加はなかった。

2．抗 HCV 療法を行わなかったが、cART を施行して経過観察した例(男性67例、女性3例　平均観察期間　86.8 ± 33.3 ヶ月)

結果を（表2）に示す。CD4 は 273 ± 205 / μL から 403 ± 219 / μL と有意に増加していた。肝機能は AST, ALT,には変化は見られなかったが、ビリルビンが 0.7 ± 0.5 mg/dL から 1.5 ± 3.0 mg/dL と有意に増加していた。血球には変化が認められず、APRI 値にも変化はなかった。

3．インターフェロンを含んだ抗 HCV 療法を cART と共に行ったものの、SVR にならなかった例(男性21例、女性2例　平均観察期間　85.4 ± 27.7 ヶ月)

結果を（表3）に示す。CD4 は 245 ± 160 / μL から 432 ± 185 / μL と有意に増加していた。肝機能は AST, ALT, ビリルビンともは変化は見られなかった。血球には変化が認められず、APRI 値にも変化はなかった。

4．インターフェロンを含んだ抗 HCV 療法を cART と共に行い、SVR に至った例（男性 17 例、女性 0 例　平均観察期間　84.2 ± 24.6 ヶ月)

結果を（表4）に示す。CD4 は 360 ± 141 / μL から 567 ± 268 / μL と有意に増加していた。肝機能は AST, ALT,とも有意に改善していたが、ビリルビンには変化は見られなかった。血小板数は上昇していた。APRI 値は改善傾向にはあったものの有意な変化はなかった。

D．考察

HIV・HCV 重複感染症においては HCV 単独感染症に比較して、線維化の進展が速いことが兼ねてから指摘されているが、日本人において実際にどの程度の速度で線維化が進展するかは不明であった。これは日本人の重複感染例の多くが血友病症例であり、肝生検による評価が難しいこと、肝生検以外に肝線維化を評価するよい指標がこれまでなかったことにある。

本検討では肝線維化の指標としてビリルビン値、血小板数、APRI を用いた。（表1）に示した無治療例からは、AST, ALT の上昇に比べて血小板数の減少が大きく、HIV 感染症を含めた他の原因により血小板数が減少していることが推定された。血小板数に比較して APRI は AST, ALT の推移とパラレルに動いているような印象がある。今後 Fibroscan など他の指標も用いた検討が必要であると思われる。

検討2では cART の効果を調べた。インターフェロンを用いた抗 HCV 療法が行えない場合、cART を施行することにより線維化の進展を抑制することができるという検討がこれまでにもある。我々の検討ではビリルビン以外の指標には変化が認められなかった。従って cART のみでも7年程度は線維化の進展を抑えることのできる可能性が示唆される。ビリルビンの上昇はプロテアーゼ阻害薬など薬剤による副反応によるものと推定される。

検討3、4ではインターフェロンを用いた抗 HCV 療法により肝線維化の抑止が可能かどうかの検討を行った。結論としては SVR が得られた症例では血球数の改善が見られ、肝線維化の改善が示唆されたが、APRI には有意な変化は見られなかった。SVR 後の観察期間が短いこと、SVR に至った例が少なかったことなどが原因として考えられる。

今後シメプレビルを用いた治療、経口抗ウイルス薬を用いた治療を行うことで抗 HCV 療法の効果は上がることが期待されている。肝線維化の改善に関しても前向き検討が今後望まれる。

E．結論

インターフェロンを用いた抗 HCV 療法を cART と併用して HCV が排除されると肝線維化は緩徐に改善する。cART のみ、あるいは抗 HCV 療法でウイルスが排除できない場合には線維化の進展速度は遅くできるものの、線維化の改善は難しい。

F．健康危険情報

なし

G．研究発表

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2．学会発表

特になし

H. 知的財産権の出願・登録状況（予定を含む。）

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

表１　　自然経過観察例

| | 観察開始時 | 最終観察時 | *p* |
|---|---|---|---|
| CD4 (/μL) | 516 ± 219 | 394 ± 176 | 0.04 |
| T Bil (mg/dL) | 0.7 ±0.4 | 1.0 ± 1.0 | 0.3 |
| AST (IU/L) | 33.2 ±15.2 | 54.7 ± 33.6 | 0.04 |
| ALT (IU/L) | 37.5 ±16.7 | 56.7 ± 16.7 | 0.04 |
| WBC (*$10^3$/uL) | 5500 ±1700 | 4800 ±2200 | 0.07 |
| PLT (*$10^4$/uL) | 22.6 ±8.9 | 16.9 ±7.5 | 0.01 |
| APRI | 0.53 ±0.43 | 1.96 ±3.70 | 0.12 |

表２　　cART 導入例

| | 観察開始時 | 最終観察時 | *p* |
|---|---|---|---|
| CD4 (/μL) | 273 ± 205 | 403 ± 219 | <0.01 |
| T Bil (mg/dL) | 0.7 ±0.5 | 1.5 ± 3.0 | 0.037 |
| AST (IU/L) | 49.3 ±45.4 | 52.3 ± 50.2 | 0.58 |
| ALT (IU/L) | 55.7 ±45.3 | 58.6 ± 42.4 | 0.63 |
| WBC (*$10^3$/uL) | 4500 ±1800 | 4800 ±1500 | 0.24 |
| PLT (*$10^4$/uL) | 18.6 ±6.6 | 18.6 ±7.8 | 0.97 |
| APRI | 1.00 ±1.34 | 1.28 ±2.24 | 0.25 |

表３　　抗 HCV 療法 nonSVR 例

| | 観察開始時 | 最終観察時 | *p* |
|---|---|---|---|
| CD4 (/μL) | 245 ± 160 | 432 ± 185 | 0.0001 |
| T Bil (mg/dL) | 1.1 ±0.9 | 1.6 ± 2.1 | 0.29 |
| AST (IU/L) | 64.3 ±48.9 | 69.1 ± 57.0 | 0.67 |
| ALT (IU/L) | 89.1 ±82.4 | 88.3 ± 61.5 | 0.96 |
| WBC (*$10^3$/uL) | 4100 ±1300 | 4800 ±1500 | 0.1 |
| PLT (*$10^4$/uL) | 16.7 ±6.6 | 17.1 ±8.0 | 0.8 |
| APRI | 1.24 ±0.99 | 1.48 ±1.37 | 0.36 |

表４　　抗 HCV 療法 SVR 例

| | 観察開始時 | 最終観察時 | *p* |
|---|---|---|---|
| CD4 (/μL) | 360 ± 141 | 567 ± 268 | 0.02 |
| T Bil (mg/dL) | 0.8 ±0.5 | 0.7 ± 0.3 | 0.44 |
| AST (IU/L) | 52.9 ±20.8 | 29.6 ± 9.3 | 0.0001 |
| ALT (IU/L) | 72.4 ±42.9 | 35.7 ± 22.4 | 0.0022 |
| WBC (*$10^3$/uL) | 4500 ±1300 | 5400 ±1800 | 0.0613 |
| PLT (*$10^4$/uL) | 15.6 ±4.1 | 17.9 ±5.0 | 0.0481 |
| APRI | 1.02 ±0.51 | 0.50 ±0.22 | 0.25 |

厚生労働科学研究費補助金（エイズ対策研究事業）
分担研究報告書

# 血液製剤によるＨＩＶ/ＨＣＶ重複感染患者における非侵襲的線維化評価

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研究要旨
血液製剤による HIV/HCV 重複感染患者に対し、非侵襲的な肝線維化評価ツールとして、超音波エラストグラフィである ARFI および FibroScan®と一般肝機能検査から算出される APRI(AST-platelet ratio index) ;(AST/AST 正常上限[IU/L])/血小板数[×109/L]×100、FIB4 ; 年齢[歳]×AST[IU/L]/(血小板数[×109/L]×(ALT[IU/L])1/2)の有用性について検討を行った。長崎大学で ARFI を施行した 30 例、国立国際医療研究センター(ACC)で Fibroscan を施行した 16 例について、ARFI・APRI・FIB4 と他の肝機能検査項目との比較を行ったところ、これら非侵襲的マーカーは既知の肝線維化マーカー(ヒアルロン酸・Ⅳ型コラーゲン)だけでなく、肝予備能(PT・アルブミン・ICG15 分値・アシアロシンチ LHL15)とも相関を認めた。血友病により肝生検が困難な同患者群に対して、肝機能や線維化の程度を推測できる有用な検査である可能性が示唆された。

## A. 研究目的

肝線維化評価には肝生検が必要であるが、本研究の対象患者であるHIV/HCV重複感染患者は血友病による凝固能異常を有しており、肝生検が困難である。近年、非侵襲的な肝線維化評価のツールとして、ARFI（Acoustic Radiation Force Impulse Imaging）、FibroScan®などの超音波エラストグラフィ、一般肝機能検査より算出可能なAPRI(AST-platelet ratio index) ;(AST/AST正常上限[IU/L])/血小板数[×109/L]×100、FIB4 ; 年齢[歳]×AST[IU/L]/(血小板数[×109/L]×(ALT[IU/L])1/2)などが注目されている。

本研究では、重複感染患者においてARFIおよびFibroScan®と既知の肝線維化マーカー、APRI・FIB4の相関を検討し、非侵襲的検査の有用性を評価することを目的とする。

## B. 研究方法

対象は重複感染患者のうち、長崎大学でARFIを施行した30名および国立国際医療研究センター（ACC）でFibroScan®を施行した16例。同時期の検査データよりAPRI・FIB4を算出し、各種肝機能と肝線維化マーカーとの相関を併せて検討した。

（倫理面への配慮）

研究の遂行にあたり、画像収集や血液などの検体採取に際して、インフォームドコンセントのもと、被験者の不利益にならないように万全の対策を立てる。匿名性を保持し、データ管理に関しても秘匿性を保持する。

## C. 研究結果

長崎大学での 30 例では、ARFI によって算出した Velocity of shear wave(Vs)は、APRI(r=0.531)、FIB4(r=0.605)といずれも有意な相関あり(いずれも $p<0.01$)。

また ARFI と一般肝機能検査では、血小板、PT%、アルブミン、ヒアルロン酸、Ⅳ型コラーゲン、アシアロシンチ LHL15 にそれぞれ相関あり。総ビリルビン値とは相

関なし。

APRI は PT%、アルブミン、ヒアルロン酸、Ⅳ型コラーゲン、ICG15 分値、アシアロシンチにそれぞれ相関を認め、FIB4 は PT%、アルブミン、ヒアルロン酸、、アシアロシンチ LHL15 にそれぞれ相関あり。

同様に ACC で FibroScan®を施行した 16 例では、弾性度（kPa）と APRI に相関を認めたが FIB4 とは相関なし（P=0.08）。

D. 考察

超音波エラストグラフィである ARFI は APRI・FIB4 いずれも相関を認め、FibroScan®は APRI と相関を認めたが FIB4 とは相関がなかった。APRI・FIB4 のいずれにおいても、ヒアルロン酸・Ⅳ型コラーゲンなどの既知の肝線維化マーカーだけでなく、PT・アルブミン・ICG15 分値・アシアロシンチ LHL15 などの肝予備能とも相関を認めた。これらの結果より、特に APRI は肝の線維化だけでなく予備能も反映している可能性を示唆しているものと思われる。

非侵襲的肝線維化評価のツールは C 型肝炎などを中心にその有用性が報告されているものの、HIV/HCV 重複感染、特に本邦における血液製剤によって重複感染を来たした血友病患者についての検討はまだほとんどなされていないのが現状である。これは本研究の対象患者群は前述の通り肝生検が難しく、病理所見との比較が困難であることが一因と思われる。引き続きデータの蓄積を行い、これら非侵襲的肝線維化マーカーの有用性を検討する必要があると思われる。

また本研究の対象患者群は、現在全国の施設でフォローされているが、これは必ずしもその地域の中核病院ではなく、肝疾患について専門的な検査が困難なケースも少なくない。このような地域による格差をなくすために、今後予後との関連を追跡することにより、APRI のような一般的な肝機能検査から算出可能な肝線維化マーカーを確立する必要があると思われる。

E. 結論

超音波エラストグラフィーや APRI は本邦における HIV/HCV 重複感染患者の肝線維化・予備能評価のツールとして有用であり、特にどこの施設でも算出可能な APRI は、今後有用な線維化マーカー、ひいては予後予測マーカーとなる可能性が示唆された。

F. 健康危険情報

なし。

G. 研究発表

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HIV/HCV 重複感染者に対する肝移植適応評価に関する検討.第 31 回日本肝移植研究会

H. 知的財産権の出願・登録状況（予定を含む。）

1．特許取得
なし

2．実用新案登録
なし

3．その他
なし

# III. 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍：

| 著者氏名 | 論文タイトル名 | 書籍全体の編集者名 | 書籍名 | 出版社名 | 出版地 | 出版年 | ページ |
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# Ⅳ．研究成果の刊行物・別刷

LIVER TRANSPLANTATION 19:666, 2013

LETTER TO THE EDITORS

# False Positivity for the Human Immunodeficiency Virus Antibody After Influenza Vaccination in a Living Donor for Liver Transplantation

Received February 13, 2013; accepted February 25, 2013.

**TO THE EDITORS:**

Because of increased productivity and availability, more people have had the chance to undergo prophylactic influenza vaccination. It has been reported that influenza vaccination has cross-reactivity with human immunodeficiency virus (HIV) antibody assays, but this information is not well known in the field of transplantation.[1] Recently, we experienced a case of living donor liver transplantation in which a healthy donor candidate was frightened and was further screened for the HIV antibody.

The patient was a 43-year-old female who was a candidate for partial liver donation for her husband, who was suffering from hepatocellular carcinoma associated with hepatitis B liver cirrhosis. She had never undergone a blood transfusion or abused drugs before her screening for living partial liver donation. According to her laboratory results, she was positive for the HIV antibody (1.7 cut off index). Otherwise, all data, including hepatitis B antibody results, were within normal limits. It was found that she had undergone vaccination for influenza 1 week before the screening. She was referred to a specialist in HIV infection, and western blotting for all antibodies (GP160, GP110/120, P68/66, P55, P52/51, GP41, P40, P34/31, P24/25, and P18/17) was negative. HIV RNA was undetectable in her blood (<40 copies/mL). Thus, she was considered to be HIV-negative with a high level of confidence and subsequently donated the left lobe of her liver. The recipient remained negative for the HIV antibody even after living donor liver transplantation.

With the prevalence of influenza vaccination and organ donation, physicians should keep in mind that recent inoculation with any brand of influenza vaccine is associated with a false-positive screening assay for HIV antibodies.[2]

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The protocol for our living donor liver transplantation received a priori approval by the institutional review committee.

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DOI 10.1002/lt.23635
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION. DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

Hepatology Research

*Hepatology Research* 2014; **44**: 17–21 doi: 10.1111/hepr.12132

***Review Article***

# Liver transplantation for HIV/hepatitis C virus co-infected patients

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**Since the introduction of antiretroviral therapy (ART) in the mid-1990s, AIDS-related death has been dramatically reduced, and hepatitis-C-virus (HCV)-related liver failure or hepatocellular carcinoma has currently become the leading cause of death in HIV/HCV co-infected patients. Liver transplantation may be one of the treatments of choices in such cases, but the indications for transplantation, perioperative management including both HIV and HCV treatments, immunosuppression and the prevention/treatment of infectious complications are all still topics of debate. With the improved understanding of the viral behaviors of both HIV and HCV and the development of novel strategies, especially to avoid drug interactions between ART and immunosuppression, liver transplantation has become a realistic treatment for HIV/HCV co-infected patients.**

**Key words:** hepatitis C virus, HIV, liver transplantation

## INTRODUCTION

IN JAPAN, IN the late 1980s, contaminated blood production of coagulation factor for hemophilia caused co-infection of HIV and hepatitis C virus (HCV). Actually, greater than 90% of HIV-infected patients have HCV as well.[1]

After antiretroviral therapy (ART) was introduced in the late 1990s, successful control of HIV was achieved in most cases and death due to AIDS was dramatically reduced, but HCV-related death due to liver failure or hepatocellular carcinoma became a serious problem, not only in Japan, but all over the world.[2–6] In such cases, liver transplantation (LT) is the only treatment option to achieve long-term survival, but several modifications of perioperative management are required. In this review, the outcome and the points of management of LT for HIV/HCV co-infected patients were reviewed.

## REPORTED OUTCOME OF LT FOR HIV/HCV PATIENTS

THE REPORTED OUTCOMES of LT for HIV and HIV/HCV co-infected patients from Western countries after the introduction of ART are summarized in Table 1.[7–11] In general, most reports concluded that the results were worse than in the cases with HCV mono-infection, with a 3-year survival of approximately 60–70%. In Japan, the Tokyo group reported six cases of living donor liver transplantation (LDLT) between 2001 and 2004, of whom four died.[12] These unfavorable outcomes are likely related to the difficulties of determining the indications for LT and of perioperative management, including HIV/HCV treatment and the prevention and treatment of infectious complications. Terrault *et al.* reported that older donor age, combined kidney–liver transplantation, an anti-HCV positive donor and a body mass index of less than 21 kg/m$^2$ were independent predictors of graft loss.[10] After transplantation, several studies showed that acute cellular rejection was more frequent and severer in HIV/HCV co-infected patients than that in HCV mono-infected patients, possibly due to the difficulties in achieving optimal immunosuppression because of interactions between antiretroviral agents and immunosuppression.[10,11]

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*Funding sources:* This study was partially supported by the Health and Labor Sciences Research Grant from the Ministry of Health, Labor and Welfare Japan, regarding Research on Indication of Liver Transplantation for HIV/HCV co-infected Patients.

*Received 1 January 2013; revision 7 April 2013; accepted 7 April 2013.*

**Table 1** Outcome of liver transplantation for HIV/hepatitis C virus co-infection

| Authors | Publication year | Country | *n* | Patient survival (%) | | |
|---|---|---|---|---|---|---|
| | | | | 1 year | 3 years | 5 years |
| de Vera *et al.*[7] | 2006 | USA | 27 | 67 | 56 | 33 |
| Schreibman *et al.*[8] | 2007 | USA | 15 | 73 | 73 | – |
| Duclos-Vallee *et al.*[9] | 2008 | France | 35 | – | 73 | 51 |
| Terrault *et al.*[10] | 2012 | USA | 89 | 76 | 60 | – |
| Miro *et al.*[11] | 2012 | Spain | 84 | 88 | 62 | 54 |

## SPECIAL ISSUES REGARDING LT INDICATIONS FOR HIV/HCV CO-INFECTION

### ART-related non-cirrhotic portal hypertension

IN HCV MONO-INFECTED patients, LT should be considered when the patients develop deteriorated liver function as indicated by a Child–Pugh classification of B or C. In HIV/HCV co-infected patients, liver failure due to HCV hepatitis was generally enhanced by ART-related hepatotoxicity, especially non-cirrhotic portal hypertension.[13–15] Accordingly, not only in cases with deteriorated liver function but also in class A cases, the patients can easily develop severe liver dysfunction suddenly,[16,17] so that all HIV/HCV co-infected patients should be carefully followed up so as not to miss the chance for LT. Also, Murillas *et al.* reported that Model for End-Stage Liver Disease (MELD) score is the best prognostic factor in HIV-infected patients,[18] so that HIV/HCV co-infected patients may be considered for LT before MELD score increase to achieve comparable results with HCV mono-infected patients. Several studies showed the aggressive fibrosis in HIV/HCV co-infected patients compared with HCV mono-infected patients,[19,20] but the mechanism of this aggressive fibrosis remains unclear. Recently, transient elastography or acoustic radiation force impulse imaging to check for liver stiffness has been introduced as an effective and non-invasive modality to determine patients' candidacy for LT.[21–23]

### Count of CD4$^+$ T lymphocytes

Generally, the count of CD4$^+$ T lymphocytes has been required to be more than 200/μL to perform general elective surgeries in HIV-infected patients,[24] but in HIV/HCV co-infected patients, current studies show that a count of more than 100/μL is acceptable,[25,26] because patients generally have portal hypertension which can cause pancytopenia. In such patients, the ratio of CD4/CD8 is reported to be a feasible marker to predict postoperative complications including opportunistic infections. When the ratio is less than 0.15, the incidence of infectious complications is significantly higher.[27]

### Preoperative infections

In regard to latent opportunistic infections that occur before LT, they are not absolute contraindications when they can be expected to be controlled.[28] Infections regarded as contraindications for LT included uncontrollable multidrug resistance HIV infection, chronic *Cryptosporidium enteritis*, progressive multifocal leukoencephalopathy and lymphoma.[29]

## MANAGEMENT OF HIV/HCV IN LT

### Management of HIV

THE NUMBER OF HIV RNA copies before LT is suggested as an independent risk factor of postoperative mortality, so that HIV should be controlled sufficiently before LT.[30] Accordingly, in the patients who are under consideration to receive LT, ART can be safely stopped before LT because HIV is generally well-controlled for a long period by ART. After LT, ART should be restarted as soon as possible because HIV RNA appears at 3–30 days after ART is stopped,[31] but the timing of restart of ART depends on the patient's condition, including liver function.[32] As long as the liver function has not fully recovered, or partial liver graft such as in LDLT has not sufficiently regenerated yet, ART cannot be started. Castells *et al.* reported in their case–control study that ART was started at a median of 8 days after LT (range, 4–28 days).[33] In principle, the ART administrated after LT should be the same as the pretransplant regimen, but the majority of ART drugs including protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) have interactions with calcineurin inhibitors

(CNI) or mammalian target of rapamycin (mTOR),[34] so that the monitoring of blood levels of immunosuppression is extremely important to avoid infectious complications or rejection. Currently, a novel HIV-1 integrase inhibitor, raltegravir (RAL), is expected to be a feasible drug because it has no interactions with CNI, unlike other drugs.[35,36]

### Management of HCV

The treatment strategy for HCV in HIV/HCV co-infected patients is the same as in HCV mono-infected patients. Combination therapy of pegylated interferon (PEG IFN) and ribavirin is the standard treatment both before and after LT. The timing of the induction therapy after LT is controversial. A Tokyo group proposed early induction as a preemptive therapy before patients develop hepatitis,[37] while several other reports showed favorable results when the treatment was administrated only after the development of hepatitis was confirmed by liver biopsy.[38,39] Theoretically, the treatment should be started as soon as possible, because in HIV/HCV co-infected patients, HCV recurrence may be accelerated in an immunocompromised state.[30,40] The novel protease inhibitor, telaprevir, is currently introduced as an effective drug to achieve sustained viral response of 70%, even in genotype 1b, with PEG IFN/ribavirin in a non-transplant setting,[41] but this drug is metabolized via cytochrome P450 as a substrate, as are CNI and various protease inhibitors of ART for HIV. Close monitoring of the CNI trough level should be performed, and although triple therapy with telaprevir/PEG IFN/ribavirin is currently reported to be effective to prevent HCV recurrence after LT in HCV mono-infected cases, special attention should be paid when this regimen is adapted in HIV/HCV co-infected patients.

## IMMUNOSUPPRESSION

AS PREVIOUSLY MENTIONED, many factors including ART, anti-HCV treatment and an HIV-related immunocompromised state make post-LT immunosuppressive treatment difficult. Many ART drugs, both PI and NNRTI, cause instability in the blood concentration of CNI through the cytochrome P3A4 (CYP3A4)-related metabolism. Most PI cause the overconcentration of CNI by inhibiting CYP3A4, while most NNRTI cause decreased levels of CNI by stimulating CYP3A4.[29,42] As mentioned earlier, RAL is introduced as a key drug in LT in HIV positive patients, because the metabolism of this drug is not related to CYP450, so it does not affect the blood concentration of CNI. Several reports have demonstrated both the *in vitro* and *in vivo* effectiveness of rapamycin in reducing HIV replication,[43–45] and Di Benedetto *et al.* found that rapamycin monotherapy was significantly beneficial in long-term immunosuppression maintenance and HIV control after LT.[46] Mycophenolate mofetil is expected to be an effective immunosuppressive drug because of its efficacy in reducing HIV infection by both virological and immunological mechanisms.[47–49] Using these drugs, a more effective regimen of immunosuppression with ART may be established.

In regard to the steroid, several studies proposed that a steroid-free regimen can be safely applied and effective in LT for HCV cirrhosis. Also, in HIV/HCV co-infected patients, steroid-free protocol may be beneficial to prevent both HIV and HCV recurrence after LT.[50,51]

## CONCLUSIONS

LIVER TRANSPLANTATION FOR HIV/HCV co-infected patients remains challenging, but with recent developments in perioperative management and novel drugs for both HIV and HCV, the results are likely to be improved.

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