Therapeutics Research • Education • AIDS Training
TREATASIA SNAPSHOTS
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Hepatitis C Treatment Snapshots: Daclatasvir

Daclatasvir is a medication used to treat and cure infection caused by the hepatitis C virus (HCV). It is used in combination with other medicines at a dose of either 30 mg or 60 mg per day, has few side effects, and can be safely used to treat HCV in people who are already receiving antiretroviral treatment for HIV infection. The World Health Organization (WHO) has included it in its Model List of Essential Medicines, which guides national governments on which drugs are most important to provide through their health programs.[1]

Acronyms:

HIV: Human immunodeficiency virus
Peg-IFN: Pegylated interferon
RBV: Ribavirin

REGULATORY APPROVALS

Daclatasvir was approved for use by the European Commission (EC) in August 2014, the United States Food and Drug Administration (U.S. FDA) in July 2015, and the Drug Controller General of India (DCGI) in December 2015. These approvals include treatment for HCV genotypes 1, 2, 3, and 4. However, different drug doses, regimen combinations, and durations of treatment are indicated depending on the genotype and whether or not there is co-infection with HIV.

U.S. FDA-approved indication for use

Genotype	Regimen*	Duration
3	Daclatasvir + sofosbuvir	12 weeks

EC-approved indications for use

Genotype	Regimen*	Duration[2]*
1 and 4 (without cirrhosis)	Daclatasvir + sofosbuvir	12 weeks
1 and 4 (with compensated cirrhosis)	Daclatasvir + sofosbuvir	24 weeks
3 (without cirrhosis)	Daclatasvir + sofosbuvir	12 weeks
3 (with cirrhosis)	Daclatasvir + sofosbuvir ± RBV	24 weeks
4	Daclatasvir + sofosbuvir ± RBV	24 weeks of daclatasvir in combination with 24–48 weeks of peg-IFN and RBV

**All regimens can be used for patients co-infected with HIV. Please refer to reference number two (below) for detailed information regarding treatment durations.*
± With or without

SAFETY AND EFFICACY

The drug's safety and efficacy were initially evaluated in four phase 2 and 3 clinical trials, with a total of 882 participants who were infected with HCV. A fifth trial was conducted in 301 individuals co-infected with both HCV and HIV.

Clinical trials involving daclatasvir

Clinical trial	Regimen	Population	Cure rates*
A1444040[3]	Daclatasvir + sofosbuvir ± RBV	Genotypes 1, 2, and 3; treatment naïve and treatment experienced	G1/24 wks/98% G2/24 wks/92% G3/24 wks/89%
A1444218[4] (Ally 3)	Daclatasvir + sofosbuvir	Genotype 3; treatment naïve and treatment experienced	G3/12 wks/96%
A1444042[5]	Daclatasvir + peg-IFN + RBV	Genotype 4; treatment naïve	G4/24 wks/82%
A1444010[6]	Daclatasvir + peg-IFN + RBV	Genotypes 1 and 4; treatment naïve	G1/24 wks/60% G4/24 wks/100%
A1444043[7]	Daclatasvir + peg-IFN + RBV	Genotype 1; treatment naïve; HIV co-infected	G1/24 wks AND 48 wks/74%

**By genotype (G) and treatment duration in weeks (wks). Cure rates for other patient groups are provided in the individual references.*
± With or without

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DOSE ADJUSTMENTS AND INTERACTIONS WITH HIV MEDICINES

Daclatasvir can interact with some HIV medicines, and doses may need to be adjusted from the standard 60 mg/day adult dose (see below). If co-administered with opiate substitution medicines (i.e., buprenorphine or methadone), no dose adjustments for daclatasvir, buprenorphine, or methadone are required.

HIV medicine	Interaction	Dose adjustments [8]
Abacavir, didanosine, emtricitabine, lamivudine, stavudine, zidovudine	Clinically relevant interactions are not expected*	No dose adjustment of daclatasvir required
Atazanavir with low-dose ritonavir	Increases concentration of daclatasvir	Reduce daclatasvir to 30 mg
Atazanavir with cobicistat	Increase in concentration of daclatasvir is expected*	Reduce daclatasvir to 30 mg
Darunavir with low-dose ritonavir	No clinically relevant changes	No dose adjustment of daclatasvir required
Efavirenz	Decreases concentration of daclatasvir	Increase daclatasvir to 90 mg
Etravirine or nevirapine	Decrease in concentration of daclatasvir is expected*	Due to lack of data, co-administration of etravirine or nevirapine with daclatasvir is not recommended
Fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate	Increase in concentration of daclatasvir is expected*	Reduce daclatasvir to 30 mg
Lopinavir with low-dose ritonavir	No clinically relevant changes	No dose adjustment of daclatasvir required
Raltegravir	Clinically relevant interactions are not expected*	No dose adjustment of daclatasvir required
Tenofovir disoproxil fumarate	No clinically relevant changes	No dose adjustment of daclatasvir required

**Clinical trials testing interactions between these drugs/regimens and daclatasvir have not been performed. These are projected interactions based on available data.*

CURRENT AVAILABILITY OF INDIAN GENERIC FORMULATIONS AND PRICING

After Indian regulatory approval, seven companies began marketing and distributing generic daclatasvir in India in January 2016. The maximum retail price according to the product packaging is ~92 USD for a four-week supply (i.e., one bottle of 60 mg tablets). At this price, a 12-week course would cost ~276 USD, and a 24-week course would cost ~552 USD for daclatasvir alone.

Cost comparison for combination therapy with Indian generic daclatasvir

Regimen	Treatment duration	Cost*
Peg-IFN + RBV	48 weeks	10,032 USD
Sofosbuvir + peg-IFN + RBV	12 weeks	3,420 USD
Daclatasvir + sofosbuvir + RBV	24 weeks	2,376 USD
Daclatasvir + sofosbuvir + RBV	12 weeks	1,188 USD

**Peg-IFN price calculated at 13,600 INR (~209 USD) per vial using the maximum retail price on Indian product packaging;*
Sofosbuvir price calculated at 19,800 INR (~304 USD) per bottle using the maximum retail price on Indian product packaging;
Daclatasvir (60 mg) price calculated at 6,000 INR (~92 USD) per bottle using the maximum retail price on Indian product packaging;
Indian generic companies provide RBV at no additional cost with the purchase of peg-IFN or sofosbuvir.

CONCLUSION

HCV combination therapy regimens that include daclatasvir are associated with higher cure rates reaching up to 100%, fewer side effects, lower cost, and shorter treatment durations compared to regimens using peg-IFN and RBV alone, which have response rates of 46–77%.[9] Daclatasvir also provides the opportunity for an all-oral treatment for HCV, without the use of RBV (which is associated with more side effects). Although drug regulators have approved daclatasvir for only four HCV genotypes, based on available clinical evidence, the European Association for Study of the Liver (EASL) recommends the use of daclatasvir and sofosbuvir combination regimens for treatment of all genotypes.

The Indian generic form of daclatasvir is currently only available in India. Generic companies need to expand its availability by proactively pursuing registration in more countries in the Asia-Pacific region. To facilitate this, other national drug regulators should allow for fast-track registration processes. The current pricing of generic versions may still be too high for national health programs in low- and middle-income settings. Advocacy work to support rapid drug registrations and additional price reductions remains an urgent priority.

1. World Health Organization. News release, WHO moves to improve access to lifesaving medicines for hepatitis C, drug-resistant TB and cancers. May 2015. http://www.who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/
2. European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003768/human_med_001792.jsp&mid=WC0b01ac058001d124
3. M.S. Sulkowski, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *The New England Journal of Medicine*. January 2014, 370:211-21.
4. D.R. Nelson, et al. All-Oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III Study, *Hepatology*. April 2015, 61:1127-1135.
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6. C. Hezode, et al. Daclatasvir plus peginterferon alfa and ribavirin for treatment-naive chronic hepatitis C genotype 1 or 4 infection: a randomised study. *Gut*. June 2015, 64:948-956.
7. Safety and efficacy study of BMS-790052 plus peg-interferon alfa 2a and ribavirin in untreated hepatitis C patients coinfected with HIV virus. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003768/WC500172848.pdf
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9. M.W. Fried, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *The New England Journal of Medicine*. September 2002, 347:975-982.

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