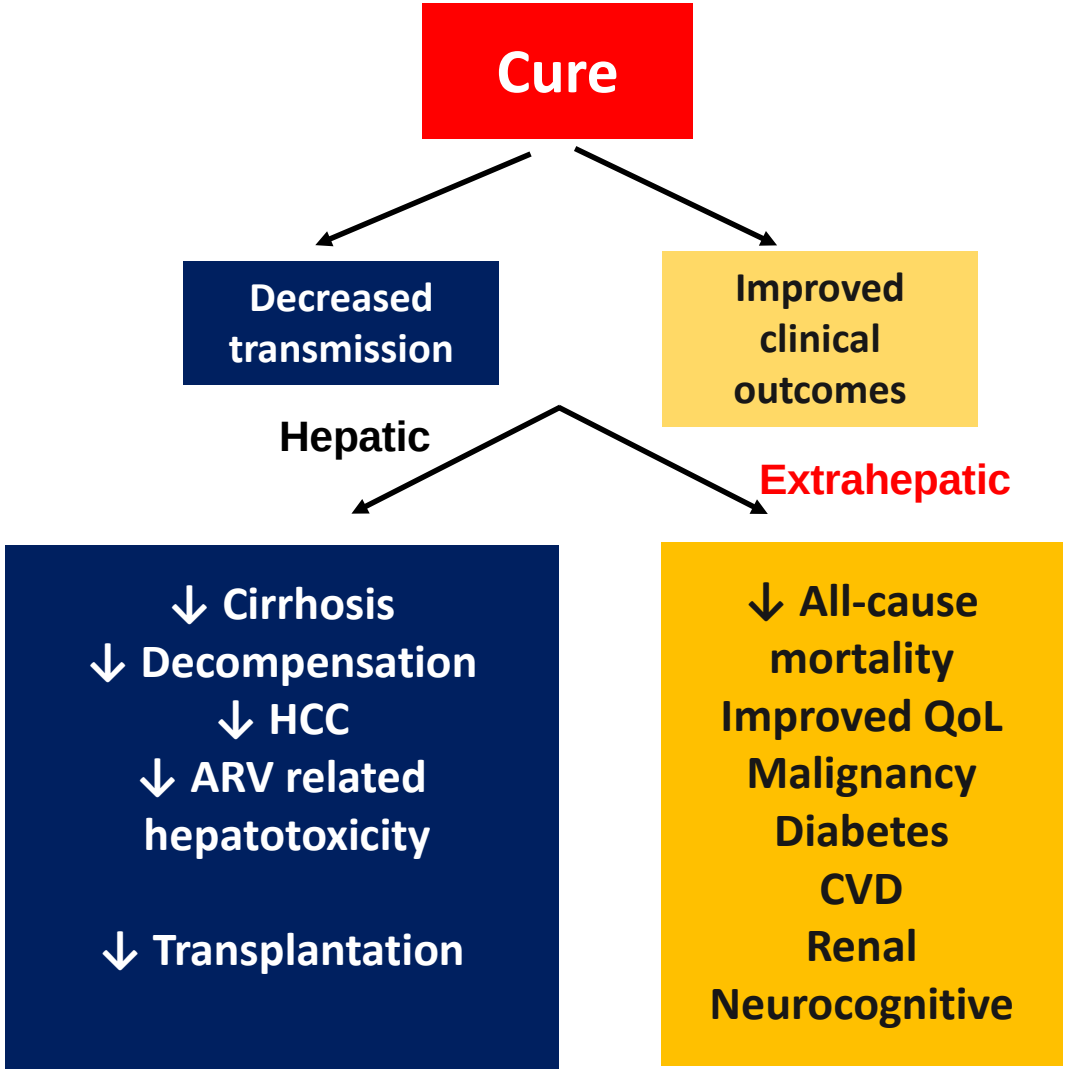
HIV model : Treatment as prevention
Rapid ART/Sameday ART



High percentage of HCV RNA in semen than HCV mono (37.8% vs 18.4%) [5]

1Terrault NA, et al. Hepatology. 2013;57:881-899. 2. Thomas SL, et al. Int J Epidemiol. 1998;27:108-117. 3. Larsen C, et al. PLoS One. 2011;6:1-9. 4. Shepard CW, et al. Lancet Infect Dis. 2005;5:558-567. 5. Briat A,. AIDS 2005;19:1827–35. 6. Chan D Sexually acquired hepatitis C virus infection: a review International Journal of Infectious Diseases 49 (2016) 47–58

HCV treatment is important among HIV/HCV co-infection : Burden of disease, high HCV transmission and high extrahepatic manifestation

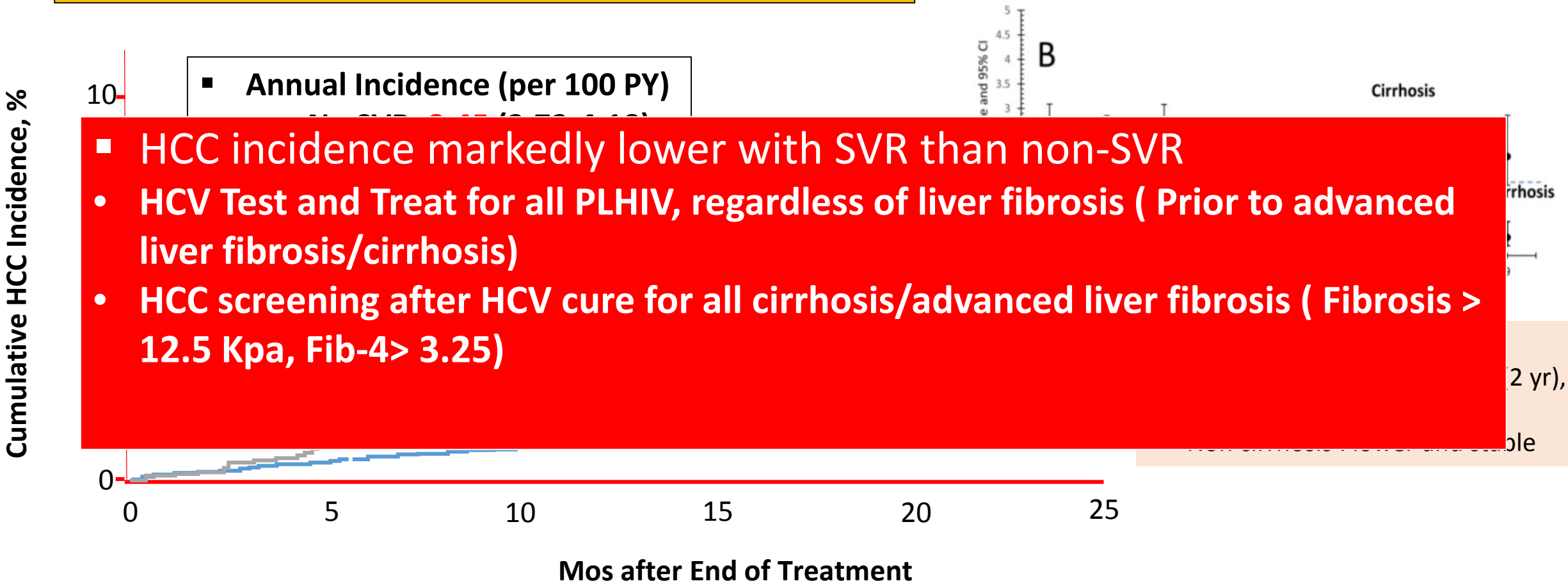


Virologic cure does not protect against reinfection

1. Smith-Palmer J, et al. BMC Infect Dis. 2015;15:19.2. Negro F, et al. Gastroenterology. 2015;149:1345-1360.3. George SL, et al. Hepatology. 2009;49:729-738.4. van der Meer AJ, et al. JAMA. 2012;308:2584-2593

HCC risk remained high in cirrhosis with SVR after DAA

22,500 patients treated with DAAs in the VA



- HCC incidence markedly lower with SVR than non-SVR
- **HCV Test and Treat for all PLHIV, regardless of liver fibrosis (Prior to advanced liver fibrosis/cirrhosis)**
- **HCC screening after HCV cure for all cirrhosis/advanced liver fibrosis (Fibrosis > 12.5 Kpa, Fib-4> 3.25)**

Kanwal. Gastroenterol. 2017;153:996. Kanwal F et al Hepatology 2019

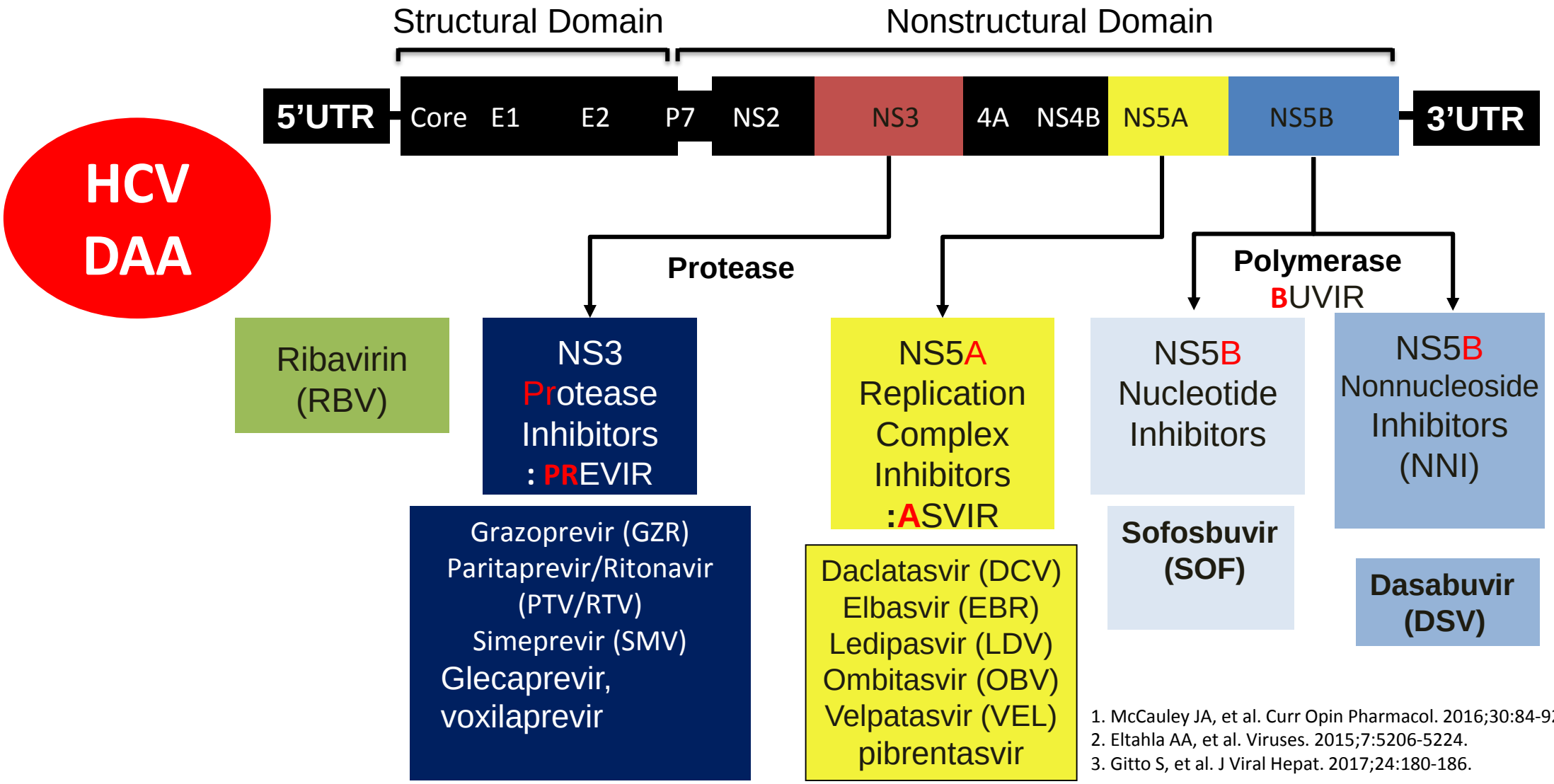
HCV treatment

PI+NS5A : Grazoprevir/elbasvir, Glecaprevir/pibrentasvir, Paritaprevir/ritonavir/ombitasvir

PI+NS5A+NS5B: Sofosbuvir/velpatasvir/voxilaprevir, Ombitasvir/paritaprevir/ritonavir + dasabuvir

NS5B+NS5A: Sofosbuvir/ledipasvir, **Sofosbuvir/velpatasvir, Sofosbuvir + daclatasvir**

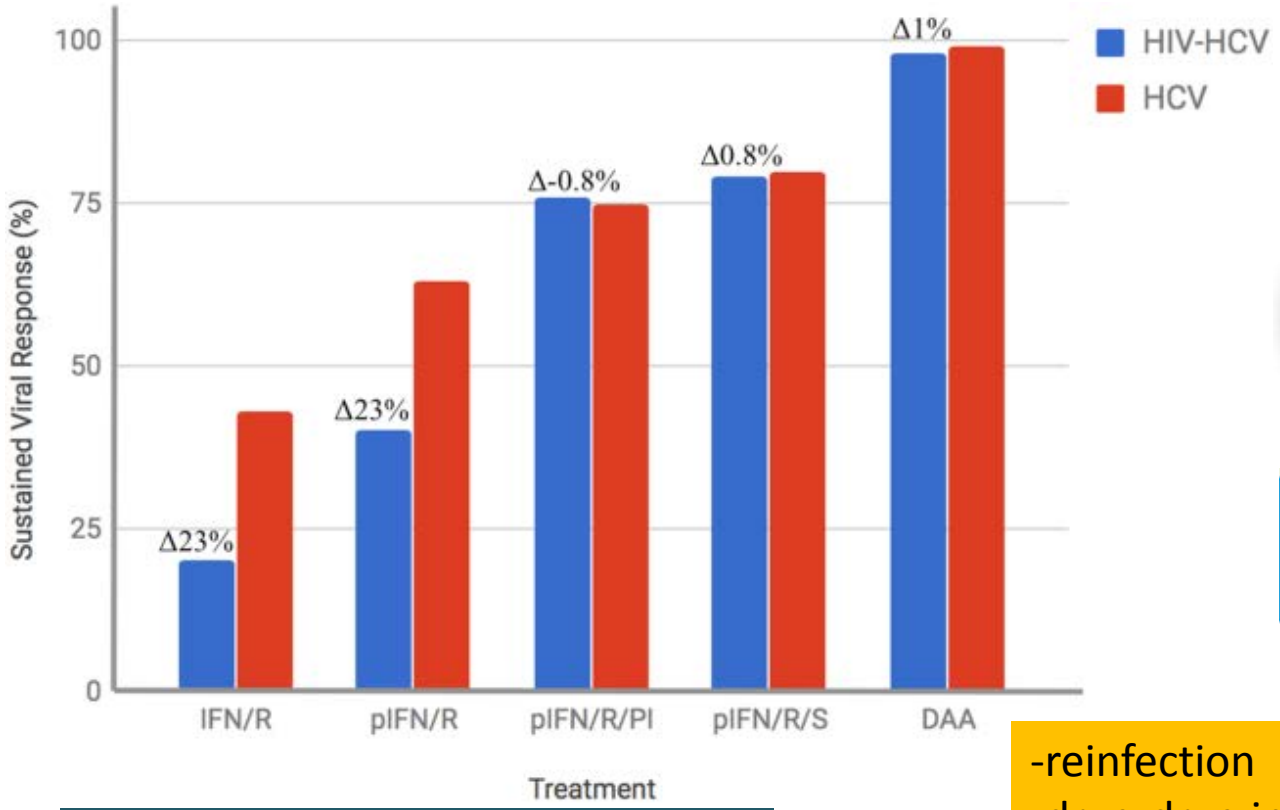
NS5B+ Peg IFN/RBV : SOF+ Peg IFN/RBV



1. McCauley JA, et al. Curr Opin Pharmacol. 2016;30:84-92.
2. Eltahla AA, et al. Viruses. 2015;7:5206-5224.
3. Gitto S, et al. J Viral Hepat. 2017;24:180-186.

Hepatitis C and HIV coinfection : DAA : simple, high SVR

>95% SVR achievable
Manageable drug-drug interaction
Less toxicity



Sustained virological response

HCV RNA negative 12 weeks (SVR12) or 24 weeks (SVR24) after stop treatment

Short duration

8-12 weeks

Cirrhosis + ribavirin

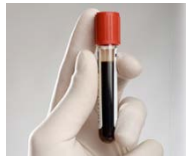
Minimal pre-testing is required

Minimal Monitoring

- 95% sustained
- virological response

-reinfection
-drug-drug interaction
-co-morbidities : diabetes, HBV
substance abuse, stigma, renal insufficiency
-extrahepatic manifestation

HCV testing and treatment in Thailand 2021: SOF/Vel



Rapid test=70 บาท
ELISA: 300 บาท

1 **1. Screening (Anti HCV)**

- ve[2]
+ ve

2 **2. HCV viral load**

1700 บาท

- HCV VL (qualitative)
- HCV core Ag
- HCV VL (Quantitative) 2300 บาท

Not detected [1]

800 บาท

Detected, Reactive

HIV/HCV : Rapid liver fibrosis progression

3 **3. Evaluation**

1) APRI/FIB-4 200 บาท

or

2) Fibroscan® 2000 บาท

or

3) Fibromarker panel 2000 บาท

- APRI ≥ 1.5/FIB4 ≥3.25 → ส่งพบแพทย์ผู้เชี่ยวชาญ (Hepatologist)
- APRI 0.5-1.5/FIB4 1.25-3.25 → เข้าสู่การรักษา
- >=7 kPa → เข้าสู่การรักษา
- >=5-<7 kPa [2]
- <5 kPa [3]
- >= F2 → เข้าสู่การรักษา
- < F2 [2]

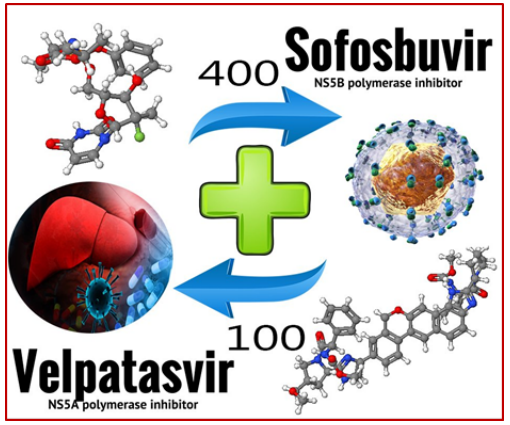
4 **4 Treatment**

HIV,
ผู้ใช้สารเสพติดแบบฉีด

20% of HIV/HCV with detectable HCV RNA with null/mild liver fibrosis progress to advanced fibrosis within 5 years

Labarga P, Antivir Ther. 2014;19:799-803

[1] =repeat>6 month and <12 month [2] = repeat>12 months [3] = repeat >24 months



Genotypes ALL

Pangenotype HCV

SOFOSBUVIR/VELPATASVIR

Sofosbuvir (400mg) + Velpatasvir (100 mg)

- HCV NS5B NU inhibitor
- HCV NS5A inhibitor

1 pill with food for 12 weeks

contraindication: Amiodarone, rifampin, **efavirenz,** etravirine, or nevirapine

cure SVR

Caution: omeprazole , SOF/vel with food and prior to omeprazole 4 hr

Avoided: eGFR <60 mL/min.

HEP Drug Interactions
https://www.hep-druginteractions.org

HIV/HCV Drug–Drug Interactions

ARV(s)	GLE/PIB	GZR/EBR	SOF/LDV	SOF/VEL	SOF/VEL/VOX	SOF + DCV
ATV + (RTV or COBI)	X	X	✓*	✓*	X	Decrease DCV dose (30 mg)
DRV + (RTV or COBI)	X	X	✓*	✓*	✓*†	✓
LPV + RTV	X	X	✓*	✓*	X	✓
EFV	X	X	✓*	X	X	Increase DCV dose (90mg)
RPV	✓	✓	✓*	✓	✓	✓
DTG	✓	✓	✓*	✓	✓	✓
RAL	✓	✓	✓	✓	✓	✓
EVG/COBI/FTC/TDF	✓*†	X	X	✓*	✓*†	Decrease DCV dose
EVG/COBI/FTC/TAF	✓†	X	✓	✓	✓†	Decrease DCV dose
3TC/ABC	✓	✓	✓	✓	✓	✓
TAF	✓	✓	✓	✓	✓	✓
TDF	✓	✓	✓*	✓*	✓*	✓

Interaction Checker - HEP Drug Interactions
https://www.hep-druginteractions.org/checker

*Monitor for tenofovir toxicity if used with TDF.
†No clinically significant drug interaction per prescribing information;
AASLD/IDSA and DHHS guideline 2020

Liverpool HEP Interactions - HEP Drug Interactions
https://www.hep-druginteractions.org/prescribing-resources

Drug-Drug Interactions With HCV Treatments


No clinically significant interaction expected.


Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.


These drugs should not be co-administered.

Table 4B. Drug-drug interactions between HCV DAAs and illicit/recreational drugs or drugs of abuse.

	SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Amphetamine	◆	◆	◆	◆	◆
Cannabis	◆	◆	◆	◆	◆
Cocaine	◆	◆	◆	◆	◆
Diamorphine	◆	◆	◆	◆	◆
Diazepam	◆	◆	◆	◆	◆
Fentanyl	◆	◆	◆	■	■
Gamma -hydroxybutyrate	◆	◆	◆	■	■
Ketamine	◆	◆	◆	◆	◆
MDMA (ecstasy)	◆	◆	◆	◆	◆
Mephedrone	◆	◆	◆	◆	◆
Methadone	◆	◆	◆	◆	◆
Methamphetamine	◆	◆	◆	◆	◆
Oxycodone	◆	◆	◆	■	■
Phencyclidine (PCP)	◆	◆	◆	◆	◆
Temazepam	◆	◆	◆	◆	◆

Table 4C. Drug-drug interactions between HCV DAAs and lipid-lowering drugs.

	SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Atorvastatin	◆	■	●	●	■
Bezafibrate	◆	◆	◆	◆	◆
Ezetimibe	◆	◆	■	■	◆
Fenofibrate	◆	◆	◆	◆	◆
Fluvastatin	◆	■	●	■	■
Gemfibrozil	◆	◆	◆	■	■
Lovastatin	◆	■	●	●	■
Pitavastatin	◆	■	●	■	◆
Pravastatin	◆	◆	■	■	◆
Rosuvastatin	◆	■	●	■	■
Simvastatin	◆	■	●	●	■

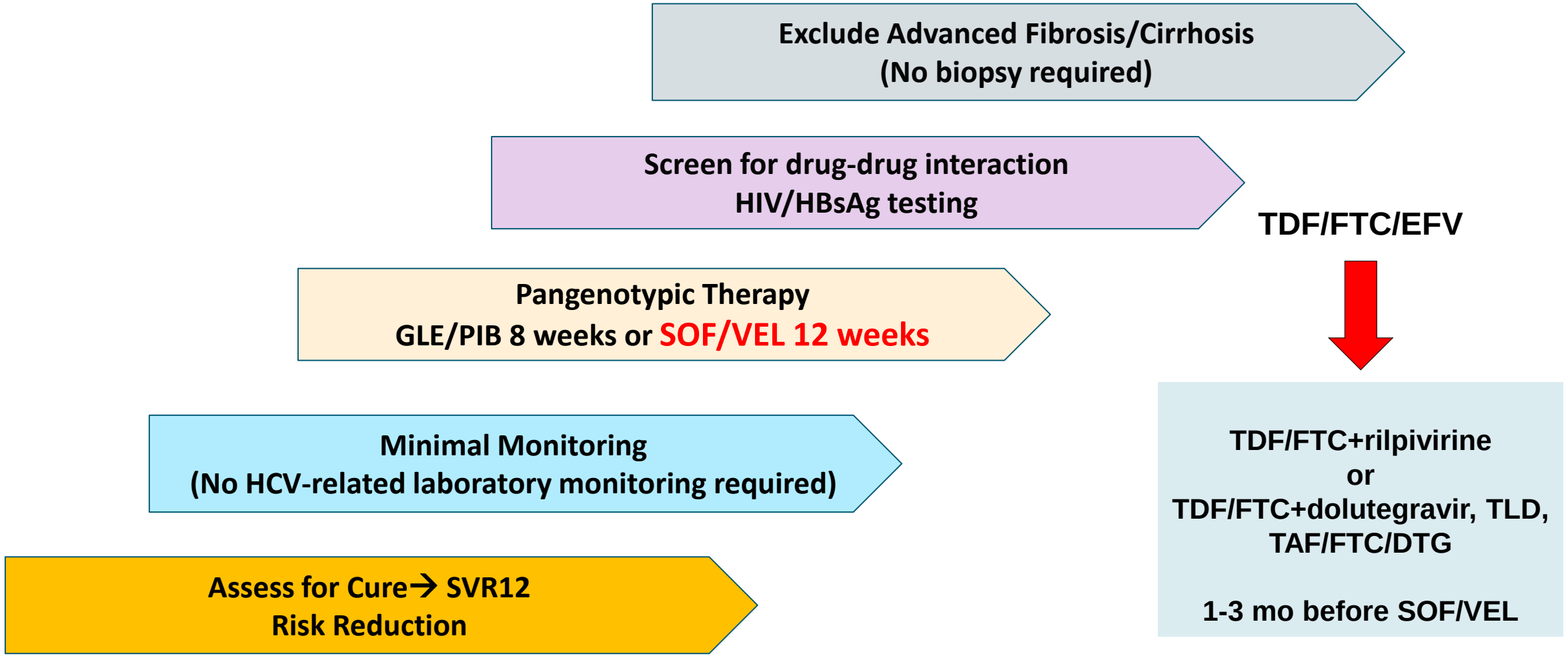
Table 4G. Drug-drug interactions between HCV DAAs and antiplatelets and anticoagulants.

	SOF	SOF/VEL	SOF/VEL /VOX	GLE/PIB	GZR/EBR
Clopidogrel	◆	◆	◆	◆	◆
Dabigatran	◆	■	●	●	■
Ticagrelor	◆	■	■	■	■
Rivaroxaban	◆	■	■	■	■
Apixaban	◆	■	■	■	■
Edoxaban	◆	■	●	■	■
Warfarin	■	■	■	■	■

HEP Drug Interactions
https://www.hep-druginteractions.org

Pawlotsky. J Hepatol. 2020;73:1170.

Simplified Treatment Guidelines for Treatment-Naïve HCV /HIV Patients Without Cirrhosis



TLD : TDF/3TC/DTG

AASLD/IDSA guideline 2020

https://www.hcvguidelines.org/treatment-naive/simplified-treatment.

Treatment of Chronic HCV among PLHIV

- HIV/HCV-coinfected persons **should be treated and retreated the same as persons without HIV infection**, after recognizing and **managing interactions with antiretroviral medications** (I,B) (12 weeks for non cirrhosis/ compensated cirrhosis)
- Decompensated cirrhosis
  - Ribavirin eligible (12 weeks)
    - **Genotype 1, 4, 5, or 6 only:** daily ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated to weight-based dose)
    - Daily sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin
  - Ribavirin ineligible (24 weeks)
    - Genotype 1, 4, 5, or 6 only: daily ledipasvir (90 mg)/sofosbuvir (400 mg) for 24weeks
    - Daily sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks

SOF/Vel 1 tab OD → 12 weeks → 12 weeks ตรวจ HCV RNA: Cure

Decompensated cirrhosis
-SOF/Vel 1 tab OD +ribavirin 12 weeks
-SOF/vel 1 tab 24 weeks

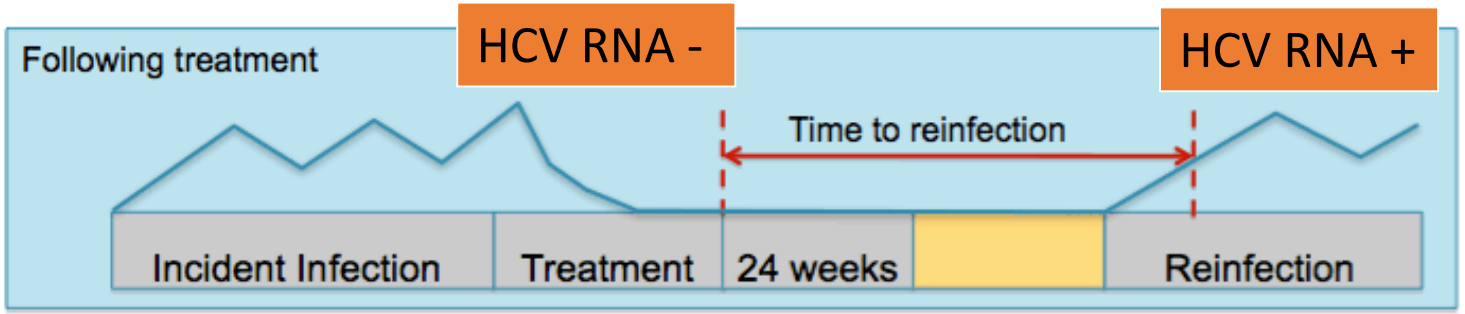
ให้ยาครบ รออีก**3** เดือน ตรวจ **HCV RNA**

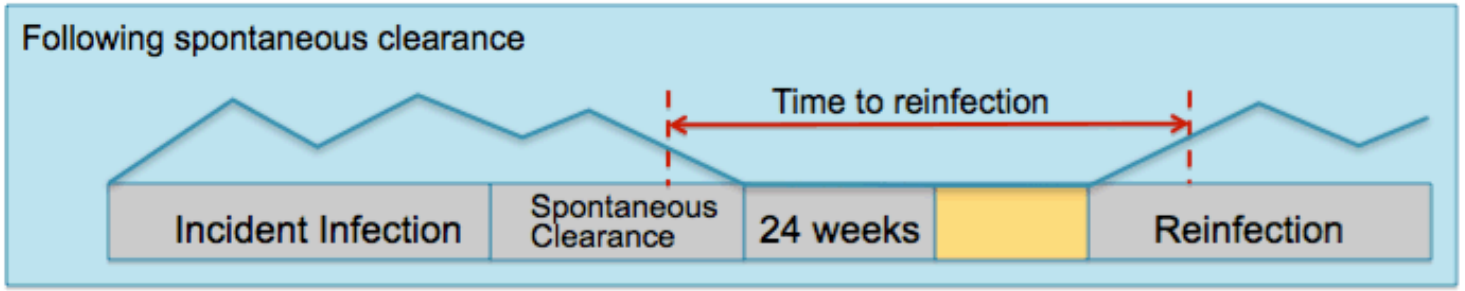
AASLD/IDSA Nov 6, 2019

Re-infection of HCV

Definitions

Reinfection
- Any newly positive HCV RNA PCR 24 weeks or more following end of treatment or clearance of the virus; or
- Newly positive HCV RNA PCR within 24 weeks of end of treatment or clearance if reinfected with a different genotype





Anti-HCV+ Anti-HCV+

ป้องกันการติดซ้ำ

HCV REINFECTION

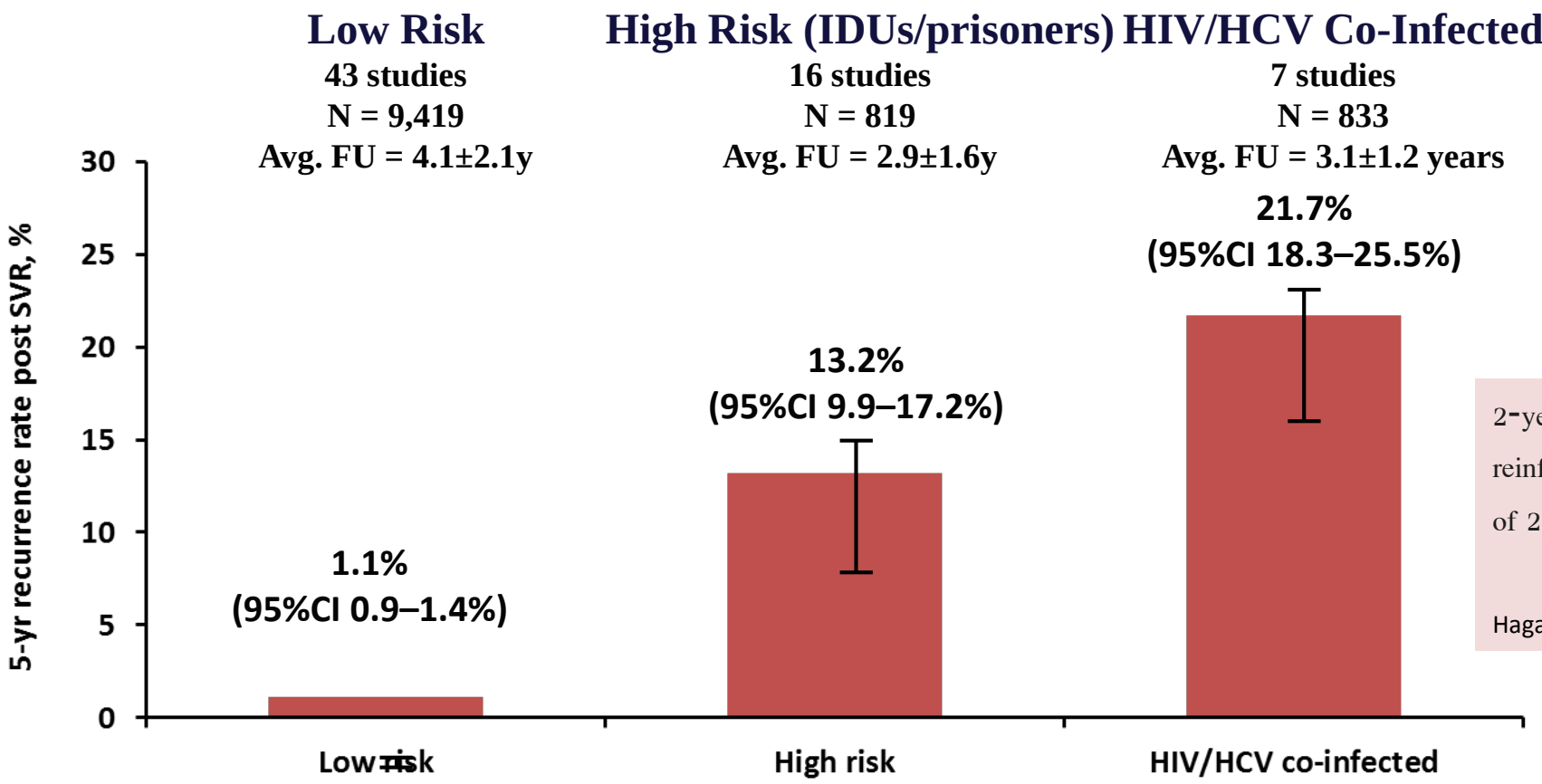
MSM IDU

HARM REDUCTION

Higher Risk of Late Relapse or Re-Infection among HIV/HCV: Meta-Analysis of 66 Studies in 11,071 Patients

How to monitor Reinfection? POC HCV RNA (quanlitative, quantitative)

Five-Year Rate (95%CI) of Recurrence Post-SVR, by Risk Group



2-year cumulative risk of reinfection of 25%-33%

Hagan H,AIDS 2015;29:2335-2345.

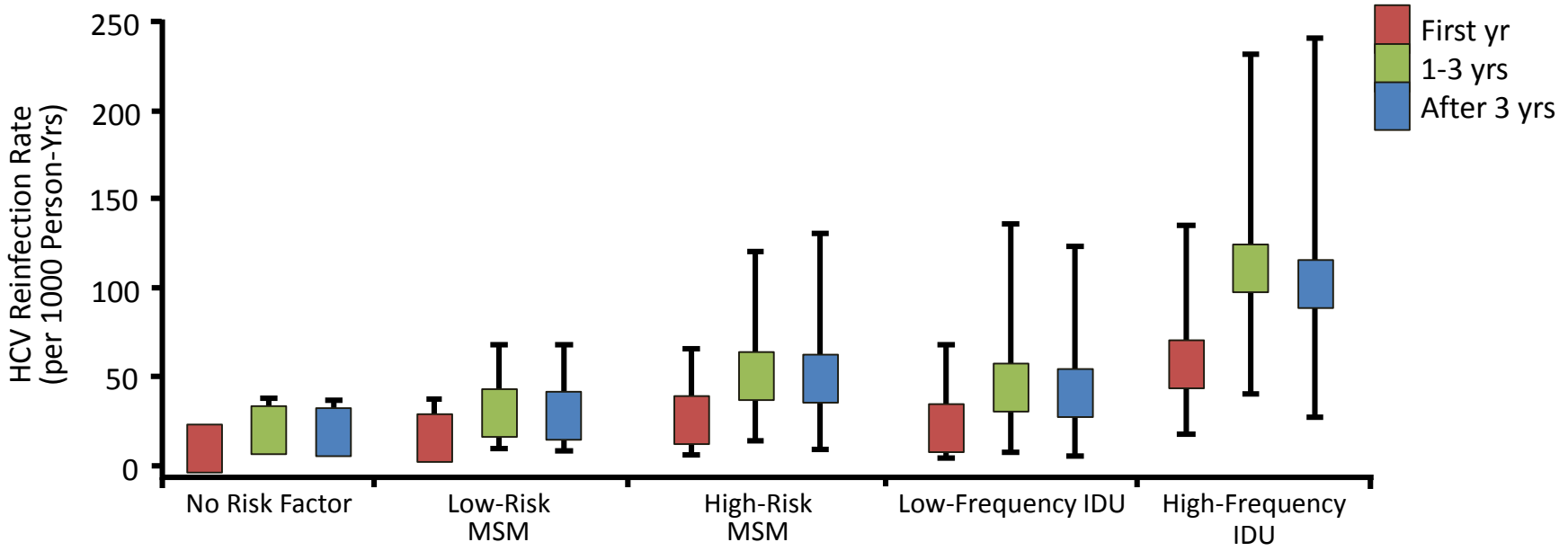
Hill AM Clin Infect Dis 2016;62:683-694.

In analyses of SVR durability, the incidence of late relapse is extremely low (<1%)

Young J, et al. Clin Infect Dis. 2017;64:1154-1162

HCV Reinfection Risk After SVR in HIV/HCV-Coinfected Pts

- Prospective cohort study of risk factors for HCV reinfection in HIV/HCV-coinfected pts achieving SVR (N = 257)



In analyses of SVR durability, the incidence of late relapse is extremely low (<1%)

Young J, et al. Clin Infect Dis. 2017;64:1154-1162.

The "MINMON" Approach : A5360

N=400

1. No pre-treatment genotyping
2. All 84 tablets dispensed at entry
3. No scheduled on-treatment clinic/labs
4. Remote contact at Weeks 4 and 22

Sustained virologic response: 95% (95% CI: 92.4, 96.7)

Wk 4: Adherence assessment

Wk 22: schedule SVR assessment

Week 0 4 8 12 16 20 22 24

Cirrhosis determination was based purely on FIB-4

ACTG AIDS CLINICAL TRIALS GROUP

HCV screening for all PLHIV
Be aware of acute HCV among MSM/HIV+, PreP users (MSM)
high extrahepatic manifestation among PLHIV

Take home message

HCV RNA : entry point of diagnosis and treatment

- Sofosbuvir/Velpatasvir
- Glecaprevir/Pibrentasvir
- Sofosbuvir+ daclatasvir
- Sofosbuvir/Velpatasvir/ Voxilaprevir – GT 1-6 (reserved for salvage therapy)

Diagnosis

Test and treat for all PLHIV, regardless of liver fibrosis

Linkage to care

Treatment

HIV and HCV drug-drug interaction

Cure

MSM/HIV+, MSM-PreP users:
- Counseling
- Harm reduction (injection and sex practices)
- **Surveillance for reinfection**

HCV core Ag
HCV VL

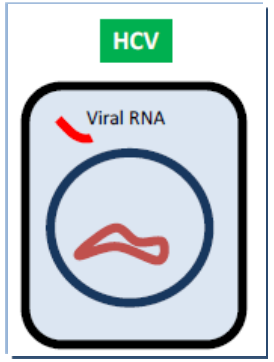
Persons with advanced fibrosis (stage 3/4)
- Counseling
- Harm reduction (alcohol and obesity)
- **Surveillance for HCC**

Characteristic	Follow-up After SVR
No advanced fibrosis (Metavir stage F0-F2), no or low risk of HCV reinfection	▪ Standard medical care, as in someone without HCV
Advanced fibrosis (Metavir stage F3 or F4) **FIB-4>3.25**	▪ Ultrasound surveillance for HCC every 6 mos ± AFP
Moderate to high risk of HCV reinfection	▪ Harm reduction ▪ HCV RNA every 12 mos

Falade-Nwulia O, et al. J Hepatol. 2017;66:267-269. AASLD/IDSA. HCV guidance. September 2017.

Summary

- ✓ All active HCV infected patients (acute/chronic) should be treated with oral DAA therapy
- ✓ The benefit of SVR goes way beyond improved outcome of liver disease
- ✓ High response rate (>95% SVR) similarly to HCV monoinfection
- ✓ Drug-drug interactions need to be considered prior to starting DAA
- ✓ High reinfection esp MSM HIV+, active IDU without harm reduction



- ✓ All patients initiating HCV DAA therapy should be assessed for HBV co-infection with HBsAg, antiHBs and anti HBc
- ✓ Cancer screening if advanced liver fibrosis/cirrhosis
- ✓ The main challenge in the DAA era for HCV cure is the improvement of screening and linkage to care