

## Open Journal of Gastroenterology and Hepatology (ISSN:2637-4986)



# EFFICIENCY OF DAA ON HCV-INFECTED KIDNEY TRANSPLANT PATIENTS AT CHO RAY HOSPITAL - VIETNAM

Tran Xuan Truong<sup>1</sup>, Thai Minh Sam<sup>2</sup>, Pham Thi Ngoc Thao<sup>3</sup>, Tran Ngọc Sinh<sup>4</sup>

<sup>1</sup>Chief of General Internal Medicine department - Cho Ray hospital – South Vietnam

<sup>2</sup>Chief of Uro-Nephrologic department - Cho Ray hospital – South Vietnam

<sup>3</sup>Vice Director of Cho Ray hospital-South Vietnam

<sup>4</sup>Uro-Nephrology Professor of University of Medical and Pharmaceutical – South Vietnam

### ABSTRACT

**Purposes:** To evaluate the efficiency of DAA (Direct Antiviral Agent), in particular sofosbuvir, ledipasvir in Hepatitis C treatment for patients with kidney transplants. Take note in the side effects and drug interactions during the treatment processes.

**Method:** Intervention, prospective, cohort, case studies, non-randomized, open on to all kidney transplant cases with chronic Hepatitis C tested positive HCV RNA (+); the patients from the cases above had agreed to be the research's subjects from 11/2015 to 8/2018 at Cho Ray hospital. Two regimens Sofosbuvir/Ribavirin and Sofosbuvir/Ledipasvir have been used for treatments, which depend on HCV genotype and liver cirrhosis levels.

**Results:** In 440 patients who had been observed after kidney transplants, 44 cases anti HCV (+), 29 cases HCV RNA(+) and 4 cases HBV/HCV Confection. There were 15 cases with chronic Hepatitis C participated in study. Males made up 66.6% of the group with the average age  $49 \pm 7.06$  yrs. There were 6.7% of them not taking full-course treatments. 80% of the patients were infected with only C virus, while 20% of the patients were co-infected with B and C virus. 40% of them had histories of previous blood transfusions. The ratio of patients with elevated liver enzymes was 33.3%. Genotype 1 (a and b) was 33.3%, genotype 2 was 6.7%, genotype 6 was 53.3% and 6.7% unidentifiable genotype. There were 2 cases which were treated with Sofosbuvir/Ribavirin regimen and 13 cases which were treated with Sofosbuvir/Ledipasvir regimen.

### \*Correspondence to Author:

Tran Xuan Truong  
Chief of General Internal Medicine department - Cho Ray hospital – South Vietnam

### How to cite this article:

Tran Xuan Truong, Thai Minh Sam, Pham Thi Ngoc Thao, Tran Ngọc Sinh. EFFICIENCY OF DAA ON HCV-INFECTED KIDNEY TRANSPLANT PATIENTS AT CHO RAY HOSPITAL - VIETNAM. Open Journal of Gastroenterology and Hepatology, 2019, 2:13

 eSciPub  
eSciPub LLC, Houston, TX USA.  
Website: <https://escipub.com/>

Rapid virologic response (RVR) is 100%. Sustained virologic response (SVR) within 12 weeks and 24 weeks is 100%. Relapse ratio 0%. In regimen using Sofosbuvir / Ledipasvir, the side effects are mild and transient, including skin irritation, digestive disorders which account for 7.7%. In regimen using Sofosbuvir / Ribavirin, side effects including severe anemia, fatigue, loss of appetite related to Ribavirin occur in 50% of cases (1/2) which lead to stopping treatment termination after 10 weeks and being replaced with treatment regimens using sofosbuvir / daclatasvir with good results. No major interactions are recorded when being used simultaneously with immunosuppressive drugs such as Prograf, Sandimmum Neoral, Mycophenolate Mofetil, Prednisone in this research. No renal failure occurs. Liver enzymes are improved during and after treatment. There is improvement scale of fibroscan after treatment.

**Conclusion:** Sofosbuvir/ Ledipasvir regimen have proven their effectiveness in treating chronic Hepatitis C genotype 1, 2 and 6 on kidney-transplanted patient, with RVR at 100%, SRV 12 and SRV 24 at 100%. Sofosbuvir/ ribavirin regimen have proven to be effective in eliminating virus and be economical in treating chronic hepatitis C genotype 2, however, the anemia side effect of ribavirin need to be considered in case it become serious and now the first-line regimens are Sofosbuvir/daclatasvir or sofosbuvir/ Velpatasvir. There is improvement of hepatic fibrosis after treatment DAA.

**Keywords:** kidney transplantation, hepatitis C, HCV, DAA, sofosbuvir, ledipasvir, ribavirin, Vietnam.

### **Back ground:**

According to the system statistics of the World Health Organization in 2016, about 110 million people infected with HCV with 80 million people with chronic HCV infection [17]. Hepatitis C reduces survival in both kidney transplant patients and patients with chronic renal failure [1,6,9,14]. According to statistics in Vietnam: there are about 4.5 million people infected with HCV, especially high proportion in the hemodialysis group with the rate from 11% to 43%. Each year 10,000-20,000 deaths are related to HCV and this number will triple in the next 10-20 years. Kidney transplantation at Viet nam beginning from 1992. In the period 1992-2011 there were 534 kidney transplantation cases

performed in 7 centers in Viet nam. Now there are 16 kidney transplant centers. Until 2016 About 1.000 cases kidney transplantation performed at Vietnam and Choray hospital performed 530 cases KTx.

Interferon is contraindicated drugs used in kidney transplant patients with HCV infection by high-risk kidney transplant rejection [2,5,7,10,16]. DAA (Direct Antiviral Agent), specifically sofosbuvir and ledipasvir have been presenting in Vietnam since the end of 2015, there have been research results in the world showing the high effectiveness of DAA in the combination of no interferon regimen for hepatitis C in the kidney transplantation patient [3,4,12,13], however, there are no specific, complete assessments of

the effectiveness of DAA on HCV in kidney transplant patients in Vietnam. Therefore, we aimed to evaluate the efficiency of DAA, in particular sofosbuvir, ledipasvir in Hepatitis C treatment for patients with kidney transplants. Take note in the side effects and drug interactions during the treatment processes.

### Patients and methods:

**Method:** We perform a intervention, prospective, cohort, case studies, non-randomized, open research on to all kidney transplant cases with chronic Hepatitis C tested positive HCV RNA (+); the patients from the cases above had agreed to be the research's subjects from 11/2015 to 8/2018 at Cho Ray hospital. Two regimens Sofosbuvir/Ribavirin and Sofosbuvir/Ledipasvir have been used for treatments, which depend on HCV genotype and liver cirrhosis levels.

About medications of study: Ledipasvir/Sofosbuvir have official launched in Vietnam since 10/2015 with trade name Ledvir. Ledvir was manufactured in India by Mylan pharmaceutical factory with license from Gilead pharmaceutical company. Ledvir is combination of sofosbuvir 400mg and Ledipasvir 90mg/ tablet. Sofosvir is sofosbuvir 400mg/ tablet and Ribazol contain 500mg ribavirin per tablet.

### Duration of treatment:

Sofosbuvir + ribavirin (HCV genotype 2) /12 weeks

Sofosbuvir + ribavirin (HCV genotype 3) / 24 weeks

Ledvir (HCV genotype 1,4,5,6 without cirrhosis)/ 12 weeks

Ledvir (HCV genotype 1,4,5,6 with compensated cirrhosis) / 24 weeks

**Inclusion criteria:** all kidney transplant cases with chronic Hepatitis C tested HCV RNA (+) and agree to be the research's subjects.

### Exclusive criteria:

With Sofosbuvir + ledipasvir combination regimen: there are contra-indications in patient

is using Amiodarone or with severe renal impairment (with eGFR <30 mL / min / 1.73 m<sup>2</sup>) [5,11]

With sofosbuvir + ribavirin combination regimen: there are contraindications to ribavirin such as: pregnant women, or nursing mothers, severe medical conditions, including severe infections, uncontrolled heart failure, chronic obstructive pulmonary disease, severe coronary artery disease, history of allergy to ribavirin, patient is using with didanosine (HIV drug). Some hematologic contraindications such as Hb <10g / dl, Neutrophil <1.5x10<sup>9</sup> T / L, platelet < 90 x 10<sup>9</sup> / L, renal failure with serum creatinine > 1.5mg%, hemoglobin disease.<sup>[17,2,5]</sup>

### Clinical examination:

Once a month for 12 months, record on the medical records.

Classification of liver disease according to criteria of Child-Turcotte-Pugh.

### Paraclinical examination:

Blood count, ALT, AST, Bun, Creatinin per month, in 12 months.

Parameters bilirubin, prothrombin time, albumine At the beginning of treatment and after 12 months or when liver enzyme outbreak. fibroscan parameters is recorded at baseline and 12 months later.

Quantitative HCV RNA was performed at the beginning of treatment, after treatment for 1 month, 2 month\*, 3 months, 6 months, 1 year, (4 times) to evaluate RVR, EVR, EOT, SVR 12 and resistance or relapse (\* only perform if HCV RNA still positive after 1 month of treatment)

**Follow up clinical adverse events** in treatment progress: all of adverse was report by manufacture such as Fever, Anorexia, Fatigue, Headache, Bradycardia, Musculoskeletal pain, Hair loss, Syncope, Hemorrhagic diarrhea, Erysipelas, digestive disorder, insomnia, anxiety, rash, pruritus will be record.

**Follow up laboratory adverse events** in treatment progress: hemoglobin deficiency, lymphocytopenia, neutropenia, leukopenia, thrombocytopenia, serum creatinine level increasing, transaminase elevation, urinary tract infection, hyponatremia, hyperglycemia, hyperuricemia will be note and recorded.

### Results:

In 440 patients who had been observed after kidney transplants, 44 cases anti HCV (+), 29 cases HCV RNA(+) and 4 cases HBV/HCV Coinfection. There were 15 cases with chronic Hepatitis C participated in study. Males made up 66.6% of the group with the average age

49± 7.06 yrs. There were 6.7% of them not taking full-course treatments. 80% of the patients were infected with only C virus, while 20% of the patients were co-infected with B and C virus. 40% of them had histories of previous blood transfusions. The ratio of patients with elevated liver enzymes was 33.3%. Genotype 1 (a and b) was 33.3%, genotype 2 was 6.7%, genotype 6 was 53.3% and 6.7% unidentifiable genotype. There were 2 cases which were treated with Sofosbuvir/Ribavirin regimen and 13 cases which were treated with Sofosbuvir/Ledipasvir regimen.

**Table 1: General characteristics**

CHARACTERISE	Number of case	Ratio
Anti HCV (+)	44 / 440	10%
Anti HCV (+) and HCV RNA (+)	29/440	6.66%
Number of cases participated	15/440	3.41%
Sex : Male	10/15	66.6%,
Female	5/15	33.4%
Child-Tourcote-Pug Classification		
Child A	15/15	100%
Child B	0	0%
Child C	0	0%
Following up time mean after KTx	8.33 yrs ± 4.4 (2yr to 17 yrs)	

**Table 2: Genotype characteristic**

Genotype of virus C	Ratio
Genotype 1(a and b)	33.3 % (5/15),
Genotype 2	6.7 % (1/15)
Genotype 3	0%
Genotype 4	0%
Genotype 5	0%
Genotype 6	53.3% (8/15)
Genotype: unidentified	6.7% (1/15)

**Table 3: Immunosuppressive regimens**

Immunosuppressive regimens	Number of case	Ratio
Prednisone + CsA + Azathioprine	3 cases	20%
Prednisone + CsA + MMF	5 cases	33.3%
Prednisone + FK506 +MMF	7 cases	46.67%

**Table 4: Fibrosis evolution**

Fibroscan	Beginning of treatment	1 year after treatment
F0	4/15	6/15
F1	8/15	9/15
F2	3/15	0
F3	0/15	0
F4	0/15	0

There is improvement scale of fibroscan after treatment.

**Table 5: Virologic response in Sofosbuvir/Ledipasvir regimen**

(in comparison with Massimo et al study and Ion-1 study)

Variable	Ledipasvir–Sofosbuvir 12 wks		
	Massimo et al study (n = 57 KTx) <sup>[12]</sup>	ION- 1 study <sup>[13]</sup> (n = 214 )	CHORAY study (n = 13 KTx)
<b>HCV RNA level less than the LLOQ during treatment, n/N (%)</b>			
<b>Baseline</b>	0/57 (0)	0/214 (0)	0/13 (0)
<b>Week 1</b>	9/57 (16)	NA	NA
<b>Week 2</b>	31/57 (54)	174/213 (82)	NA
<b>Week 4 (RVR)</b>	50/57 (88)	213/213 (100)	13/13 (100)
<b>Week 8</b>	56/56 (100)*	NA	NA
<b>Week 12 (EOT)</b>	56/56 (100)*	213/213 (100)	13/13 (100)
<b>HCV RNA level less than the LLOQ after end of treatment, n/N (%)</b>			
<b>SVR4</b>	57/57 (100)	211/212 (99)	NA
<b>SVR12</b>	57/57 (100)	211/212 (99)	13/13 (100)
<b>Overall virologic failure</b>	0/57(0)	0/213 (0)	0/13(0)
<b>Relapse n/N (%)</b>	0/0 (0)	1/212	0/13 (0)

Rapid virologic response (RVR) is 100%. Sustained virologic response (SVR) within 12 weeks is 100%. Relapse ratio 0%. The results are similar with Massimo et al study<sup>[12]</sup>, Ion-1 study<sup>[13]</sup> and many other researchs in the world<sup>[4]</sup>.

**Table 6: Clinical adverse events of sofosbuvir + Ledipasvir regimen (13 cases)**

Side effects	Number of case	Ratio %	3 months After stop treatment	Ratio %
Fever	0	0	0	0
Anorexia	0	0	0	0
Asthenia	0	0	0	0
Headache	0	0	0	0
Nausea	0	0	0	0
Rash	1	7.66%	0	0
Bradycardia	0	0	0	0

In regimen using Sofosbuvir / Ledipasvir, the side effects are mild and transient, including skin irritation, digestive disorders which account for 7.66%.

**Table 7: Paraclinical adverse events of sofosbuvir + Ledipasvir regimen (13 cases)**

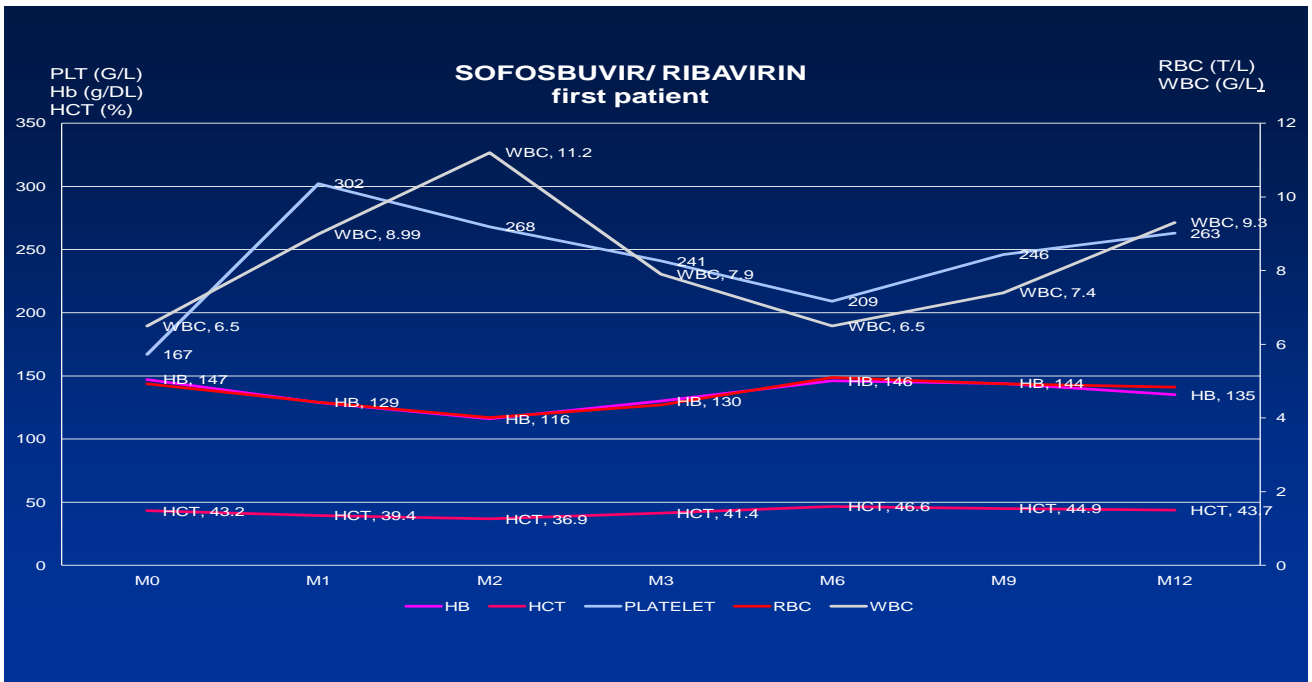
Side effects	Number of case	Ratio %	3 months After stop treatment
Transaminase elevation	0	0	0
Anemia	0	0	0
Thrombocytopenia	0	0	0
Leucopenia	0	0	0
Digestive disorder	1	7.66%	0
Renal failure	0	0	0

In regimen using Sofosbuvir / Ribavirin, 2 cases were reported with RVR is 100%. One case get SVR 12, one case get RVR and negative HCV RNA at 10<sup>th</sup> week, however haft of them with severe side effects: anemia, fatigue, loss of appetite related to ribavirin which lead to stopping treatment termination after 10 weeks and being replaced with treatment regimens

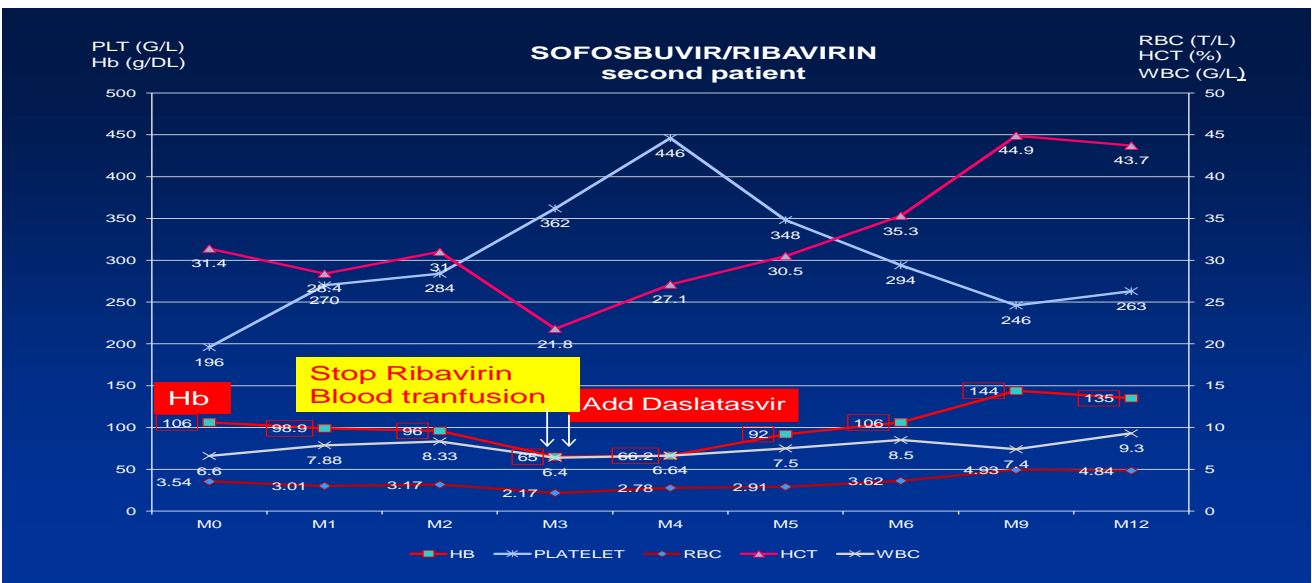
using sofosbuvir/daclatasvir with good results (get SVR 12, SVR 24). (Figure 1, 2 and table 9) No major interactions are recorded when being used simultaneously with immunosuppressive drugs such as Prograf, Sandimmum Neoral, Mycophenolate Mofetil, Prednisone in this research. No renal failure occurs. Liver enzymes are improved during and after treatment. (Table 8)

**Table 8: Biochemie progress of all regimens (15 cases)**

Variable	Beginning treatment	of	1 month after	3 months after	3 moths after stop treatment
GLYCEMIE (mg %)	76,32 ± 33,20		87,43±18,72	85,57± 14,92	91,67 ± 20,36
BUN (mg%)	18,43 ± 5,04		19,29 ± 4,68	17,71± 6,67	16,33 ± 4,46
CREATININE (mg%)	1,39 ± 0,25		1,31± 0,20	1,31± 0,21	1,22 ± 0,16
(U/L)	38,71± 16,93		25,86 ± 5,57	26,85 ± 9,60	27,67± 8,50
(U/L)	37± 20,85		23,71± 7,24	21,29± 8,78	27,67 ± 10,47



**Figure 1: Hematologic progress of sofosbuvir/ ribavirin in first patient**



**Figure 2: Hematologic progress of sofosbuvir/ ribavirin in second patient**

**Table 9: adverse events of sofosbuvir + ribavirin regimen (2 cases)  
(In comparison with results of Ion-1 study)**

Variable	Regimen 12wks		Regimen 12wks
	ION 1 study LDV-SOF (N= 214) <sup>[13]</sup>	ION- 1 study LDV-SOF + RBV (N= 217) <sup>[13]</sup>	Cho ray hos. study SOF + RBV (N= 2)
Common adverse events — no. of patients (%) †			
Fatigue	44 (21)	79 (36)	1 (50%)
Headache	53 (25)	49 (23)	1 (50%)
Insomnia	17 (8)	45 (21)	0
Nausea	24 (11)	37 (17)	0
Asthenia	14 (7)	23 (11)	1 (50%)
Diarrhea	24 (11)	18 (8)	0
Rash	16 (7)	21 (10)	1 (50%)
Pruritus	11 (5)	22 (10)	0
Anemia	0	25 (12)	1 (50%)
Hematologic abnormality — no. of patients (%)			
Decreased hemoglobin level			
<10 g/dl	0	20 (9)	0
<8.5 g/dl	0	1 (<1)	1 (50%)
Lymphocyte count <350 per mm <sup>3</sup>	0	1 (<1)	0
Neutrophil count 500 to <750 per mm <sup>3</sup>	1 (<1)	0	0
Platelet count 25,000 to <50,000 per mm <sup>3</sup>	1 (<1)	0	0

**Conclusion:** Sofosbuvir/ Ledipasvir regimen have proven their effectiveness in treating chronic Hepatitis C genotype 1, 2 and 6 on kidney-transplanted patient, with RVR at 100%, SRV 12 and SRV 24 at 100%. Sofosbuvir / ribavirin regimen have proven to be effective in eliminating virus and be economical in treating chronic hepatitis C genotype 2, however, the anemia side effect of ribavirin need to be considered in case it become serious and now the first-line regimens are Sofosbuvir

/daclatasvir or sofosbuvir/ Velpatasvir <sup>[8,16,15]</sup>. There is improvement of hepatic fibrosis after treatment DAA.

### References

1. "NIH consensus statement on management of hepatitis C: 2002," *NIH Consensus State Sci Statements*, vol. 19, no. 3, pp. 1–46, 2002.
2. AASLD and IDSA 2015 ."Recommendations for Testing, Managing, and Treating Hepatitis C ".
3. AASLD-IDSA -2016. "Recommendations for Testing, Managing, and Treating Hepatitis C"



4. D. Sawinski, N. Kaur, A. Ajeti, J. Trofe-Clark, M. Lim, M. Bleicher, S. Goral, K. A. Forde, R. D. Bloom. 2016. "Successful Treatment of Hepatitis C in Renal Transplant Recipients With Direct-Acting Antiviral Agents". *American Journal of Transplantation* Volume 16, Issue 5, May 2016, Pages 1588–1595
5. European Association for the Study of the Liver. 2015 "EASL Recommendations on Treatment of Hepatitis C 2015". *Journal of Hepatology* 2015 vol. 63j 199–236
6. Fabrizi F, Martin P, Dixit V, Bunnapradist S, and Dulai G (2005). "Hepatitis C virus antibody status and survival after renal transplantation: meta-analysis of observational studies". *American Journal of Transplantation*, vol. 5(6), pp. 1452–1461
7. J. Levitsky, K. Doucette (2013). Viral Hepatitis in solid organ transplantation. *American Journal of Transplantation*, vol 13, pp 147-168
8. Jordan J. Felt, Hamant Shah, 2016. "Management of hepatitis C infection". In practice. Provided by Clinical Care Options, LLC, and Boston University
9. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. 2012. Volume 2, Issue 4, August 2012.
10. Marco Carbone, Paul Cockwell and James Neuberger. (2011). "Hepatitis C and Kidney Transplantation". Review Article, *International Journal of Nephrology*. Volume 2011, Article ID 593291, 17 pages, doi:10.4061/2011 /593291
11. Mark S. Sulkowski . (2016) . "Hepatitis C Management in Special Populations"
12. Massimo Colombo, Alessio Aghemo, Hong Liu, Jie Zhang et al .2017. "Treatment With Ledipasvir–Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic Hepatitis C Virus Genotype 1 or 4 Infection: A Randomized Trial". *Ann Intern Med*. 2017;166(2):109-117.
13. Nezam Afdhal, Stefan Zeuzem, Paul Kwo, Mario Chojkier, Norman Gitlin, Massimo Puoti, Manuel Romero-Gomez, Jean-Pierre Zarski, Kosh Agarwal, Peter Buggisch, Graham R. Foster, et al (2014). "Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 infection". *The New England Journal of Medicine*, May 2014, 370, (20), pp 1889-1898.
14. Scott DR, Wong JK, Spicer TS, et al (2010). "Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand". *Transplantation*; vol. 90(11), pp. 1165–1171.
15. World Health Organisation, (2018). *Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C infection. Guideline, July 2018*". World Health Organization. Printed in France
16. World Health Organisation. 2016. "Guidelines for the screening care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016.
17. World Health Organization. 2016. "Guidelines for the screening care and treatment of persons with chronic hepatitis C infection".

