EPIDEMIOLOGY:

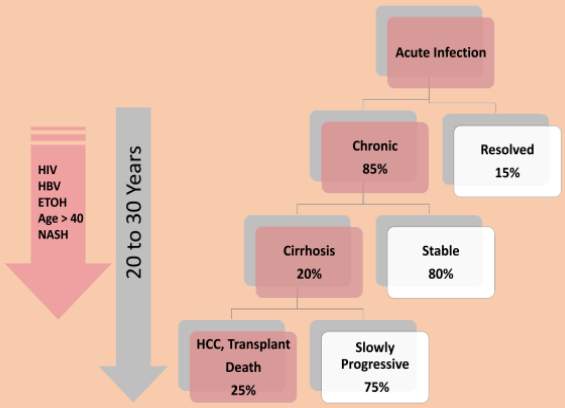
- 180 million people infected worldwide
  - Most infected 20-40 years ago before virus identification and screening
- HCV is a leading cause of hepatocellular carcinoma (HCC)
  - 22% of new cases of all HCC per year are attributed to HCV
- 350,000 deaths per year

HCV TRANSMISSION: blood to blood contact

PERCUTANEOUS	• Injection drug use
	  ○ Highly efficient mode of transmission
	  ○ Prevalence 50-90% of after 5 years
	• Transfusion, transplant from infected donor
	  ○ Prior to 1992
	• Nosocomial transmission
	  ○ Contaminated equipment
	  ○ Unsafe injection practices
	  ○ Occupational (needle-stick)

PERMUCOSAL	• Perinatal • Sexual

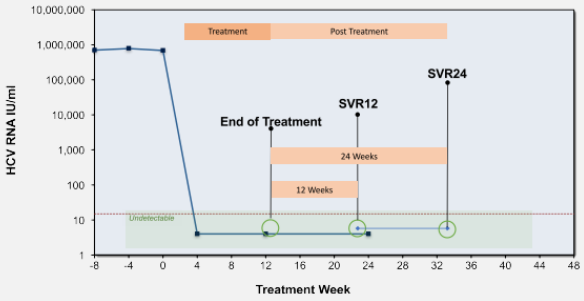
NATURAL HISTORY OF HCV INFECTION:



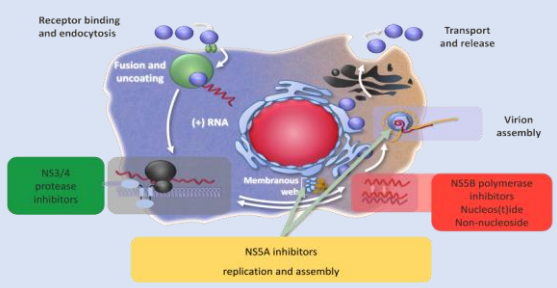
METAVIR STAGES OF HEPATIC FIBROSIS:

NO FIBROSIS	F0	No fibrosis
MILD FIBROSIS	F1	Fibrous Portal Expansion
MODERATE FIBROSIS	F2	Few bridges or septa
SEVERE FIBROSIS	F3	Numerous bridges of septa
CIRRHOSIS	F4	Cirrhosis

SUSTAINED VIROLOGIC RESPONSE (SVR) = marker for CURE



HCV LIFE CYCLE: targets for direct-acting antivirals (DAAs)



PEG-IFN/RBV ADVERSE REACTIONS:

INTERFERON *Up to 85% of pts have contra-indications for INF therapy!!*	**Systemic**	• **Flu-like symptoms** (muscle aches, headaches, nausea, vomiting, loss of appetite, fever, chills)
	Mood	• Insomnia, **depression,** personality changes, forgetfulness, irritability, anxiety
	Endocrine	• Hypo- or hyper-thyroidism
	Dermatologic	• Rash, dry, itchy skin; hair loss
	GI	• Nausea, diarrhea, anorexia, weight loss
	HEME	• Mild bone marrow suppression → **leucopenia, thrombocytopenia**
RIBAVIRIN	• **Anemia (34%)** • Dizziness • Fatigue • Nausea	• Itchiness • Dry skin • RESP problems: mild SOB, nasal or sinus congestion, cough

DIRECT-ACTING ANTIVIRAL AGENTS (DAAs):

NS3 Protease Inhibitors "…PREVIR"	Potency	• High
	Coverage	• Multigenotypic to pangenotypic ○ 2nd gen (voxil- & gleca- previr) = pan
	Resistance	• Low barrier to resistance
	CI	• Decompensated cirrhosis (Child-Pug Class B or C)
	ADRs	• Rash, photosensitivity, fatigue • ↑ bilirubin with 1st gen ○ Minimal with 2nd gen
	DDIs	• Moderate to high potential • Less with second generation drugs
NS5A Replication Complex Inhibitors "…ASVIR"	Potency	• High
	Coverage	• Multigenotypic to pangenotypic ○ 2nd gen (velpat- & pibrent- asvir) = pan
	Resistance	• Low barrier to resistance
	ADRs	• Unkniwn, but combo therapies well tolerated
	DDIs	• Low to moderate potential • **Acid reducing therapies decrease absorption**
NS5B Nucleotide Inhibitors (NI) *Sofosbuvir*	Potency	• Intermediate
	Coverage	• Pangenotypic
	Resistance	• High barrier to resistance
	CI	• Renally eliminated = **not recommended in pts with mod-severe renal impairment** (CrCl < 30)
	ADRs	• Fatigue, nausea, headache
	DDIs	• Low potential • Do not co-admister with **amiodarone** due to risk of serious bradycardia
NS5B Non-NI Inhibitors *Dasabuvir*	Potency	• Intermediate
	Genotypic	• Limited genotypic coverage
	Resistance	• Low barrier to resistance

FACTORS DETERMINING HCV TREATMENT REGIMEN:

- **GENOTYPE:** 1a, 1b, 2, 3, 4, 5, 6
- **TREATMENT HISTORY:** treatment naïve or experienced
- **FIBROSIS SCORE:** mild to moderate fibrosis vs. cirrhosis

DAA REGIMENS:

Regimen	Type	Geno-type	Txt (wks)	Previous DAA txt	RBV *	DDI	CKD	CP BC
SOF/LDV	NS5B + NS5A-I	1, 4, 5, 6	8-12	No	TE, CC*	+	X	√
GZR/EBR	NS3/4A PI + NS5A-I	1, 4, 6	12-16	No	TE with PI baselines, RAVs	+++	√	X
SOF/VEL	NS5B + NS5A-I	All	12	No	DC only, TE Gt3	+	X	√
GLE/PIB	NS3/4A PI + NS5A-I	All	8-16	Yes	No	++	√	X
SOF/VEL/ VOX	NS5B + NS5A-I + NS3/ 4A PI	All	12	Yes	No	++	X	x

SOFOSBUVIR (NS5B) / **LEDIPASVIR** (NS5A) : HARVONI

APPROVED	• Health Canada approval Oct 2014
INDICATION	• Treatment of chronic HCV genotype 1,4,5,6 in adults
CLASS & MOA	• **Ledipasvir:** NS5A inhibitor • **Sofosbuvir:** nucleotide analog NS5B polymerase inhibitor
DOSING	• SOF/LVD 400/90 mg one table orally once daily • With or without food
DURATION	• Txt naïve with or without cirrhosis: 8-12 weeks • Txt experienced without cirrhosis: 12 weeks • Txt experienced with cirrhosis: 24 weeks or 12 weeks + RBV
ADRs	• Fatigue, headache
DDIs	• **SOF:** P-gp substrate (rifampin, antiepileptics, SJS) • **LVD:** acid reducing therapy (PPIs, H2 blockers)

GRAZOPREVIR (NS3/4A) / **ELBASVIR** (NS5A) : ZEPATIER

APPROVED	• Health Canada approval Jan 2016
INDICATION	• Treatment of chronic HCV genotype 1 or 4 • Contraindicated in pts with decompensated cirrhosis
CLASS & MOA	• **Elbasvir** NS5A inhibitor • **Grazoprevir:** NS3/4A inhibitor
DOSING	• GZR/EBR 100/50 mg one tablet orally once daily • With or without food
DURATION	• Without baseline NS5A polymorphisms: 12 weeks • With baseline NS5A polymorphisms: 16 weeks
ADRs	• Fatigue, headache, nausea • Increase in ALT > 5x normal in 1% of subjects
DDIs	• **EBR & GZR:** substrates of CYP3A and P-gp o Co-administration of mod and strong CYP3A inducers and inhibitors are contraindicated • **GZR:** substrate of OATP1B1/3 + weak CYP3A inhibitor

SOFOSBUVIR (NS5B) / **VELPATASVIR** (NS5A) = EPCLUSA

APPROVED	• Health Canada approval Jul 2016
INDICATION	• Treatment of chronic HCV genotype 1-6 in adults o Without cirrhosis or with compensated cirrhosis (CP A) o With decompensated cirrhosis (CP B-C) + RIBAVIRIN
CLASS & MOA	• **Sofosbuvir:** NS5B polymerase inhibitor • **Velpatasvir:** 2nd generation NS5A inhibitor o Pangenotypic and improved resistnace profile
DOSING	• SOF/VEL 400/100 mg one tablet orally once daily o With or without food • RBV: < 75 kg = 1000 mg, ≥ 75 kg = 1200 mg, divided BID
DURATION	• Non-cirrhotic or compensated cirrhosis: 12 weeks • Decompensated cirrhosis: 12 weeks with RIBAVIRIN
ADRs	• Headache, fatigue, nausea
DDIs	• **SOF & VEL:** p-gp substrate (rifampin, AEDs, SJS), amiodarone • **VEL:** acid reducing therapy

RIBAVIRIN CONSIDERATIONS:

- Most patients won't need it!
- If they do….
  - Discuss contraception
  - Check baseline hemoglobin and test for anemia throughout treatment
  - Dosage adjustment for renal dysfunction
  - In cirrhosis, start low and titrate up as tolerated
  - Counsel on anemia symptoms
    - Anemia can be managed for most while completing HCV therapy (dosage reduction and PRBC transfusions)

IMPACT OF ACID REDUCING AGENTS ON BIOAVAILABILITY OF VARIOUS DAAs:

- A significant percentage of patients with HCV take acid reducing agents
- Most acid reducing agents can be obtained by the patients without prescription
- Some medical conditions require long-term treatment with acid reducing agents
  - Refractory GERD
  - Erosive esophagitis
  - Zollinger-Ellison Syndrome
  - NSAID-induced ulcers
  - Chronic anticoagulation after GI bleed
  - Barrett's esophagus
- Assess whether ARA can be safely discontinued
  - If not, select a DAA regimen least affected by ARA
  - Use the lowest dose and potency ARAs

GLECAPREVIR (NS3/4A) – **PIBRENTASVIR** (NS5A) : MAVIRET

APPROVED	• Health Canada approved Aug 2017	
INDICATION	• Treatment naive patients genotypes 1-6 without cirrhosis or with compensated cirrhosis • HCV genotype 1 previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, ***but not both***	
CLASS & MOA	• **Glecaprevir:** NS3/4A protease inhibitor • **Pibrentasvir:** NS5A inhibitori	
DOSING	• GLE/PIB 300/120 mg total dose • **Three** tablets orally once daily WITH FOOD	
DURATION	Txt naïve with no cirrhosis	8 wks
	Txt naïve with compensated cirrhosis	12 wk
	Genotype 1 treated with NS5A inhibitor	16 wk
	Genotype 1 treated with NS3/4A PI	12 wk
	Genotype 1, 2, 4, 5, 6 treated with PEG + RIB +/- sofosbuvir (no cirrhosis)	8 wk
	Genotype 1, 2, 4, 5, 6 treated with PEG + RIB +/- sofosbuvir (compensated cirrhosis)	12 wk
	Genotype 3 txt w/ PEG + RIB +/- sofosbuvir	16 wk
ADRs	• Most common headache and fatigue	
DDIs	• Substrates of CYP3A4, BCRP and P-gp o Rifampin, carbamazepine, CSA • Weak inhibitor: CYP3A4, P-gp and OATP 1B1/3 o ↑ digoxin, EE, dabigatran, statins	

SOFOSBUVIR / VELPATASVIR / VOXILAPREVIR : VOSEVI

APPROVED	• Health Canada approved Aug 2017
INDICATION	• Adult patients without cirrhosis or with compensated cirrhosis • Genotype 1-6 infection previously treated with an HCV regimen containing an NS5A inhibitor • Genotype 1-4 infection previously treated with HCV regimen containing sofosbuvir **without** an NS5A inhibitor
CLASS & MOA	• **Sofosbuvir:** NS5B inhibitor • **Voxilaprevir:** NS3/4A protease inhibitor • **Velpatasvir:** NS5A inhibitor
DOSING	• SOF/VEL/VOX 400/100/100 mg • one tablet taken orally once daily with food
DURATION	12 weeks for all treatment
ADRs	• Most common headache, fatigue, N/D
DDIs	• Similar to **SOF/VEL** (EPCLUSA) • **VOX:** substrate and inhibitor of P-gp, BCPR and OATP 1B1/3 o Coadministration with BCRP substrates not recommended (MTX, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine)

GOAL IS ELIMINATION OF HEPATITIS C INFECTION:

- 2030 WHO Targets
  - 90% diagnosed
  - 80% treated
  - 65% reduced mortality