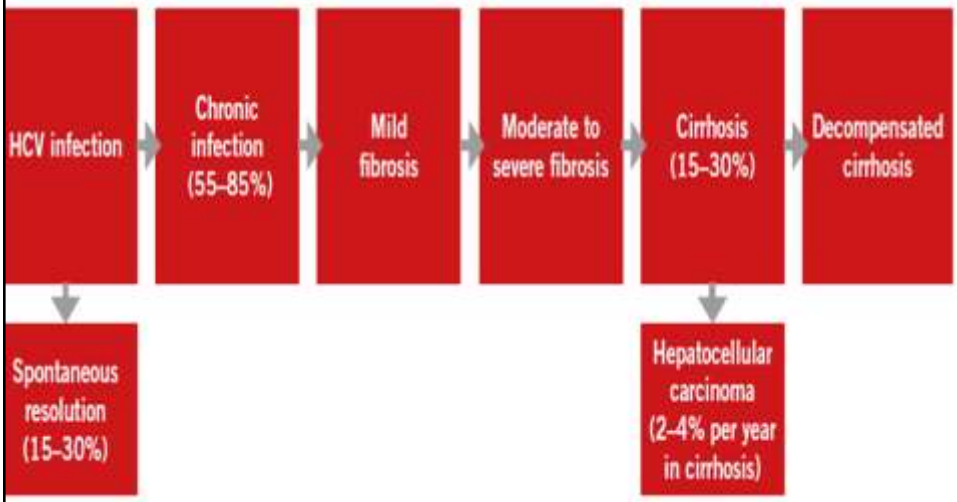
Anti HCV therapy cardiac pre-assessment

Dr. Aysar Abd Al Aziz, M.D
Ass. Prof. Military Medical academy

introduction

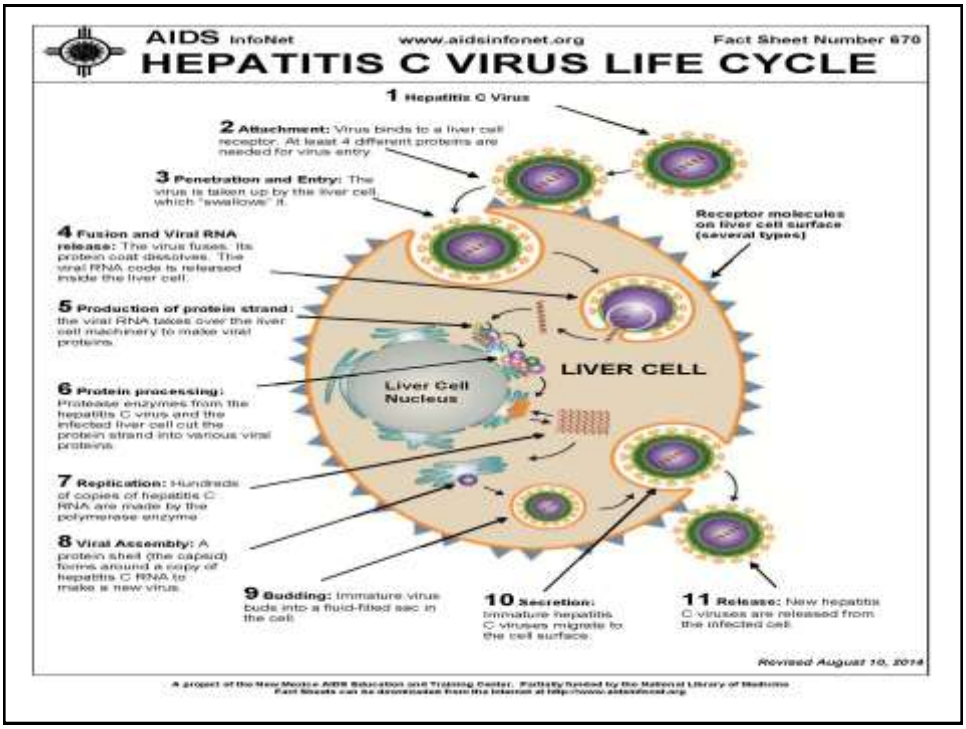
- Chronic HCV endemic in egypt
- About 12 percet of egyptian population are infected with HCV
- About 3 percent of world population (120-130 million)are infected with HCV
- 90 percent of HCV infection with geno type4 in egypt.
- The cornerstone of treatment is standered or pegylated interferon plus ribavirin but has more cardio-toxic effects
- Enterance of next generation of HCV with oral direct antiviral treatmen(DDAs) is expected fundamentally changes HCV treatment Algorithm

Natural History…



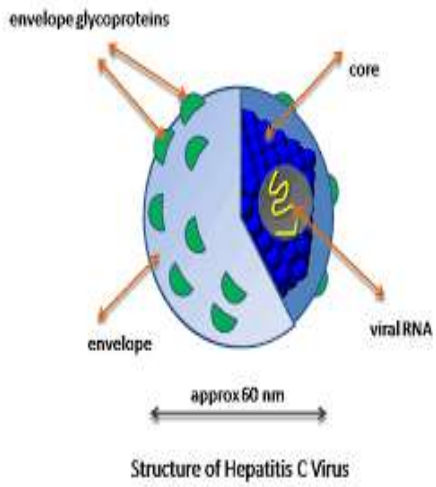
Extrahepatic manifestations of HCV include:

- cryoglobulinaemia,
- glomerulonephritis,
- thyroiditis
- Sjogren syndrome,.
- insulin resistance, type 2 diabetes,
- skin disorders such as porphyria cutanea tarda and lichen planus.
- cognitive dysfunction, fatigue and depression



The virus and distribution of genotypes

- The HCV is a small, positive stranded RNA-enveloped virus.
- It has a highly variable genome, which has been classified into six distinct Genotypic groups
- Genotype 1 is the most common, accounting for 46.2% of all HCV infections, followed by genotype 3 (30.1%)



Structure of Hepatitis C Virus

Goals of therapy:

Primary Goal :

- Eradicate HCV infection .

Secondary Goals:

- Slow disease progression
- Improve histology
- Reduce risk of Hepatocellular Carcinoma
- Improve health related Quality of life

Combination therapy:

- Interferon (standard or pegylated) taken with antiviral drug ribavirin (Virazole) is the treatment of choice for chronic hepatitis C.

Drug	Form	Recommended Treatment Regimn
Ribavirin (Rabetol) For viral genotype 1	Capsule	Weight 75 kg (165 lb) or greater: three 200-mg capsules twice daily (total daily dose of 1,200 mg)
		Weight less than 75 kg: two 200-mg capsules every morning and three 200-mg capsules every evening (total daily dose of 1,000 mg)
For genotype 2,3		All weights: two 200 mg capsules twice daily (total daily dose of 800 mg)

Treatment:

Treatment of Acute Hepatitis:

- Treatment of acute hepatitis C Include Alpha and Beta interferon Monotherapy.
- It significantly decreases the number of patients that become chronic carriers.

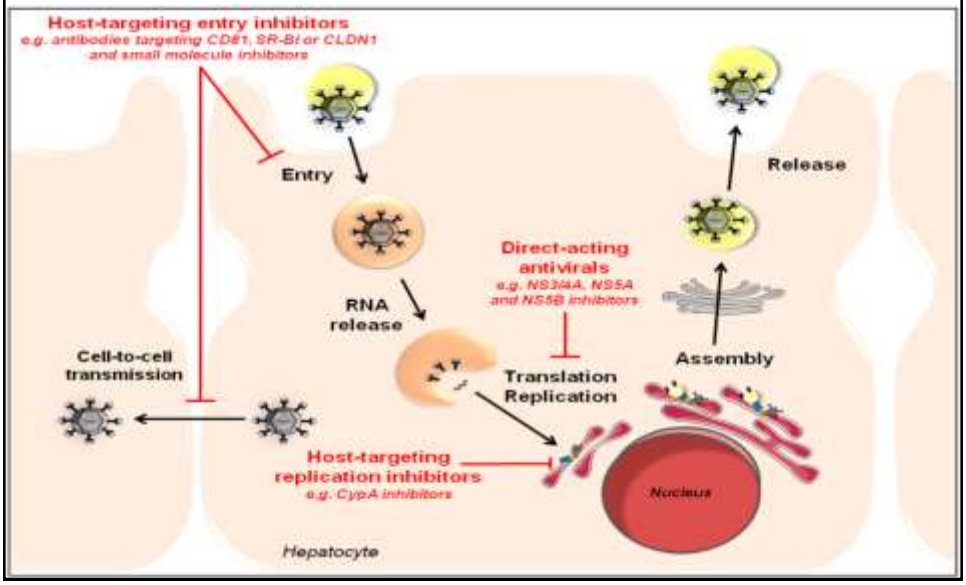
Acute Hepatitis C	Treatment
Genotype 1,2,3,4	Interferon Monotherapy
	Interferon+Ribavirin
	Peginterferon Monotherapy
	Peginterferon+Ribavirin

Therapeutic Uses:

- Peginterferon alpha is indicated for the treatment of patients with chronic hepatitis C who have compensated liver disease.

- Advantages over conventional Interferons:
- They have slower absorption
- Reduced distribution
- lower elimination rate
- Greater therapeutic efficacy
- The current recommendations include the use of a combination therapy with pegylated IFNalfa and ribavirin as the standard treatment.

Mechanism of Action:



Ribavirin (Virazole):

- It is an antiviral drug,a purine nucleoside analogue with a modified base and D-Ribose sugar.
- It inhibits the replication of wide range of RNA and DNA viruses.

Ribavirin side effects

- Birth defects
- Haemolytic anaemia
- Heart problems, arrhythmis,angina
- Decrease warfarin effect
- Pulmonary ebolism
- Digitalis toxcity

- Respiratory ,bronchospasm,bronchilitis,sinusitis

Interferon side effects

- Interferon adverse effects
- Myelo-suppressive
- Git troubles
- Cardiotoxic effects
- arrhythmias 58
- acute coronary syndrome 21
- cardiomyopathies 12
- pericarditis 9
- conductive disease 1
- Side effects are reversible except pulmonary hypertension serious and irreversible

ARRHYTHMIAS AFTER INTERFERON

- Arrhytmias considered 58 percent of INF cardiac side effects
- Several reports indicated an association between INF &arhythmias(direct cadiotoxic,secondary to endocrine-thyrioditis or pulmonary disease
- Some reports arrhy sub clinical,non sustained and reversible
- Another reports consider serious symptomatic arrhythmias brady (sinus brady-torsade de points)or tachy(sinus tachy ,Af,frequent PVCs)

Cardiac work up for evaluation &treatment for arrythmias

- ECG to dect type of arrythmias,
- Holter monitoring in symptomatic patient for fequent PVCs to assess PVCs burden~10 or hidden serious arrhytmias,.
- Echo to assess LV function ,apical ,septal hypertrophy
- LAB thyriod function,Na K
- Stop INF with serious arrhytmias,if associated with myocardial affection
- Modyfying the dose in symptomatic palpitation and not associated with structural heart affection

Pericarditis,myocarditis after INF for chronic HCV patient

- Chronic HCV may cause pericarditis and INF used to treat associated pericarditis
- Teragawa et al.1996 INF therapy could provocate of autoimmunity ,immune reaction may explain pericarditis and myocarditis.
- May produce Gravis disease ,sarciodosis,SLE like clinical data
- Pericarditis may occur seven months after starting therapy,but IN dialysis patient within two weeks.
- Myocarditis is serious side effects,cardiogenic shock,fatal sequence

Cardiac work up,treatment for pericarditis

- Some authers repoted if pericarditis and myocarditis is an extrahepatic cardiac manifestation,INF contraindicated as it may potentiate more autoimmune reaction.
- Others report that TTT with INF improve pericarditis when treating HCV
- If pericarditis,effusion ,or myocarditis during treatment with INF , stop INF is not enough but we need steriod therapy to treat autoimmune phenomenon
- Clinical exam ,ECG ,weekly echo ,lab data for SLE may help to detect early immune reaction

Acute coronary syndrome,INF ,Ribvirin therapy

- ACS are among rare HCV infection therapy,INF vasospasm.,or febrile reaction that increase oxgen demand
- Sudden onset of haemolysis and anaemia of ribavirin may cause myocardial infarction in pre –excisting CAD,,CVS patients

Cardiac work up&management of ACS

- High risk patient whom in active CAD,.or recent stroke
- Ribaverin & INF in HCV ttt should alert the physicians for dose modification (serious consideration)
- Strict patient and family awareness about anginal symptoms,weekly ECGs ,echo
- Weeky CBC for ealy haemolysis detection and anaemia

Hepatitis c virus has been proven to be a risk factor for coronary artery disease
The usual way to reduce heart disease risk is insuffcient for those with virus.
Researcher suggested that this elevated cardiovascular risk could be due to incresed inflamation,immune activation,and blood clotting in peaple wih HCV
Any choice to inhibit HCV will benefit lier and heart

Cardiomyopathies,&INF for chronic HCV treatment

- HCV has been reportedely associted with cardiomyopathy
- INF has been suggested for TTT of HCV associated cardiomyopathy
- INF therapy has reported to induce PW & septal hypertrophy,also may produce dilated cardiomyopathy
- INF may iduce microvascular injury for myocardial and may pericipitate or augment rate of cardiomyopathies specially in dilated cardio-myopathic patient
- Retinopathy is microvascular complication and associated with INF induced cardiomyopathy,

Cardiac workup for INF induced cardiomyopathy

- History ,clinical exam.
- Echo LV dimensions,follow up
- Fundus Exam for retinopathy
- Labs,CK ,CKMb,Trop T ,N terminal pro BNP to follow myocardial affection
- Individualised for every patient may stop INF ,may re-administrate with dose modification
- Routine antifalure management,Strict control BP to imprve retinopathy
- Reversible side effects with tratment and after therapy cessation

Pulmonary injury &INF therapy for HCV

- Pulmonary dysfunction due to INF therapy with spirometric changes FEV1/FVC
- Broncheolitis obliterans,organizing pneumnias,Interstatial pneumonitis and these are reversible side effects of INF therapy
- Pulmonary hypertension is irreversible side effects

Cardiac work up&management for pulmonary injury

- History,.clinical exam.
- CXR-CT chest
- ECG RV strain
- Echo RVSP/RT side study
- Spirometery
- Stop interferon with increasing PAP because irreversible severe pulmonary hypertension

Does Treatment Work???

Interferon alone:

- 10 – 15% chance of clearing the virus from the blood

Interferon & ribavirin:

- Up to 40% chance of clearing the virus

Pegylated interferon alone:

- About the same as interferon & ribavirin 40%

Pegylated interferon & ribavirin:

- Up to 50% chance of clearing the virus

The newly developed Directly Acting Antivirals –

DAAs - acts only at the virus Level with no effect

on the host immune system i.e the host immunity

is passive during these new lines of therapy

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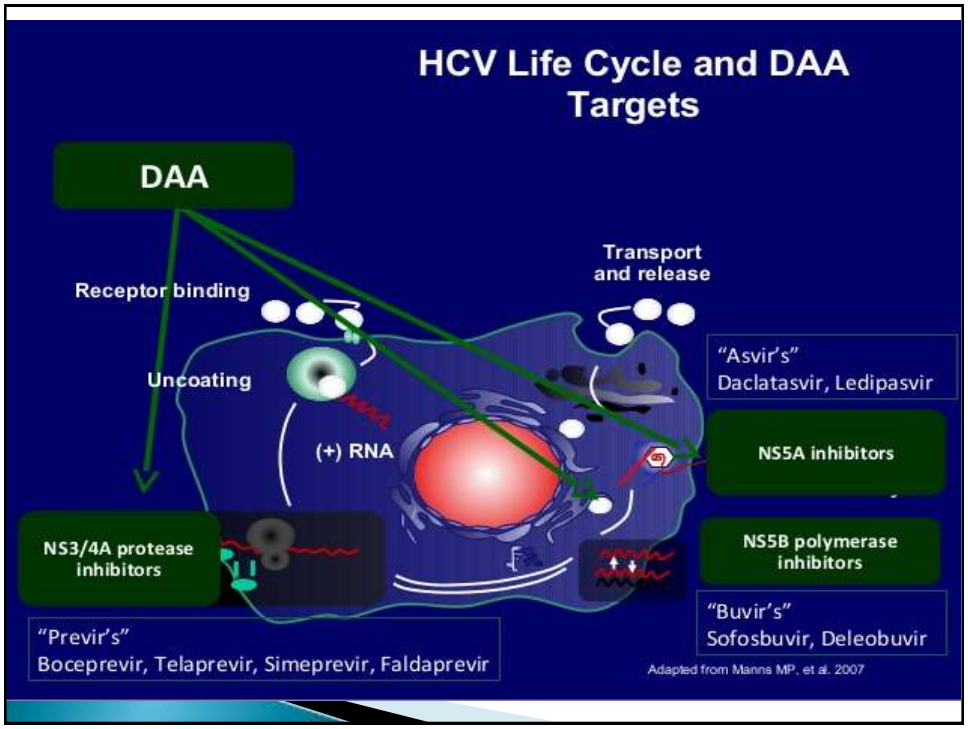
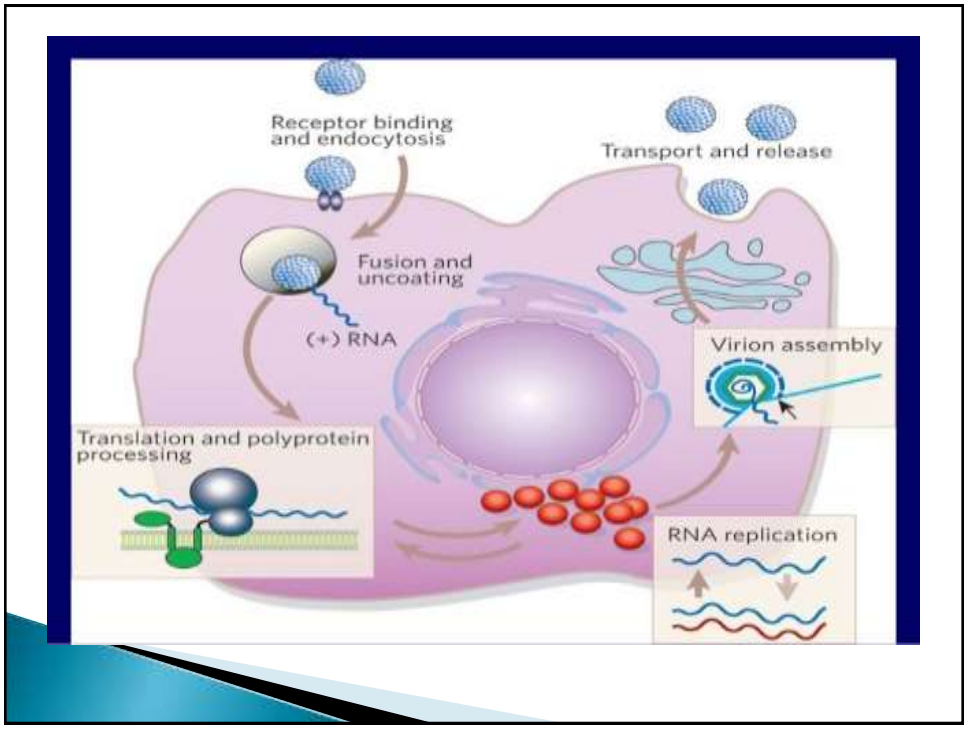
The Direct Acting Anti-viral Agents….

- Oral medicines that directly inhibited the replication cycle of HCV.
- They target three important regions within the HCV genome: NS3/4A protease, NS5A and NS5B RNA-dependent polymerase.
- These medicines
  - have higher sustained virological responses (SVRs) than interferon-based regimens,
  - are shorter in treatment duration,
  - are orally administered and
  - have fewer side-effects


HCV Life Cycle and DAA Targets
DAA
Receptor binding
Uncoating
(+) RNA
Transport and release
"Asvir's"
Daclatasvir, Ledipasvir
NS5A inhibitors
NS5B polymerase inhibitors
"Buvir's"
Sofosbuvir, Deleobuvir
NS3/4A protease inhibitors
"Previr's"
Boceprevir, Telaprevir, Simeprevir, Faldaprevir
Adapted from Manns MP, et al. 2007


Receptor binding and endocytosis
Transport and release
Fusion and uncoating
(+) RNA
Virion assembly
Translation and polyprotein processing
RNA replication

lasses of DAAs licensed for the treatmen f HCV (as of October 2015)

Protease (NS3/4A) inhibitors	NS5A inhibitors	Polymerase (NS5B) inhibitor, nucleos(t)ide analogue	Polymerase (NS5B) inhibitor, non-nucleoside analogue
Asunaprevir	Daclatasvir	Sofosbuvir	Dasabuvir
Paritaprevir	Ledipasvir		
Simeprevir	Ombitasvir		

Older Direct acting Antivirals(DAA).

Boceprevir & Telaprevir:

- Boceprevir and Telprevir are **Pretease inhibitor.**
- Developed in May of 2011, boceprevir and telprevir were the first drugs to act directly on the HCV virus.
- Boceprevir and teleprevir increased the cure rate for HCV genotype 1 to 70%.
- A treatment regime with boceprevir or telaprevir, with interferon and ribavirin lasts 24–48 weeks.

Removal of recommendation for treatment with telaprevir or boceprevir

New recommendation

The use of boceprevir- or telaprevir-containing regimens is no longer recommended for the treatment of persons with hepatitis C infection.

Strong recommendation, moderate quality of evidence

Summary of recommended preferred regimens with treatment durations

Persons with cirrhosis

	Daclatasvir/ sofosbuvir	Daclatasvir/ sofosbuvir/ ribavirin	Ledipasvir/ sofosbuvir	Ledipasvir/ sofosbuvir / ribavirin	Sofosbuvir/ ribavirin
Genotype 1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 2					16 weeks
Genotype 3		24 weeks			
Genotype 4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
Genotype 5			24 weeks	12 weeks[b]	
Genotype 6			24 weeks	12 weeks[b]	

Summary of recommended preferred regimens with treatment durations

Persons without cirrhosis

	Daclatasvir/ sofosbuvir	Ledipasvir/ sofosbuvir	Sofosbuvir/ ribavirin
Genotype 1	12 weeks	12 weeks[a]	
Genotype 2			12 weeks
Genotype 3	12 weeks		24 weeks
Genotype 4	12 weeks	12 weeks	
Genotype 5		12 weeks	
Genotype 6		12 weeks	

Contraindications/warnings: Therapy with direct-acting antivirals:

Drug	Contraindication/warning
Ledipasvir/sofosbuvir	• Amiodarone co-administration • P-glycoprotein (gp) inducers • Renal failure (eGFR <30 mL/min/1.73 m^2)
Daclatasvir	• Drugs inducing or inhibiting CYP3A
Sofosbuvir	• Amiodarone co-administration (caution also with beta-blockers) • Renal failure (eGFR <30 mL/min/1.73 m^2)
Ombitasvir/dasabuvir/ paritaprevir/ritonavir or ombitasvir/dasabuvir/ ritonavir	• Child–Pugh Class B and C cirrhosis • Drugs inducing or inhibiting CYP3A or CYP2C8 • Hypersensitivity to any component including ritonavir • Untreated HIV-1 infection because ritonavir can lead to antiretroviral drug resistance
Simeprevir	• Child–Pugh Class B and C cirrhosis • CYP3A interaction

Direct Acting Antivirals DAAs

I Generation **2011**

Boceprevir (Victrelis)
Telaprevir (Incivek, Incivo)

II Generation **2013-2014-2015-2016**

Simeprevir (Olisio)
Sofosbuvir (Sovaldi)
Daclatasvir (Daklinza)
Dasabuvir (Exviera)
Sofosbuvir/ledipasvir (Harvoni)
Ombitasvir/Paritaprevir/Ritonavir +dasabuvir (Viekira PaK)
Ombotasvir/Paritaprevir/Ritonavir **(Viekirax)**
Grazoprevir/Elbasvir (Zepatier)
Sofosbuvir/Velpatasvir (Epclusa) 2016 July

Drug-drug interactions between HCV DAAs and CVS drugs

		SIM	DCV	SOF	SOF/LDV	3D
Antiarrythmics	Amiodarone	•	•	•	•	•
	Digoxin	•	•	•	•	•
	Flecainide	•	•	•	•	•
	Vernakalant	•	•	•	•	•
Antiplatelet and anticoagulants	Clopidogrel	•	•	•	•	•
	Dabigatran	•	•	•	•	•
	Warfarin	•	•	•	•	•
Beta blockers	Atenolol	•	•	•	•	•
	Bisoprolol	•	•	•	•	•
	Propranolol	•	•	•	•	•
Calcium channel blockers	Amlodipine	•	•	•	•	•
	Diltiazem	•	•	•	•	•
	Nifedipine	•	•	•	•	•
Hypertension and heart failure agents	Aliskiren	•	•	•	•	•
	Candesartan	•	•	•	•	•
	Doxazosin	•	•	•	•	•
	Enalapril	•	•	•	•	•

Drug-drug interactions between HCV DAAs and lipid lowering drugs

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

Cardiac work up

- Full history
- Current medication
- Clinical exam
- Las Total ck,Ckmb,tropinin ,urea ,creat,liver
- ECG ,corected QT,arrhytmias,conduction problem
- Echo LV diameter(ESD-EDD-IVS-PW-EF)
- Spirometer for respiratory function tests
- Fundus exam

conclusion

- Most cardio- toxic effects are due interferon - ribavirin protocols.
- Interferon free regimens with New DAAs more effective treatment for chronic HCV with less cardio-toxic effects
- So cardiac extrahepatic side effects of chronic HCV virus can be treated with new DAAs ,INF free protocols.
- New DAAs combination with cordarone may induce serious brady -cardia that may need pacemaker
- For cardiologist the most important point is cardiac drug -drug interaction.

- Increase effect of digtalies that may lead to toxcity with New DAAs
- New DAAs increses myopathy when combined with statines
- New DAAs has no drug interaction with warfarin
- New DAAs cardiac side effects is irreversible

Thank you