

# Nuove frontiere nella gestione dell'epatite C nel detenuto co-infetto HIV-HCV.



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Cagliari - 04 Giugno 2015

## Clinical Practice Guidelines

## CIRRHOSIS

## Patients with HIV coinfection

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- Individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)

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Treatment is justified

- Patients with moderate fibrosis (F2)

Treatment can be deferred

- Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations

Treatment is not recommended

- Patients with limited life expectancy due to non-liver related comorbidities

# Co-infezione HIV-HCV

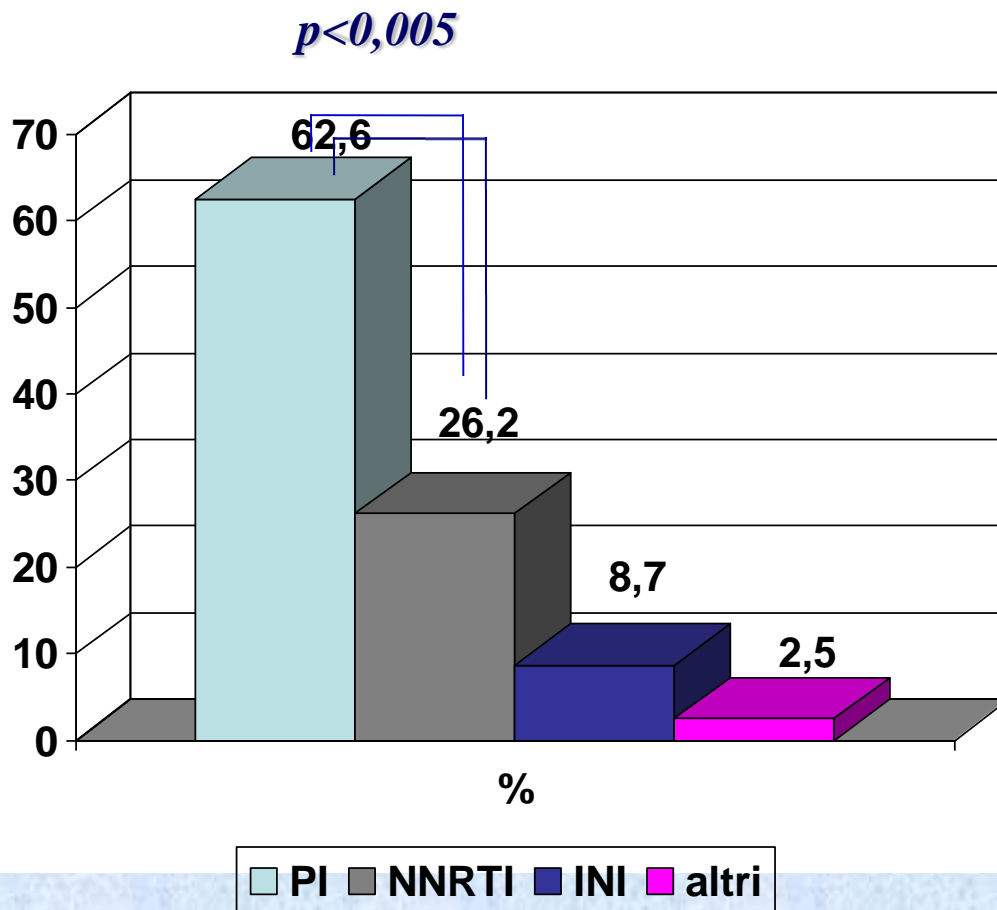
- **Frequente co-infezione con HCV**
- **Nostro Istituto fino a 7 aa fa: 91%**
- **Nostro Istituto fino ad oggi: 80,6%**
- **Nostro Istituto il 23 Gennaio u.s.: 73,1%**
- **PrHep 1 (dati preliminari): dal 42% al 76%**
- **Progetto CCM: 51,6%**



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# Indagine puntuale su persone detenute in Italia [SIMIT-SIMSPe 07/2013]

**Regimi Antiretrovirali  
somministrati  
a 275 detenuti in terapia  
Antiretrovirale**



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ANTIRETROVIRAL DRUGS	n (%)
<b>Protease inhibitors (PI)</b>	
Atazanavir	88 (32.0%)
Lopinavir	51 (18.5%)
Darunavir	23 (8.4%)
Fosamprenavir	9 (3.3%)
Saquinavir	1 (0.4%)
Total	172 (62.6%)
<b>Non nucleoside reverse transcriptase inhibitors (NNRTI)</b>	
Efavirenz	50 (18.2%)
Nevirapine	9 (3.3%)
Rilpivirine	8 (2.9%)
Etravirine	5 (1.8%)
Total	72 (26.2%)
<b>3 Nucleoside Reverse Transcriptase Inhibitors (NRTI)</b>	
Abacavir-Lamivudine-Zidovudine	6 (2.2%)
<b>Integrase inhibitors (INI)</b>	
Raltegravir	24 (8.7%)
<b>CCR5 inhibitors</b>	
Maraviroc	1 (0.4%)
<b>NRTI backbone</b>	
Tenofovir disoproxilfumarate-emtricitabine	194 (70.5%)
Abacavir-lamivudine	41 (14.9%)
Zidovudine-lamivudine	12 (4.4%)
Other	28 (10.2%)

# Le terapie antiretrovirali - CCM

Combinazione	N	%
2 NRTI + PI	145	62,8
2 NRTI + NNRTI	48	20,8
Raltegravir + PI	14	6,1
2 NRTI + INI	5	2,1
3 NRTI	4	1,7
Altre combinazioni	15	6,5
Totale	231	100

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# AASLD/IDSA Guidance for HIV/HCV Coinfection

- Same recommendations as in HCV-monoinfected patients, but consider drug–drug interactions
  - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Avoid LDV if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PI
  - OMV/PTV/RTV + DSV can be used with raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, atazanavir
  - SMV can be used with: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir
- Other interactions at [aidsinfo.nih.gov/guidelines](http://aidsinfo.nih.gov/guidelines), [hiv-druginteractions.org](http://hiv-druginteractions.org)

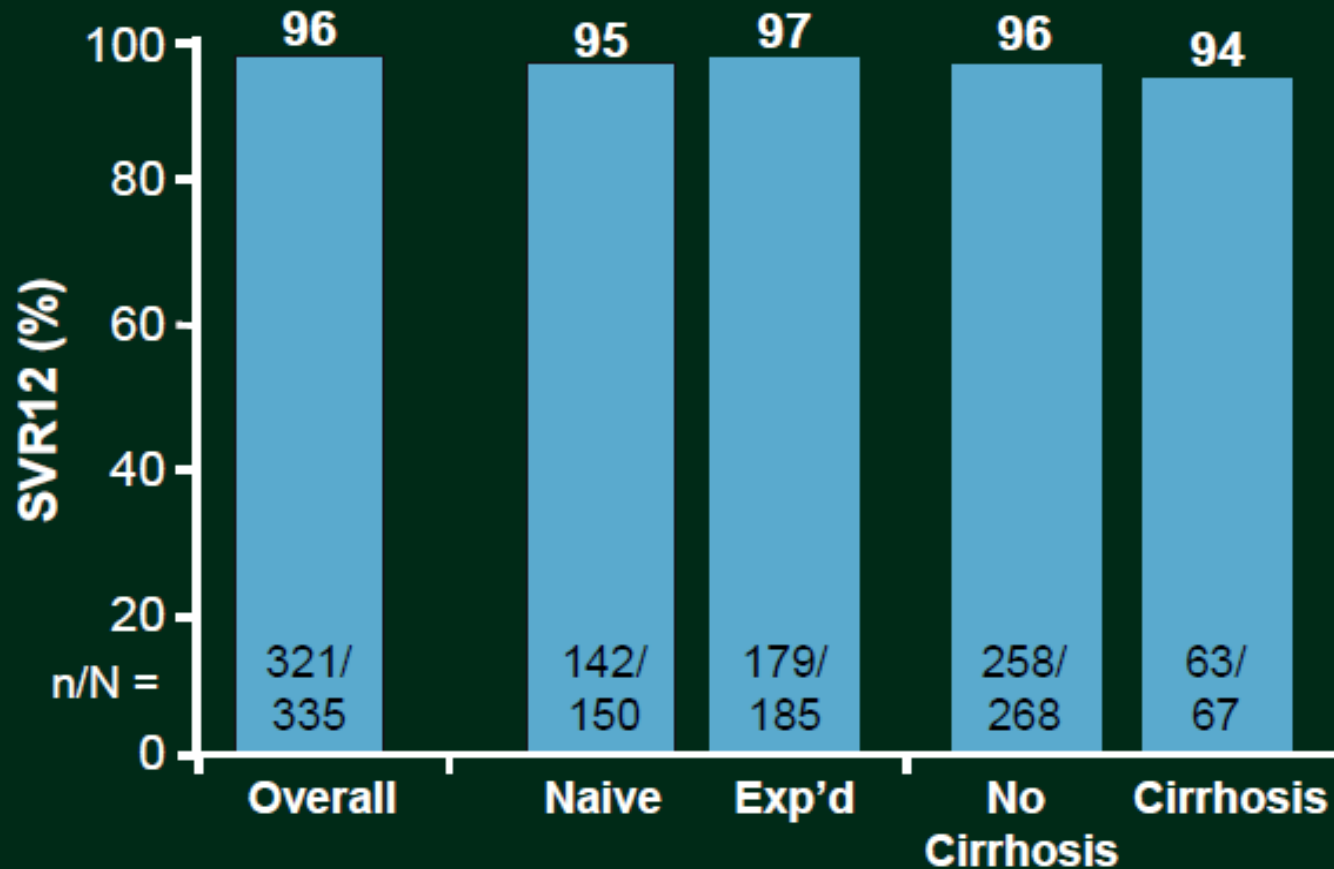
AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C.

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# ION-4: LDV/SOF for 12 Wks in HCV/HIV-Coinfected Patients

- GT1 or 4 HCV, 20% with compensated cirrhosis, 55% treatment experienced

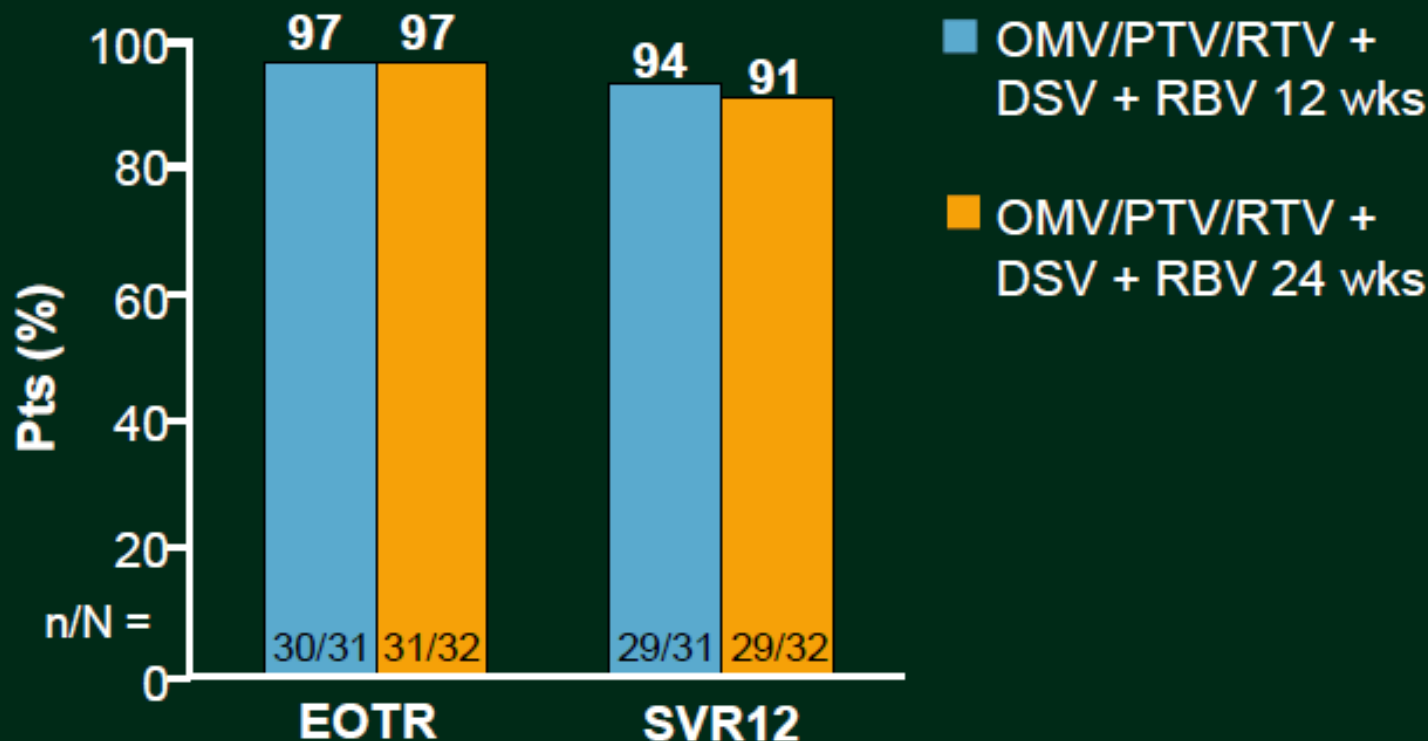


Naggie S, et al. CROI 2015. Abstract 152LB.

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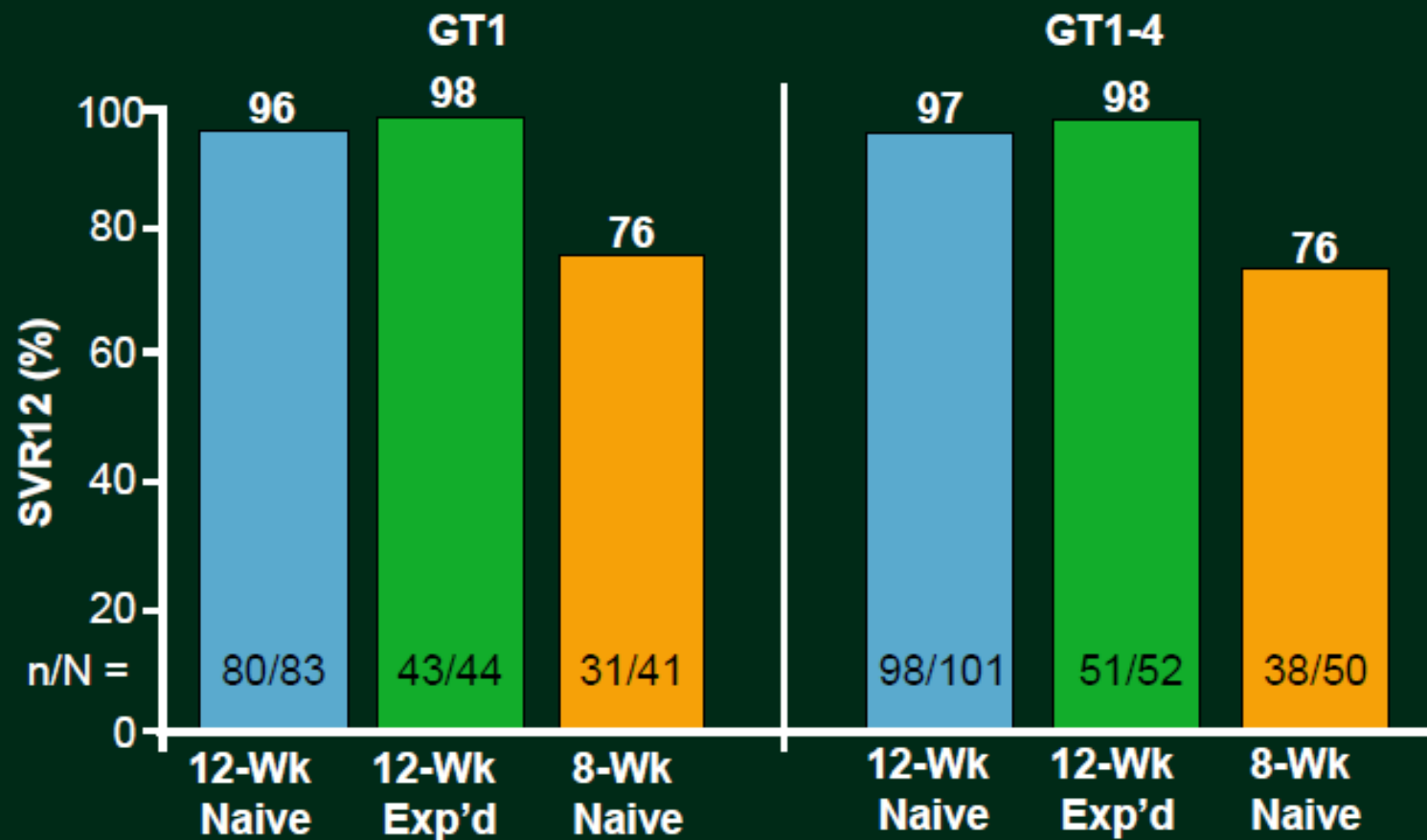
# TURQUOISE-1: OMV/PTV/RTV + DSV+ RBV for 12 vs 24 Wks in GT1 HCV/HIV Coinfection



- 65% HCV treatment-naïve pts in 12-wk arm, 69% in 24-wk arm
- 19% patients with METAVIR F4 fibrosis

Sulkowski M, et al. JAMA. 2015;313:1223-1231.

# ALLY-2: SOF + DCV in HCV/HIV- Coinfected Patients



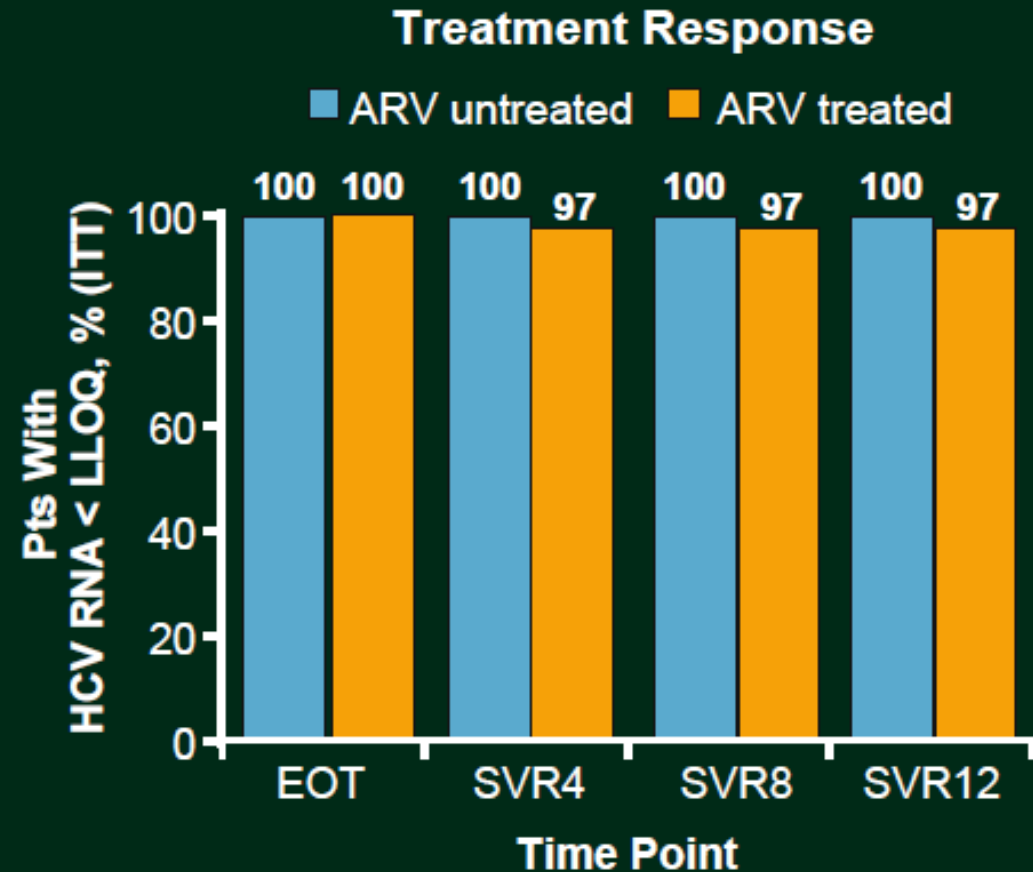
- 12 pts with relapse, 10 in 8-wk arm

Wyles DL, et al. CROI 2015. Abstract 151.

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# ERADICATE: SOF/LDV in HCV Tx-Naïve, Noncirrhotic HCV/HIV-Coinfected Pts

- Nonrandomized, open-label phase II study in HCV/HIV-coinfected noncirrhotic pts with GT1 HCV
  - 13 ARV-untreated pts
  - 37 pts with HIV-1 RNA suppression on TDF/FTC with EFV, RAL or RPV



Townsend KS, et al. AASLD 2014. Abstract 84.

Table 3. Approved HCV drugs in the European Union in 2015.

Product	Presentation	Posology
PegIFN- $\alpha$ 2a	Solution for injection containing 180, 135 or 90 $\mu$ g of PegIFN- $\alpha$ 2a	Once weekly subcutaneous injection of 180 $\mu$ g (or less if dose reduction needed)
PegIFN- $\alpha$ 2b	Solution for injection containing 50 $\mu$ g per 0.5 ml of PegIFN- $\alpha$ 2b	Once weekly subcutaneous injection of 1.5 $\mu$ g/kg (or less if dose reduction needed)
Ribavirin	Capsules containing 200 mg of ribavirin	Two capsules in the morning and 3 in the evening if body weight <75 kg or Three capsules in the morning and 3 in the evening if body weight $\geq$ 75 kg
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Paritaprevir/ombitasvir/ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily (morning)
Dasabuvir	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)



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# Interazioni

- Liverpool University web site sulle interazioni farmacologiche delle molecole DAAs impiegate per il trattamento anti-HCV:

[www.hep-druginteractions.org](http://www.hep-druginteractions.org)



Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	*	*	*	*	*
	Didanosine	*	*	*	*	*
	Emtricitabine	*	*	*	*	*
	Lamivudine	*	*	*	*	*
	Stavudine	*	*	*	*	*
	Tenofovir	*	*	*	*	*
	Zidovudine	*	*	*	*	*
NNRTIs	Efavirenz	*	*	*	*	*
	Etravirine	*	*	*	*	*
	Nevirapine	*	*	*	*	*
	Rilpivirine	*	*	*	*	*
Protease inhibitors	Atazanavir; atazanavir/ritonavir	*	*	*	*	*
	Darunavir/ritonavir; darunavir/cobicistat	*	*	*	*	*
	Fosamprenavir	*	*	*	*	*
	Lopinavir	*	*	*	*	*
	Saquinavir	*	*	*	*	*
Entry/ Integrase inhibitors	Dolutegravir	*	*	*	*	*
	Elvitegravir/cobicistat	*	*	*	*	*
	Maraviroc	*	*	*	*	*
	Raltegravir	*	*	*	*	*

Table 4C. 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	*	*	*	*	*



# Daclatasvir

- Substrato di CYP3A4
- Substrato ed induttore di Pgp
- Ridurre a 30 mg: RIF, ivermectina, carbamazepina
- Aumentare a 90 mg: EFV



# Daclatasvir

## Description of the interactions

*Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration (AMBER)*

- **Daclatasvir and Atazanavir:** Coadministration of atazanavir/ritonavir (300/100 mg once daily) and daclatasvir (20 mg once daily) increased daclatasvir AUC, C<sub>max</sub> and C<sub>min</sub> by 110%, 35% and 265%, respectively (results dose-normalised to 60 mg dose). The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir. No dose reduction is required with atazanavir alone.
- **Daclatasvir and Efavirenz:** Coadministration of efavirenz (600 mg once daily) and daclatasvir (60 or 120 mg once daily) decreased daclatasvir AUC, C<sub>max</sub> and C<sub>min</sub> by 32%, 17% and 59%, respectively (results dose-normalised to 60 mg dose). The dose of daclatasvir should be increased to 90 mg once daily when coadministered with efavirenz.
- **Daclatasvir and Elvitegravir/cobicistat:** Coadministration has not been studied but is expected to increase daclatasvir concentrations due to inhibition of CYP3A4 by cobicistat. The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with cobicistat.
- **Daclatasvir and Etravirine:** Coadministration has not been studied but is expected to decrease daclatasvir concentrations due to induction of CYP3A4 by etravirine. Due to the lack of data, coadministration is not recommended.
- **Daclatasvir and Fosamprenavir:** Coadministration has not been studied but is expected to increase daclatasvir concentrations due to inhibition of CYP3A4 by fosamprenavir/ritonavir. The dose of daclatasvir should be reduced to 30 mg once daily.
- **Daclatasvir and Nevirapine:** Coadministration has not been studied but is expected to decrease daclatasvir concentrations due to induction of CYP3A4 by nevirapine. Due to the lack of data, coadministration is not recommended.
- **Daclatasvir and Ritonavir:** Coadministration with ritonavir alone has not been studied but is expected to increase daclatasvir concentrations due to inhibition of CYP3A4 by ritonavir. Coadministration of atazanavir/ritonavir (300/100 mg once daily) and daclatasvir (20 mg once daily) increased daclatasvir AUC, C<sub>max</sub> and C<sub>min</sub> by 110%, 35% and 265%, respectively (results dose-normalised to 60 mg dose). The dose of daclatasvir should be reduced to 30 mg once daily.
- **Daclatasvir and Saquinavir:** Coadministration has not been studied but is expected to increase daclatasvir concentrations due to inhibition of CYP3A4 by saquinavir/ritonavir. The dose of daclatasvir should be reduced to 30 mg once daily.
- **Daclatasvir and Tipranavir:** Coadministration has not been studied but is expected to increase daclatasvir concentrations due to inhibition of CYP3A4 by tipranavir/ritonavir. The dose of daclatasvir should be reduced to 30 mg once daily.

# Sofosbuvir

- Non è metabolizzato dal citocromo P450
- E' trasportato da PgP: i suoi induttori riducono SOF (rifampicina, carbamazepina, ivermectina)



# Sofosbuvir & ART

Anti-hepatitis Treatment	Co-medications
Sofosbuvir	Abacavir Atazanavir Darunavir Dolutegravir Efavirenz Elvitegravir/cobicistat Emtricitabine Etravirine Fosamprenavir Lamivudine Lopinavir Maraviroc Nevirapine Raltegravir Rilpivirine Ritonavir Saquinavir Tenofovir Zidovudine

This report lists the potentially clinically significant interactions (i.e. "red" and "amber" classification) (i.e. no clinically significant interaction expected) have been checked but are not shown on this report.

For full details of all interactions, see [www.hep-druginteractions.org](http://www.hep-druginteractions.org).

## Description of the interactions

No interactions to display.

# Ledipasvir

- E' trasportato da PgP: i suoi induttori riducono LED (rifampicina, carbamazepina, ivermectina)
- Aumento concentrazioni TDF se presente RTV o cobicistat o EFV



# Ledipasvir

## Description of the interactions

### *Drugs that should not be co-administered (RED)*

- **Ledipasvir/Sofosbuvir and Tipranavir:** Coadministration of ledipasvir/sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect. Coadministration is not recommended.

### *Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration (AMBER)*

- **Ledipasvir/Sofosbuvir and Efavirenz:** Coadministration of ledipasvir/sofosbuvir (90/400 mg once daily) and efavirenz/emtricitabine/tenofovir (600/200/300 mg once daily) had no effect on efavirenz, emtricitabine or sofosbuvir exposure but increased tenofovir AUC by 98% and decreased ledipasvir AUC by 34%. Although no a priori dose adjustment is recommended, the combination should be used with caution with frequent renal monitoring.
- **Ledipasvir/Sofosbuvir and Elvitegravir/cobicistat:** Coadministration of elvitegravir/cobicistat (150/150 mg once daily) and ledipasvir/sofosbuvir (90/400 mg once daily) decreased elvitegravir C<sub>max</sub> by 12%, but increased AUC and C<sub>min</sub> by 2% and 36%; cobicistat C<sub>max</sub>, AUC and C<sub>min</sub> increased by 25%, 59% and 325%, respectively. Ledipasvir C<sub>max</sub>, AUC and C<sub>min</sub> increased by 63%, 78% and 91%, respectively and sofosbuvir C<sub>max</sub> and AUC increased by 33% and 36%. The combination is also expected to increase tenofovir concentrations. The safety of increased tenofovir concentrations in this setting has not been established and coadministration is not recommended. The combination should be used with caution with frequent renal monitoring if other alternatives are not available.
- **Ledipasvir/Sofosbuvir and Maraviroc:** Coadministration has not been studied but may increase maraviroc concentrations due to inhibition of P-gp by ledipasvir. Although this is unlikely to be clinically relevant, it is possible that a dose reduction may be necessary.
- **Ledipasvir/Sofosbuvir and Tenofovir:** Coadministration of tenofovir (in combination with efavirenz/emtricitabine or rilpivirine/emtricitabine) increased tenofovir exposure. Tenofovir concentrations may also be increased when given with ledipasvir/sofosbuvir and an HIV protease inhibitor/ritonavir or with ledipasvir/sofosbuvir and elvitegravir, cobicistat and emtricitabine. The safety of increased tenofovir concentrations in these settings has not been established. If coadministration of ledipasvir/sofosbuvir and tenofovir with an HIV protease inhibitor/ritonavir is necessary, monitor for tenofovir-associated adverse reactions, including frequent renal monitoring. Note, coadministration of ledipasvir/sofosbuvir and tenofovir with elvitegravir, cobicistat and emtricitabine is not recommended.

# Paritepravir, dasabuvir e ombitasvir/r

- Paritaprevir: metabolizzato da CYP3A4
- Ombitasvir e dasabuvir: possono essere metabolizzati da CYP3A4
- Ritonavir: noto





# Paritepravir, dasabuvir e ombitasvir/r

## Description of the interactions

### *Drugs that should not be co-administered (RED)*

- **OBV/PTV/r + DSV and Efavirenz:** Coadministration is contraindicated. Subjects had severe tolerability issues when efavirenz plus tenofovir, emtricitabine was administered with ombitasvir/paritaprevir/ritonavir and dasabuvir and the study was discontinued.
- **OBV/PTV/r + DSV and Elvitegravir/cobicistat:** Coadministration is contraindicated in the European product label. The regimens of elvitegravir/cobicistat and ombitasvir/paritaprevir/ritonavir + dasabuvir both contain a pharmacokinetic booster and could increase concentrations of ombitasvir, paritaprevir and dasabuvir due to inhibition of CYP3A4.
- **OBV/PTV/r + DSV and Etravirine:** Coadministration is contraindicated in the European product label. Coadministration has not been studied but is expected to decrease plasma concentrations of ombitasvir/paritaprevir/ritonavir + dasabuvir due to CYP3A4 induction and reduce their therapeutic effect.
- **OBV/PTV/r + DSV and Lopinavir:** Coadministration is contraindicated in the European product label and not recommended in the US product label. Lopinavir/ritonavir (800/200 mg once daily or 400/100 mg twice daily) in combination with ombitasvir/paritaprevir/ritonavir + dasabuvir increased paritaprevir AUC by up to 2.2-fold. This is due to the higher total dose of ritonavir (300 mg/day).
- **OBV/PTV/r + DSV and Nevirapine:** Coadministration has not been studied but is contraindicated in the European product label. The effect is difficult to predict since there could be a 2-way interaction. Nevirapine is expected to decrease ombitasvir, paritaprevir, ritonavir and dasabuvir plasma concentrations and reduce their therapeutic effect. In addition, nevirapine is metabolised by CYP3A4 and therefore exposure could increase due to inhibition by ritonavir.
- **OBV/PTV/r + DSV and Ritonavir:** Ombitasvir/paritaprevir/ritonavir + dasabuvir is a complete regimen containing ritonavir. Coadministration with additional ritonavir is not recommended.
- **OBV/PTV/r + DSV and Saquinavir:** Coadministration is contraindicated in the European product label. Coadministration has not been studied but concentrations of paritaprevir are expected to increase due to inhibition of CYP3A4 by saquinavir.
- **OBV/PTV/r + DSV and Tipranavir:** Coadministration is contraindicated in the European product label. Coadministration has not been studied but tipranavir could cause a marked change in the exposure of ombitasvir/paritaprevir/ritonavir + dasabuvir.

# Paritepravir, dasabuvir e ombitasvir/r

*Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration (AMBER)*

- **OBV/PTV/r + DSV and Atazanavir:** Atazanavir should be taken without ritonavir with ombitasvir/paritaprevir/ritonavir + dasabuvir since ritonavir is included in the regimen. Atazanavir plus additional ritonavir is not recommended with ombitasvir/paritaprevir/ritonavir + dasabuvir.
- **OBV/PTV/r + DSV and Darunavir:** Coadministration with ombitasvir/paritaprevir/ritonavir + dasabuvir decreased darunavir C<sub>trough</sub> by ~50%, although C<sub>max</sub> and AUC did not show a clinically significant change. Coadministration of darunavir with ombitasvir/paritaprevir/ritonavir + dasabuvir is not recommended.
- **OBV/PTV/r + DSV and Fosamprenavir:** Coadministration of fosamprenavir with ombitasvir/paritaprevir/ritonavir + dasabuvir is not recommended. Fosamprenavir is hydrolysed to amprenavir and then metabolised by CYP3A4. However amprenavir also inhibits CYP3A4. Exposure of ombitasvir/paritaprevir/ritonavir + dasabuvir and fosamprenavir may be altered.
- **OBV/PTV/r + DSV and Maraviroc:** Coadministration has not been studied. Maraviroc is a substrate of CYP3A4 and its exposure may increase due to CYP3A4 inhibition by ritonavir. Monitor the subjects. A decrease in maraviroc dose may be needed as with other boosted regimens.
- **OBV/PTV/r + DSV and Rilpivirine:** Coadministration of rilpivirine and ombitasvir/paritaprevir/ritonavir + dasabuvir is not recommended unless the benefit outweighs the risk due to potential for QT interval prolongation with higher concentrations of rilpivirine. Rilpivirine is a substrate of CYP3A4 and its exposure increased significantly (~3-fold increase in AUC) when administered with ombitasvir/paritaprevir/ritonavir + dasabuvir. Coadministration should only be considered in patients without known QT-prolongation, and without other QT-prolongation co-medications.

# Simeprevir

- Substrato di CYP3A4
- Alto legame farmaco-proteico
- Moltissime contro-indicazioni  
nella co-somministrazione

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# Simeprevir

## Description of the interactions

### *Drugs that should not be co-administered (RED)*

- **Simeprevir and Atazanavir:** Coadministration of simeprevir with ritonavir-boosted or unboosted HIV protease inhibitors is not recommended as it may result in altered simeprevir concentrations due to CYP3A inhibition or induction by the HIV PI.
- **Simeprevir and Darunavir:** Coadministration is not recommended as it resulted in increased plasma concentrations of simeprevir due to CYP3A inhibition by darunavir/ritonavir. Coadministration of darunavir/ritonavir (800/100 mg once daily for 7 days) and simeprevir (150 mg once daily alone, 50 mg once daily in combination) was studied in 25 subjects. In combination, simeprevir C<sub>max</sub>, AUC and C<sub>min</sub> increased by 1.79-, 2.59- and 4.58-fold when compared to 150 mg alone (note, higher concentrations would be expected if the licensed dose of simeprevir were given in combination). Darunavir C<sub>max</sub>, AUC and C<sub>min</sub> increased by 4%, 18% and 31%, respectively. Ritonavir C<sub>max</sub>, AUC and C<sub>min</sub> increased by 23%, 32% and 44%, respectively.
- **Simeprevir and Efavirenz:** Coadministration is not recommended as it may result in significantly decreased plasma concentrations of simeprevir due to CYP3A4 induction by efavirenz and the loss of therapeutic effect of simeprevir. Coadministration of efavirenz (600 mg once daily for 14 days) and simeprevir (150 mg once daily for 7 days) was studied in 23 subjects. Simeprevir C<sub>max</sub>, AUC and C<sub>min</sub> decreased by 51%, 71% and 91%, respectively. Efavirenz C<sub>max</sub>, AUC and C<sub>min</sub> decreased by 3%, 10% and 13%.
- **Simeprevir and Elvitegravir/cobicistat:** Coadministration of simeprevir with cobicistat-containing products is not recommended as it may result in significantly increased simeprevir concentrations due to strong CYP3A inhibition by cobicistat.
- **Simeprevir and Etravirine:** Coadministration has not been studied and is not recommended. Decreased plasma concentrations of simeprevir are expected due to CYP3A4 induction by etravirine.
- **Simeprevir and Fosamprenavir:** Coadministration of simeprevir with ritonavir-boosted or unboosted HIV protease inhibitors is not recommended as it may result in altered simeprevir concentrations due to CYP3A inhibition or induction by the HIV protease inhibitor.
- **Simeprevir and Lopinavir:** Coadministration of simeprevir with ritonavir-boosted or unboosted HIV protease inhibitors is not recommended as it may result in altered simeprevir concentrations due to CYP3A inhibition or induction by the HIV protease inhibitor.
- **Simeprevir and Nevirapine:** Coadministration has not been studied and is not recommended. Decreased plasma concentrations of simeprevir are expected due to CYP3A4 induction by nevirapine.
- **Simeprevir and Ritonavir:** Coadministration is not recommended as it resulted in increased plasma concentrations of simeprevir due to strong CYP3A inhibition by ritonavir. Coadministration of ritonavir (100 mg twice daily for 15 days) and simeprevir (200 mg once daily for 7 days) was studied in 12 subjects. Simeprevir C<sub>max</sub>, AUC and C<sub>min</sub> increased by 4.70-, 7.18- and 14.35-fold, respectively. [Note: this interaction study was performed with a higher than recommended dose for simeprevir, but the dosing recommendation is applicable to the recommended dose of simeprevir 150 mg once daily.]
- **Simeprevir and Saquinavir:** Coadministration of simeprevir with ritonavir-boosted or unboosted HIV protease inhibitors is not recommended as it may result in altered simeprevir concentrations due to CYP3A inhibition or induction by the HIV protease inhibitor.
- **Simeprevir and Tipranavir:** Coadministration of simeprevir with ritonavir-boosted or unboosted HIV protease inhibitors is not recommended as it may result in altered simeprevir concentrations due to CYP3A inhibition or induction by the HIV protease inhibitor.

**Grazie per  
l'attenzione...**