Chronic Hepatitis C: Do Generics Work as Well as Branded Drugs?

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India has a large share of the hepatitis C virus (HCV) burden of the world. Unsafe medical practices and blood transfusions are the leading modes of transmission of HCV in India. The commonest HCV genotype in India is genotype 3 followed by genotype 1. While directly acting antivirals (DAAs) agents have become available at reasonable rates in India, cost of therapy remains a major barrier for control of HCV in India. Generic DAAs have been proven to be cost-saving in prior studies. We examined data from various studies in India and elsewhere using generic DAAs, and evaluated whether they are equally efficacious as the branded drugs. Since the availability of generic DAAs in the Indian market, there is a lot of real life data as well as prospective studies in special patient populations such as hematological disorders (thalassemia and hemophilia), chronic kidney disease, hemodialysis patients, post liver and renal transplant patients on immunosuppression, intravenous drug users, confections and other high risk groups. Control of HCV infection in India requires multi pronged approach. There is a need to formulate a health educational curriculum targeting not only the high-risk population but also the general population regarding the transmission of HCV. Adopting the dual approach of treating the old cases (decreasing the reservoir pool of HCV) and decreasing the incidence of new ones would help curtail the disease and decrease liver related mortality. In this scenario, the role of efficacious low cost generic medications is essential. (J CLIN EXP HEPATOL 2017;7:253–261)

The prevalence of hepatitis C virus (HCV) infection is estimated to be more than 70 million people worldwide and between 6 and 11 million in India.¹ Chronic HCV infection is one of the prevalent causes of the disease burden of cirrhosis, hepatocellular carcinoma (HCC) and liver-related deaths in India. Untreated HCV infection also leads to substantial economic burden and a hidden social cost.² Despite a low to moderate (1–1.5%) prevalence of HCV, India accounts for a significant share of global HCV infections due to the large population; approximately 12–18 million population is infected with HCV. In 2015, about 60,000 deaths were reported to be related to HCV alone in India.³

New directly acting antivirals (DAAs) for HCV treatment are efficacious, providing rates of sustained

virological response (SVR) exceeding 95%.⁴ However the patented drugs are expensive limiting treatment to those with advanced disease. Thus, these drugs offer a hope of reducing the burden of HCV, reducing disease transmission and complications of liver disease. Hence, in India a dual approach reducing incidence and increasing treatment is appropriate in showing short-term improvements in advanced stage outcomes with reductions in prevalence.¹ However, these drugs are very costly in several countries.⁵ In India, the three DAAs [sofosbuvir (SOF), ledipasvir (LDV) and daclatasvir (DCV)] are available from several generic manufacturers at a price as low as \$110 for 12 weeks therapy.⁶ This is in stark contrast to the cost of 12-week sofosbuvir therapy being approximately US \$42,017, ranging from US \$37,729 in Japan to US \$64,680 in the United States.⁵ In a recent report, the use of generic DAAs in Indian hepatitis C patients was reported to increase the life expectancy by 8.02 years, increase quality-adjusted life years (QALYs) by 3.89, avert 19.07 disability-adjusted life years (DALYs), and reduce the lifetime healthcare costs by \$1309 per-person treated, when compared with untreated HCV infected patients.⁷ Treatment became cost-effective within 2 years, and cost-saving within 10 years of its initiation in all subjects and within 5 years in patients with cirrhosis.⁷ Almost all published cost and efficacy analyses have been conducted in developed nations under patent rules where DAAs have a prohibitive cost limiting widespread use.^{9–11} The efficacy of generic DAA is under scrutiny, and in this study we report the pooled data from different trials in India and

Keywords: generic direct antivirals, DAAs, chronic hepatitis C, real life efficacy study

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Abbreviations: ALT: alanine aminotransferase; CHC: chronic hepatitis C; CI: confidence interval; DAAs: direct-acting antiviral agents; DCV: daclatasvir; EASL: The European Association for the Study of the Liver; GT: Genotype; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; IL: interleukin; INASL: Indian National Association for study of the Liver; LDV: ledipasvir; Peg-IFN: pegylated interferon; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virologic response; VEL: velpatasvir

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elsewhere using sourced generic DAA therapy. We found generic DAA to be cost-effective in view of low treatment prices and also be cost-saving in terms of improvement of both public health burden and economic cost perspective. The Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) is a public health initiative by the government of Punjab to tackle the HCV burden in the state (<http://pbhealth.gov.in/SOPs%20for%20MMPHCRF.pdf>).¹² The results from this treatment program will drive physicians and public health professionals toward central funding of HCV treatment, and may make it easier for health administrators and political leaders take an informed decision. We therefore estimated the efficacy of treatment of HCV-infected persons in India and elsewhere using low-priced DAAs, and evaluated the results from various published and unpublished clinical data from different centers across the country. This question is also of interest for other countries where it may be possible to obtain DAAs at low prices.

MANAGEMENT OF HCV IN INDIA

In India, pegylated interferon alfa (Peg-IFN α) plus ribavirin (RBV) combination therapy has been replaced by DAAs. These drugs have lower side effects, better tolerability, and are simpler to administer. In view of their potential efficacy and safety (SVR > 90% in most studies), DAAs have the potential to eliminate one of the most common causes of liver related morbidity and mortality.¹² The nucleoside non-structural protein non-structural (NS) 5B inhibitor SOF became available in India in March 2015, which was followed in 2016 by the NS5A replication complex inhibitors, LDV and DCV. Velpatasvir (VEL), a pangenotypic DAA, is now available in India and the Indian National Association for Study of the Liver (INASL) guidelines are accordingly going to be updated. The INASL guidelines are based on considerations for the treatment of HCV in India including the cost of therapy, the poorer response of the predominant genotype (GT 3) and the non-availability of many of the DAA recommended by other guidelines.^{4,5} The widespread uptake of DAA in India is possible, as these have so far been marketed at a fraction of the cost in the west.

COST EVALUATION OF DAAS

Aggarwal et al.⁷ have presented a model for healthcare payer's perspective. For effectiveness outcomes, they used QALYs, a commonly used metric in cost-effectiveness analysis, and DALYs, as recommended by the WHO. The cost of SOF/LDV (with or without RBV), or SOF/DCV combination treatment was taken as Indian Rupees (INR) approximately 6711 (USD 100) for every 28 days' supply. The costs of pre-treatment testing (for disease staging and HCV genotyping) were taken as INR 8000

(approximately USD 119), and those for tests while on and after treatment were taken as INR 6000 (approximately USD 89). The authors presented a minimalistic cost model representing a conservative scenario by underestimating the savings resulting from DAA use; however, this was supplemented by sensitivity analyses using a wide range of costs.⁷ A recent pharmacoeconomic study established that the use of generic DAAs in Indian HCV patients would increase the life expectancy by 8.02 years, increase QALYs by 3.89, avert 19.07 DALYs, and reduce the lifetime health-care costs. Treatment became cost-effective within 2 years, and cost-saving within 10 years of its initiation overall and within 5 years in persons with cirrhosis.^{8,9}

The high cost of patented DAA drugs needs to be reevaluated in the setting of cheaper and efficacious generic alternatives. The business model relies on using patent protection laws against free market competition with little revenue being directed at new drug research, with more stress on drug marketing (25% of revenues) rather than new drug discovery (1.3% of revenues).¹⁰ Generic versions of DAAs are manufactured in India under voluntary license from Gilead Sciences, and by other Indian companies who are not licensees, and in other countries which are not bound by patent law. In many countries it is legal to import drugs for personal use by ordering them online. In other countries imports of generic drugs are restricted to those carried through customs by individuals in quantities sufficient for personal use. Hence over the last two years a large pool of data has emerged from India, the Middle Eastern countries and also 'buyers' clubs' in the west using imported generic medicines.¹³ Bioequivalence studies also establish efficacy of generic medications. A test group of 25–50 subjects takes a single dose of originator medication, and the blood levels of the drug(s) are measured at various time points over the next 24 h. After a washout period, the same group then takes the generic version and once again the blood levels of the drug(s) are measured. A drug is deemed bioequivalent when the blood levels at all time points are a statistically near identical match. Bioequivalence proves, not only do the tablets contain the active ingredient(s) in the correct quantity, but more importantly that they deliver these into the patient's system in a similar fashion to the originator version.¹⁴ Preliminary reports of the generic DAA have shown reasonable results (Table 1).

Hill et al reported people who purchased the drugs were cured of hepatitis C at a cost of around \$700–\$900 in South-East Asia and Eastern Europe. The price of treatment remains a major barrier to curing hepatitis C for millions of people, and where rationing of treatment, lack of health insurance or lack of a national treatment program deny access to these drugs, people are turning to internet-based community portals or 'buyer's clubs' to obtain generic versions of direct-acting antivirals.^{20–23} Freeman et al.²³ showed very high cure rates when using

Table 1 Efficacy and Safety of Sofosbuvir-based Therapy for Chronic Hepatitis C Infection in “Real-Life” Cohort in India.

Author/year	n	Study type	Primary end point (SVR 12)	Adverse events
Mehta R et al., 2016 ¹³	107	Observational study; SOF and RBV with or without Peg-IFN	Overall—94.3% (99/105) GT3—92.5% (62/67) GT1—97.4% (37/38)	29.9%
Satsangi S et al., 2016 ¹⁵	158 [TN = 128 (89%), TE = 30 (19%)]	Observational study; SOF and RBV with or without Peg-IFN	Overall—98.7% (156/158) GT3—99.3% (134/135) GT1—97.5% (39/40)	SOF + RBV = 9.7% SOF + RBV + Peg-IFN = 32.7%
Shah SR et al., 2016 ¹⁶	117	Observational study; SOF and RBV	GT1—90% (95% CI, 73–98) and 96% (95% CI, 82–100) of patients following 16 and 24 weeks of treatment GT3—100% (95% CI, 88–100) and 93% (95% CI, 78–99) after 16 and 24 weeks of therapy	Mild or moderate in severity, occurred in 69% and 57% of patients receiving 16 and 24 weeks of treatment, respectively
Sood A et al., 2016 ¹⁷	736 [GT3 (80%), GT1 (14.7%), GT4 (4.9%). Cirrhosis— 330 (44.8%) (CTP-A 75.8%; CTP B 18%; CTP C: 6%).]	Observational study; GT1, GT4 and GT5—SOF and RBV with Peg-IFN and GT3—SOF and RBV with Peg-IFN	Overall—95.8% (453/473) GT1—97.0% (97/100) GT3—95.6% (563/571) GT4—93.1% (27/29) Noncirrhotics >> cirrhotics (P = 0.003) CC >> DC (P = 0.0018)	Triple therapy >> dual therapy
Dhiman RK and Grover GS, 2017 (Unpublished) ¹⁸	n = 11105 Noncirrhotic—10219 Cirrhotic—886	Prospective observational study (MMPHCRF); Public health care setting. Non-cirrhotic: GT1 to GT4—SOF + DCV for 12 weeks. Cirrhotic: GT1 and GT4—SOF + DCV + RBV for 12 weeks or Sofo + Dacla for 24 weeks GT3—SOF + DCV + RBV for 24 weeks	Noncirrhotic—92.5% Cirrhotic—92.7% GT3—92.6% Nongenotype 3—93.1%	
Goel A et al., 2017 ¹⁹	160 patients (90% TN; CHC 49%, CC 32%, and DC 19%),	39 (24%) received Peg-IFN, sofosbuvir and ribavirin, 21 (13%) received sofosbuvir and ribavirin, and 100 (63%) received SOF and DCV, with or without RBV.	On intention-to-treat basis, RVR, ETR, and SVR12—146/160 (91.3%), 151/160 (94.4%), and 147/160 (91.9%), respectively	Dual-DAA-based regimens were safe and highly effective in treating genotype-3 HCV infection in CHC and CC patients
Sidhu et al., 2017 ²⁰	CHC -G3 (n = 931)	Group 1; Dual therapy (n = 432) = SOF 400 mg + weight-based RBV, daily × 24 weeks Group 2; Triple therapy (n = 499)—Peg-IFNα 2a 180 mcg weekly, SOF 400 mg plus weight-based RBV, daily × 12 weeks	Overall SVR rates were 91 and 92% in the dual and triple therapy arms. In non cirrhotics, Dual therapy: SVR in TE was 67% and 74% in TN. In cirrhotics SVR was 44% (dual therapy) and 58% (triple therapy) Triple therapy: SVR 50% in TE and 97% in TN	Triple therapy was more efficacious especially in TE or cirrhotic patients.

CI, confidence intervals; CHC, chronic hepatitis C; CC, compensated cirrhosis; DC, decompensated cirrhosis; CTP, Child Turcotte Pugh; SVR 12, sustained virological response 12 weeks; GT, genotype; Peg-IFNα, pegylated interferon-α; SOF, sofosbuvir; RBV, ribavirin; RVR, rapid virological response; DCV, daclatasvir; LDV, Ledipasvir; MMPHCRF, Mukh Mantri Punjab Hepatitis C Relief Fund; TE, treatment experienced; TN, treatment naïve.

generic versions of direct-acting antivirals, and also provided evidence that the products purchased contained the necessary levels of active drug. The studies presented this week, in which data supplied by patients and their physicians were analyzed by St Stephen's AIDS Trust in London, measured virological responses. Two studies identified the generic products used, and one study was able to measure levels of active ingredients. The preliminary results of the three studies show cure rates comparable to those achieved with branded products. The REDEMPTION-1 trial data presented at European Association for the Study of the Liver (EASL) International Liver Congress (ILC) 2016 clearly demonstrates that the safety and efficacy of generics, at least the generics used in the study, are equivalent to the originator medications and deliver the expected 90%+ sustained virological response (SVR) rates. The REDEMPTION trial evaluated pooled data of 1160 patients with sourced generic SOF, LDV, DCV, VEL and RBV from suppliers in India, Bangladesh, China and Egypt at 240 locations in 88 countries spanning 5 continents.^{23,24} In addition to routine assessment, HCV RNA load was estimated at baseline, on treatment, and post treatment for SVR4, SVR12 and SVR24. The data provided clues to two pertinent questions raised about the quality and efficacy of generic drugs and also safety in terms of adverse events.²⁴⁻²⁶

FixHepC Buyer's Club

The FixHepC is an online service which directs people toward generic sources of hepatitis C drugs and arranges testing of the drugs to ensure that they contain the correct levels of active ingredients. Freeman et al.²³ presented data on extended follow-up on 438 of the 448 patients at the International Liver Congress in 2016. Fifty-nine per cent of patients contributing data to this study had less advanced fibrosis (F0-F2), 11% had F3 fibrosis and 27% had cirrhosis.

Analysis of SVR 12 responses by genotype showed that patients with GT 3 were substantially less likely to achieve a SVR compared to other genotypes. Eighty per cent of GT 3 patients, predominantly treated with SOF/DCV, achieved SVR 12, compared to 94% of genotype 1 patients and all patients with genotypes 2, 4, 5 and 6. Overall, 90% of patients who had obtained drugs through the FixHepC Buyer's Club and who had completed the 12-week post-treatment follow-up have achieved SVR 12 to date.^{27,28}

South-East Asia Buyer's Club

In Thailand a 12-week course of Sovaldi and Daklinza costs around \$10,000, and is similarly priced in most other countries in the region. A new web based portal directs people to online pharmacies in India to purchase generic versions of SOF and either LDV or DCV. In this data set, 237 patients were on treatment. SVR 4 results are available for 33 patients and SVR12 results for 24. Results to date

show that one patient failed to achieve rapid virologic response on SOF/RBV, and one patient failed to achieve an end-of-treatment virologic response on SOF/LDV. Two patients on SOF/RBV experienced virologic rebound between weeks 4 and 12 post-treatment, resulting in a 85% SVR 12 rate to date on this combination. All other patients who have reached 12-week post-treatment follow-up have achieved SVR.²⁹

Russia and Eastern Europe Buyer's Club

The Russian hepatitis C treatment program does not offer sofosbuvir yet, and private treatment with the drug costs around \$9500 for a 12-week course of treatment. Again community based platforms for treatment have been set up such as the Gepatikta group which offers therapy at a cost of around \$700-\$900 per treatment course by sourcing drugs from India and China. The collected data from this treatment program were assembled from private physicians and AIDS clinics in Russia, Estonia, Israel, Belarus, and Ukraine. About 56% of patients in this cohort had genotype 3 infection, and 41% had genotype 1 infection. As expected virological responses were poorer in genotype 3 patients. At week 2, the rates of RVR (HCV RNA < 25 IU/ml) were GT 3 (82%), GT 1(90%) and GT 2(88%). Difficulties with making comparisons across these cohort data is that due to heterogeneity of collection from different sources, there may be loss of follow up, and missed measurements. Longer-term follow-up of these large groups of patients will be needed in order to produce more robust estimates of the proportions achieving SVR12, as well as any consistent differences by genotype (Table 2).³⁰

Merat et al.³² reported the data of effectiveness and safety of a generic fixed dose combination of sofosbuvir/daclatasvir, manufactured in Iran. Among 100 recruited cirrhotic patients with genotype 1 or 3 (5 with decompensated cirrhosis and 4 post-liver transplantation), the overall sustained virologic response (SVR) was 92% by intention-to-treat analysis, which was comparable to that from, phase 3 clinical trials of the branded SOF plus DCV in cirrhotic patients (12-14). Among those completed the study ($n = 94$), SVR was 98% in both groups of patients with genotype 1 (52/53) and genotype 3 (40/41). Yakoot et al.³³ assessed the applicability of the early virus response kinetics and the very rapid virologic response (vRVR) rate as quick outcome measures for accelerated comparative efficacy in 50 eligible chronic HCV patients. They were randomized to either one of two generic sofosbuvir products (Gratisovir or Grateziano) manufactured in Egypt at a daily dose of one 400 mg tablet plus a weight-based ribavirin dose. Data were compared between the groups for early virus response kinetics and vRVR rates in relation to the rates of final sustained virologic response at week 12 post-treatment (SVR12). There was a significant association between the vRVR and the SVR12, with 100% positive predictive value (38/38 of those who had vRVR, achieved a

Table 2 Real Life Data From Different Treatment Cohorts Using Generic Drugs Outside India.

Author/year	n	Study type	Primary end point (SVR 12)	Salient results
Qing-Lei Zeng et al. 2017 ³¹	Group 1: Non cirrhotic—63 Group 2: Cirrhotic—65 Group 3: Non cirrhotic—64 All GT 1b	Open-labeled observational study Group 1 & 2: Generic SOF/LDV plus 1000–1200 mg of RBV daily for 12 and 8 weeks respectively Group 3: SOF/LDV for 8 weeks	SVR12 rates Group 1: 96.8% (61/63) Group 2: 96.9% (63/65) Group 3: 96.9% (62/64)	This study demonstrated that 8 or 12 weeks of generic SOF/LDV with or without RBV are safe and effective for patients with GT 1b CHC.
FixHepC.com International cohort with people enrolling from the UK, Europe, Australia, the United States, Thailand, Africa and South America (n = 448) ^{22–27}	Half the participants were TN (51%) and almost one-third (31%) had cirrhosis	Baseline GT was approximately 64% for GT1, 5% GT2, 27% GT3, 3% GT4 and <1% GT5/6.	95% (92/97) for GT1, 100% (6/6) for GT2, 90% (26/29) for GT3, 100% (3/3) for GT4 and 100% (2/2) for GT5/6	Generic imported HCV drugs are at least as effective as originator branded drugs seen in clinical trials
Hajarizadeh B et al. Iran, 2017 ³²	100 recruited cirrhotic patients with G1 or 3 (5 with DC and 4 post-liver transplantation)	Generic SOF/DCV × 24 weeks	SVR 12 (92%) GT 1:52/53 (98%) GT 3: 40/41 (98%)	Generic DAA manufactured in Iran. All patients were cirrhotic in this study
Yakoot et al., 2016 ³³	50 CHC GT 4 HCV RNA load ≥104 ± elevated liver enzymes; 18 and 70 years old; Interferon naïve and relapsers nonresponders	RCT evaluated the virus response kinetics and vRVR rates in relation to the rates of final sustained virologic response at week 12 posttreatment (SVR12) RCT randomized to two generic SOF 400 mg tablet plus a weight-based RBV dose	SVR12 rates were 96% (95% CI, 79.6–99.9%) in Grateziano group (24/25) and 95.7% (95% CI, 78–99.9%) in Grateziano group (22/23).	There was no statistically significant difference in the efficacy of the generic DAAs with comparable SVR when compared to published branded trials.
Elsharkawy A et al., 2017 ³⁴	n = 14 409; GT 4 Dual therapy: SOF + RBV Triple therapy: SOF + RBV + PEG IFN	Group 1 (interferon eligible) were treated with triple therapy for 12 weeks and Group 2 (interferon ineligible) were treated with dual therapy for 24 weeks	SVR12 was 94% in group 1 and in group 2 the SVR12 was 78.7%	Similar rates of SVR12 as seen in phase III efficacy studies

CI, confidence intervals; CHC, chronic hepatitis C; CC, compensated cirrhosis; DC, decompensated cirrhosis; CTP, Child Turcotte Pugh; SVR 12, sustained virological response 12 weeks; GT, genotype; Peg-IFN α , pegylated interferon- α ; SOF, sofosbuvir; RBV, ribavirin; RVR, rapid virological response; DCV, daclatasvir; LDV, ledipasvir; MMPHCRF, Mukh Mantri Punjab Hepatitis C Relief Fund; TE, treatment experienced; TN, treatment naïve.

final SVR12) and 82.6% sensitivity (among the total 46 with SVR12), 38 were having vRVR. The largest data set has come from the Egyptian HCV treatment program, which has published data in 2017 on GT 4 patients who were treated with SOF/RBV or SOF/RBV/Peg-IFN α based regimens.³⁴ They showed a high SVR12 rate in the patients on triple therapy (94%) but only a 78.7% rate in the patients on dual therapy. The limitation with this data is the poor follow up, and treatment interruptions. Nonetheless, this is the largest experience with generic DAAs in GT4 patients worldwide and provides a roadmap for how

public health interventions can reduce the burden of disease due to HCV.³⁴

Table 3 shows the data generated from various small studies in special patient populations using generic DAAs. This has changed the course of illness in conditions as varied as fibrosing cholestatic hepatitis,³⁵ hematological diseases,^{36,37} IV drug users,³⁸ postrenal transplantation³⁹ and chronic kidney disease on dialysis.^{40,41} They have shown a high efficacy of generic drugs and offers better answers for determining choice of therapy in this difficult to treat populations.

Table 3 Real Life Data From Different Treatment Cohorts Using Generic Drugs in Special Populations-post Liver/Renal Transplantation, Hematological Disorders, Intravenous Drug Use (IDU), Chronic Kidney Disease (CKD) on Hemodialysis.

Author/year	Special populations (n)	Study type	Primary end point (SVR 12)
Wadhawan M et al., 2016 ³⁵	Post-liver transplantation Fibrosing cholestatic hepatitis (n = 4) SOF + RBV × 12 weeks	All patients had SVR 12 and improved parameters	100% response
Mehta R et al., 2017 ³⁶	Bleeding disorders SOF (400 mg) and DCV (60 mg) for 12 weeks (hemophilia) or 24 weeks (idiopathic thrombocytopenia purpura) ITP/Evan's syndrome n = 7	All the patients achieved ETR and SVR12	
Nagral A et al., 2017 ³⁷	Thalassemia (n = 29) GT1 (17), GT3 (11), unclassified (1)	GT 1; SOF/LDV GT3: SOF/DCV	SVR 12 = 100%
Solomon et al., 2017 ³⁸	Injection drug users n = 50; all male. Cirrhosis—20% Patients were randomized 1:1 to (SOF + PEG IFN + RBV) for 12 weeks (Arm 1) vs (SOF + RBV) for 24 weeks (Arm 2).	Of 22 who completed SOF + IFN + RBV, all achieved SVR12 (22/25 = 88%) 15 of 22 who completed SOF + RBV achieved SVR12 (15/25 = 60%; P = .05)	In SOF + RBV, SVR12 was significantly less in ongoing substance use (36% vs 100%) and missed doses. Active substance use and missed doses did not impact SVR with SOF + PEGIFN + RBV
Taneja S et al., 2017 ³⁹	Post-renal transplantation Total subjects = 47 n = 14—SOF and RBV for 24 weeks. n = 22—SOF and LDV n = 12—SOF and DCV for 12/24 weeks depending on the fibrosis assessment (F0 – F1) = 31 (65.96%) (F2) = 11 (23.4%) > F3 = 5 (10.64%)	SVR12 rates were 100% in all groups except in the SOF and RBV group (86%)	DAAs including SOF, DCV and LDV with or without RBV are safe and effective for the treatment of chronic hepatitis C in renal transplant recipients
Ravichandran et al., 2017 ⁴⁰	CKD on hemodialysis n = 22. SVR 12 on SOF and RBV alone (72%) Patients with SOF/RBV failure—4 treated with SOF/LDV × 12 weeks (GT1; n = 3) or SOF/DCV × 12 weeks (GT 3; n = 1)	SVR 12 100%. Anemia on RBV (45%)	Safety in CKD on dialysis
Choudhary N et al., 2017 ⁴¹	CKD on hemodialysis n = 16. GT 1 = 11; GT 3 = 4; GT4 = 1. Regimen 1 = SOF, RBV and low dose PEGIFN (n = 8); 6 (GT1); 1 (GT3); 1 (GT 4) Regimen 2: SOF and DCV (n = 7); Regimen 3: sofosbuvir, ribavirin, and daclatasvir (n = 1)	SVR 12 (80%). Anemia significant on RBV (43%)	Safety in CKD on dialysis established.

CI, confidence intervals; CHC, chronic hepatitis C; CC, compensated cirrhosis; DC, decompensated cirrhosis; CTP, Child Turcotte PuGTh; SVR 12, sustained virological response 12 weeks; GT, genotype; Peg-IFN α , pegylated interferon- α ; SOF, sofosbuvir; RBV, ribavirin; RVR, rapid virological response; DCV, daclatasvir; LDV, ledipasvir; MMPHCRF, Mukh Mantri Punjab Hepatitis C Relief Fund; TE, treatment experienced; TN, treatment naïve.

ANTECEDENTS FOR GENERIC DRUG EFFICACY—SUCCESS STORIES IN HIV, AND CANCER

Across Europe, high drug prices can limit access to treatment for hepatitis C, cancer and for HIV, excluding the more vulnerable from adequate therapy. A similar scenario arose fifteen years ago, when it was shown that antiretrovirals for HIV/AIDS could be mass produced at very low costs. This led to treatment programs, which now supply drugs to more than 17 million people with HIV worldwide.⁴² Similar analyses of drug production show that viral hepatitis, tuberculosis and certain cancers can also be treated at very low costs. Several key drugs will become generic in Europe within the next 5 years, for example imatinib in the treatment of chronic myelogenous leukemia.⁴³ There is a potential to expand treatment coverage for key diseases, while lowering overall costs of treatment. For mass treatment with low-cost generic drugs to be successful, several key conditions need to be met.⁴⁴

Firstly, when any drug becomes generic, is available for public health programs at prices close to the cost of production, with a reasonable profit margin. Secondly, pharmaceutical companies should not be able to inflate the prices of drugs after initial approval. Thirdly, when a drug becomes generic and a low price is established, the effects of this lower price on the value of other drugs should be evaluated. Fourthly, bioequivalence of the generic drug to the branded or patented drug needs to be enforced stringently.

MANAGEMENT OF HEPATITIS C IN RESOURCE CONSTRAINED SCENARIO

Unlike Peg-IFN α /RBV therapy, with the use of DAA, there is no need for IL28B testing, frequent viral loads for response guided therapy, repeated monitoring of blood count and thyroid functions. However, therapy of HCV in India is not borne by state or insurance in the majority. Many patients cannot even afford baseline investigations; leave alone the cost of the DAA. HCV viral load testing, HCV genotype testing and fibrosis assessment may be optional in non-cirrhotic treatment naïve patients. HCV RNA testing can be done only at baseline and 12 weeks after end-of-treatment for obtaining SVR 12.¹⁵ HCV core-Ag is a cheaper alternative to HCV RNA testing in resource-constrained settings and can be done by smaller laboratories where PCR based HCV RNA testing may not be feasible. If there is no clinical or ultrasound evidence of cirrhosis, genotype testing could be avoided and patients can be treated with the pangenotypic combination of DCV/SOF.⁵ For example, the state of Punjab has an overall hepatitis-C prevalence of 3.29%, with rural prevalence as 3.4% and urban as 3.1%. Using the above prevalence estimates, more than 9 lakhs citizens are estimated to be

infected with hepatitis-C, of which ~6 lakhs are expected to be viremic and will require treatment. With the growing cognizance of the HCV burden in the state, the Government of Punjab launched a public health program under the Mukh Mantri Punjab Hepatitis-C Relief Fund (MMPHCRF) that offers free hepatitis-C treatment to all residents of Punjab through a highly decentralized network of 22 District Hospitals and 3 Government Medical Colleges. Considering the pangenotypic efficacy of DCV/SOF therapy, it is considered as first-line therapy for all non-cirrhotic patients without genotype testing and end of the treatment viral load. Patients with cirrhosis are managed according to their genotypes (i.e. DCV/SOF and RBV for genotype 3 and LDV/SOF and RBV for genotypes 1 and 4). This approach has been proven to be most cost effective (less than US \$150 for 12 weeks therapy including diagnostic testing for noncirrhotic hepatitis C patients and less than US \$350 for 24 weeks therapy with DCV/SOF and RBV for cirrhotic hepatitis C genotype 3 patients). The overall results obtained using this cost-effective regimen with generics are ~93%. Situations such as this, where pharmacological treatments have been found to be cost-saving, are rare. Thus, hepatitis C treatment with low-priced DAAs is a win-win situation, warranting the use of public money to fund it.

Our results provide a compelling case for India to invest in hepatitis C treatment. Unlike most other pharmacological interventions, hepatitis C treatment with generic DAAs is not merely cost-effective, but also cost-saving. The goal of MMPHCRF is to eliminate hepatitis C from Punjab in approximately 10 years. This will result in reduction in all-cause mortality (deaths) and liver-related deaths, reduction in risk of developing HCC and reduction in risk of developing end-stage liver disease and need for liver transplantation. Thus eliminating HCV from Punjab would save thousands of lives. In order to effectively decentralize HCV care in the state, 250 medical specialists from state government hospitals have been identified for training on diagnosis and treatment of hepatitis C. Of these 250 medical specialists, roughly half of them have already been trained through a 4-h long training session followed by regular INASL-Punjab Government-Extension for Community Healthcare Outcomes (ECHO) Clinic, where difficult patient cases are presented and consulted with senior hepatologists from Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh using an online interface.^{1,12}

Though the cost of DAAs has come down, the cost of diagnosis and testing remain high. Thus, with the availability of pan-genotypic DAA-based regimens, it would be important for public-health programs to develop and implement simplified treatment guidelines that obviate the use of pre-treatment HCV genotype testing. Similarly, it would be useful to limit the post-treatment testing to only one occasion, i.e. 12 weeks after completing

treatment. Also, in future, use of HCV core antigen test as a cheaper alternative to HCV RNA testing, and reducing the cost of testing through negotiations with service providers, could make HCV treatment with DAAs even more economically attractive. The licensing agreements that have made low-cost generic DAAs available in India, allow for sale of these drugs in several other low- and low-middle-income countries at low prices.

CONCLUSIONS

Despite a low to moderate prevalence of HCV, the India contributes significantly toward the global HCV burden due to the large population. The evidence for the clinical safety and efficacy of HCV generics is compelling. Yet a small fraction of HCV infected persons in India receive therapy. A combined role of preventive strategies and improving access to therapy are required to control the burden of disease in India. In conclusion, we found that low-cost generic DAAs available in India are efficacious and cost effective. Therefore, HCV treatment should be a priority for health planners of this country, and other countries where low-cost DAAs are available, not only from the public health viewpoint, but also from the economic perspective.

CONFLICTS OF INTEREST

The authors have none to declare.

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