Title Page

Hepatitis C Treatment From "Response-guided" to "Resource-guided" therapy in the transition era from IFN-containing to IFN-free regimens

Running title: Resource-guided therapy from Response-guided therapy in era transition from IFN to DAA for HCV

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Main Text

Abstract

Peginterferon/ribavirin has been the standard-of-care for chronic hepatitis C virus (HCV) infections: 48-week for genotype 1 or 4 (HCV-1/4) and 24-week for HCV-2/3. Response-guided therapy recommended shorter 24-week and 16-week regimens for HCV-1 with lower baseline viral loads (LVL, <400,000-800,000 IU/ml) and rapid virological response (RVR, undetectable HCV RNA at week 4) and HCV-2/3 with RVR, respectively; and extending to 72 and 48 weeks for HCV-1 slower responders and HCV-2 non-RVR patients, respectively, to improve the efficacy.

The progress of directly-acting-antivirals (DAA), moving from interferon-containing regimens in 2011 to interferon-free regimens in 2013, has greatly improved the treatment success. **Interferon-containing regimens** include boceprevir or telaprevir or simeprevir or daclatasvir plus peginterferon/ribavirin, 24-48 weeks, for HCV-1 or 4. However, adding these DAA has no benefit for HCV-1 with LVL/RVR. Instead, 12-week sofosbuvir plus peginterferon/ribavirin attained SVR rates of >90% for HCV-1/3-6. **Interferon-free regimens** include two main categories: NS5B nucleotide inhibitor (sofosbuvir)-based regimens and NS3/4A inhibitor/NS5A inhibitor-based regimens (daclatasvir/asunaprevir, paritaprevir/r/ombitasvir/dasabuvir and grazoprevir/elbasvir). 8-24 weeks interferon-free regimens could achieve SVR rates of 82%-99% for corresponding HCV genotypes.

Although the newly DAA interferon-free regimens have high efficacy and safety, the huge budget impact increases the treatment barriers. The current recommendation should, therefore, base on the availability, indication and cost-effectiveness in the transition era of DAA. Based on the concept of "**Resource-guided therapy"**, peginterferon/ribavirin might be applied for easy-to-treat interferon-eligible patients in resource-constrained areas. Prioritizing patients for interferon-free regimens according to "time-degenerative factors" (age and fibrosis) is justified before the regimens becoming available and affordable.

Key words: HCV, Resource, DAA, IFN

Text

Introduction

Chronic hepatitis C virus (HCV) infections have been one of the leading causes of hepatocellular carcinoma (HCC), end-stage liver diseases and liver-related mortality. It is estimated around 185 million people are infected with the virus worldwide(1) and more than half of the infected persons reside in Asia-Pacific regions where exist several HCV hyperendemic areas with prevalence rates of antibodies to HCV (anti-HCV) as high as 30% to 67% in the villages located at southwestern coasts of Taiwan.(2) Interferon (IFN)-based regimens have been the backbone of antiviral therapy for chronic HCV infections for more than two decades. (3) Successful antiviral therapy, the achievement of sustained virological response (SVR), is durable in persistent undetectable serum HCV RNA(4), and has been associated with significantly favorable long-term outcomes, including diseases regression and a great risk reduction of cirrhosis, HCC, hepatic decompensation and mortality.(5-8)

Since 2004, the "standard-of-care" in the treatment of chronic hepatitis C (CHC) has been based on viral genotypes, 48 weeks of pegylated IFN (PegIFN) plus weight-based dose of ribavirin, 1,000-1,200 mg/d for HCV genotypes 1 or 4 (HCV-1/4) and 24 weeks of PegIFN plus fixed, low dose of ribavirin at 800 mg/d for HCV-2/3.(9) With the strategy of "Genotype-guided therapy", the SVR rates could achieve 50%-55% and 80%-85% for HCV1/4 and HCV-2/3, respectively, in western countries, compared to 60%-75% and 85%-90% for HCV1/4 and HCV-2/3, respectively, in Asian countries(3). The substantial higher SVR rates of HCV1/4 to 48 weeks of PegIFN plus ribavirin was largely resulted from the higher proportion of favorable interleukin-28B (IL28B) genotype distribution in Asian population(10), which has significantly better response to PegIFN/ribavirin for HCV-1 patients(10, 11), but not for HCV-2 patients(12). The SVR rate could be as high as 75%(13) and 90%(14) for HCV-1 and HCV-2 patients, respectively, in Taiwan. Given the genotype distribution of 50% for HCV-1 and 45% for HCV-2 in Taiwan,(15) the adjusted overall SVR rate of HCV treatment in Taiwan was expected to be as high as 80%(2). Nevertheless, the high clinical efficacy cannot be translated to community effectiveness. We found that there existed a huge gap between clinical efficacy at 80% and community effectiveness at 11% only in Taiwan, due to the low rates of disease diagnosis/awareness, accessibility and acceptance of treatment recommendation(2). The most reasons of not being treated with PegIFN plus ribavirin combination therapy were patients' fear of adverse events of and the ineligibility to PegIFN

and/or ribavirin.(2) The observation highlighted the urgency to develop new antivirals with high potency and safety profiles to increase the acceptance rate of anti-HCV therapy, to ensure the treatment success and to toward the goal of HCV elimination.

Recently, the rapid progress in the development of directly-acting antivirals (DAA) has remarkably improved the treatment efficacy and safety. The DAA-containing regimens have become the mainstay of HCV treatment in most western countries and some Asian countries since 2011(16-19). Given the high cost of DAA regimens and late introduction of DAA in Asian countries, it is mandatory to develop "Resource-guided therapy" from in the transition era from IFN-containing to IFN-free DAA regimens in resource-constrained areas where DAA remain unavailable or unaffordable.

Response-guided therapy in the era of IFN-based therapy

Before the introduction of IFN-free DAA regimens in 2013, the mainstay of HCV therapy was different treatment duration of PegIFN/ribavirin based on HCV genotype, baseline and on-treatment viral loads, the "response-guided therapy"(3, 16, 20). The recommended treatment duration with PegIFN/ribavirin is 48 weeks for HCV-1/4 patients and 24 weeks for HCV-2/3 patients. It could be truncated to 24 weeks for HCV-1 patients who have a lower baseline viral load (LVL, HCV RNA < 400,000-800,000 IU/ml) and achieve a rapid virological response (RVR, defined as undetectable HCV RNA after four weeks of treatment)(13, 21), and to 16 weeks for HCV-2 patients who attain a RVR(14), without compromising the treatment efficacy. These groups, with SVR rates of 94%-96% and >98%, respectively, to truncated regimens of PegIFN/ribavirin could be considered as "easy-to-cure" population. For HCV-1 slow responders, patients who achieved a partial early virological response (pEVR, defined as HCV RNA decline ≥ 2 logs but remains positive at treatment 12), extending treatment to 72 weeks is recommended to enhance the treatment efficacy(22). For HCV-2 patients without a RVR, extending treatment duration of PegIFN plus weight-based ribavirin from 24 weeks to 48 weeks could significantly increase the SVR rate from 46% to 70%(23).

For the poor responders, PegIFN/ribavirin should be terminated at treatment week 12 or 24 if patients lack of EVR (HCV RNA decline ≥ 2 logs at treatment week 12) or HCV RNA detectable at treatment week 24 due to extremely low chance of achieving an SVR (< 5%)(20, 24). Recently, researchers dedicated to identify the non-responders to PegIFN/RBV as early as possible to avoid unnecessary treatment. A collaborator study in Taiwan demonstrated

that a poor week 4 response, defined as a HCV RNA reduction of <1 log IU/mL at week 4 or a week 4 HCV RNA > 10,000 IU/mL with IL-28B unfavorable genotype, could serve as a rapid stopping rule. It had a negative predictive value of 95% with a false negative rate of only 0.8% and a coverage rate of 43.4% for non-responders(25). More recently, the serum levels of interferon-γ at treatment week 4(26) and the fold change of 8-gene signatures in peripheral mononuclear cells at as early as treatment week 1(27) could predict the treatment success/failure. Nevertheless, the markers are not applicable for most clinical practice to serve as a routine use.

New era of DAA-based therapy

IFN-containing DAA therapy

The first approved DAA was first wave of first generation of HCV non-structural protein 3/4A (NS3/4A) protease inhibitors (PI), boceprevir and telaprevir in 2011. The triple therapy of PI plus PegIFN/ribavirin for 24-48 weeks based on strategies of response-guided therapy, could improve the SVR rate from 40%-44% to 68%-75% for treatment-naïve HCV-1 patients and from 15%-21% to 59%-67% for treatment-experienced HCV-1 patients(20, 28, 29). However, the two compounds are currently no longer recommended due to the pill burdens, increased adverse events and complicated regimens.

Simeprevir, a second wave of first generation of PI, plus PegIFN/ribavirin for 12 weeks, followed by additional 12 or 36 weeks of PegIFN/ribavirin based on prior treatment history was approved for HCV-1 patients, which could increase the SVR rate from 36%-50% to 79%-80%, except HCV-1a with HCV nonstructural protein 3/4 (NS3/4) Q80K resistance-associated substitution (RAS)(29).

Daclatasvir, a NS5A inhibitor (NS5AI), 24 weeks plus PegIFN/ribavirin, 24 weeks or 48 weeks based on on-treatment virological response was approved in the treatment of HCV-4 patients in Europe with an increasing SVR rate from 50% to 84% (30)

Sofosbuvir, a NS5B nucleotide analogue, plus PegIFN/ribavirin for 12 weeks could achieve an SVR rate of 89%-100% for all HCV genotypes (31-33). With the advance of IFN-free DAA regimens, the IFN-containing DAA regimens are currently no longer recommended in US and Europe where DAA are available and affordable(16, 19).

The IFN-based therapy is effective for the treatment of IFN-eligible CHC patients with an average SVR rate of 80% in Taiwan. However, the community effectiveness was estimated to be only 11% in Taiwan(2), because of low disease awareness, low rate of accessibility and patients' fear of or ineligibility to receiving IFN-based therapy.

IDN-free DAA regimens

The development of IFN-free DAA regimens are based on two strategies: 1) NS3/4A PI plus NS5AI, with/without 3rd DAA with/without ribavirin; 2) NS5B nucleotide analogue with/without 2nd DAA with/without ribavirin.

- NS3/4A PI plus NS5AI based IFN-free DAA regimens
  - Daclatasvir plus asunaprevir

  Daclatasvir plus asunaprevir, a NS3/4A PI, for 24 weeks is the first approved IFN-free, ribavirin-free DAA regimen for HCV GT1b patients in Japan. The SVR rate ranged from 81%-87% for IFN-ineligible/intolerant patients and 90% for IFN-naïve patients (34, 35). However, HCV-1b patients harboring resistance-associated substitution (RAS) at NS5A L31 or Y93 responded to daclatasvir plus asunaprevir very poor (39%), compared to that 94% of those with neither NS5A L31 nor Y93 RAS could achieve a SVR (36). Excluding HCV-1b patients with NS5A RAS at L31 and/or Y93 from daclatasvir plus asunaprevir is recommended to avoid treatment-emerging multidrug resistance (37).
  - Paritaprevir/r/ombitasvir with/without dasabuvir with/without ribavirin

  Paritaprevir, a NS3/4A PI, boosted by ritonavir, co-formulated with ombitasvir, a NS5AI, plus dasabuvir, a NS5B nonnucleoside analogue (PrOD regimen) plus ribavirin for 12 weeks is effective in the treatment of HCV-1 patients with SVR rates of 96% for non-cirrhotic naïve or IFN-experienced patients (38, 39) and 92% for cirrhotic naïve or IFN-experienced patients (40). However, the SVR rate was only 80% for cirrhotic IFN-experienced HCV-1a patients with a 12-week PrOD plus ribavirin, compared to 93% with a 24-week regimen (40).

  Instead, 12 weeks of PrOD regimen without ribavirin was highly effective in the treatment of HCV-1b patients, with an average SVR rate of 99% for cirrhotic/non-cirrhotic, naïve/IFN-experienced HCV-1b patients, but only 90% for HCV-1a non-cirrhotic patients (41-43). Paritaprevir/r/ombitasvir without ribavirin had SVR rates of 96% for HCV-1b non-

cirrhotic patients and 90.5% for HCV-1b cirrhotic patients in a Japanese trial, and was approved in the treatment for HCV-1b in Japan (44).

Paritaprevir/r/ombitasvir plus ribavirin could achieve an SVR rate at 100% for HCV-4 patients (45), and become the first approved IFN-free regimen for HCV-4 patients.

■ Grazoprevir/elbasvir with/without ribavirin

Grazoprevir (a second generation of NS3/4A PI)/elbasvir (a second generation of NS5AI) fixed-dose combination is effective in the treatment of HCV-1 and HCV-4. Twelve weeks of grazoprevir/elbasvir could attain SVR rates of 95% for naïve patients and 92% for IFN-experienced patients (46, 47). However, for HCV-1a patients with NS5A RAS at 28, 30, 31, 58 and 93, the SVR rate was only 52%-58% with a 12-week regimen of grazoprevir/elbasvir, compared to 100% with a 16-week of grazoprevir/elbasvir plus ribavirin (46, 47).

- NS5B nucleotide analogue-based IFN-free DAA regimens

The strategy is based on the only approved NS5B nucleotide analogue currently, sofosbuvir.

■ Sofosbuvir plus ribavirin

Sofosbuvir plus weight-based dose of ribavirin is the first approved IFN-free DAA regimen in the treatment of HCV-2 and HCV-3. A 12-week regimen attain SVR rates of 93%-97% for HCV-2, naïve/IFN-experienced, cirrhotic/non-cirrhotic patients(31, 48, 49). Instead, a 12-week regimen was suboptimal for HCV-3 patient with an SVR rate of 56%, compared to 85% with a 24-week regimen(31, 48, 49).

■ Sofosbuvir/ledipasvir with/without ribavirin

Sofosbuvir/ledipasvir fixed dose combination for 12 weeks is highly effective in the treatment of HCV-1/4/5/6 patients, with SVR rate of 94%-98% for HCV-1 (50, 51), 93% for HCV-4 (52), 95% for HCV-5(53) and 96% for HCV-6 patients(54) but only 64% for HCV-3 naïve patients(54). For naïve non-cirrhotic HCV-1 patients, a shorter treatment duration of 8-week sofosbuvir/ledipasvir had similar efficacy to 12-week regimen (94% versus 95%)(55). However, for HCV-1 IFN-experienced cirrhotic patients, 12 weeks of sofosbuvir/ledipasvir had an SVR rate of only 86%, compared to 96% with 12 weeks of sofosbuvir/ledipasvir plus ribavirin or 97% with 24 weeks of sofosbuvir/ledipasvir(51, 56).

■ Sofosbuvir plus daclatasvir with/without ribavirin

A 12-week sofosbuvir plus daclatasvir had high SVR rates of 97%-98% for HCV-1/2/3/4 patients coinfected with HIV(57) and 96% for non-cirrhotic HCV-3 mono-infected patients, but only 63% for cirrhotic HCV-3 patients(58). Adding ribavirin to sofosbuvir plus daclatasvir for 12-16 weeks could enhance the SVR rate to 83%-89% for cirrhotic HCV-3 patients(59).

- Sofosbuvir plus simeprevir

Twelve weeks of sofosbuvir plus simeprevir was effective in the treatment o HCV-1 patients (SVR rate: 97% for non-cirrhotic patients and 83% for cirrhotic patients), except for cirrhotic HCV-1a patients with NS3 Q80K RAS(60).

- Sofosbuvir/velpatasvir with/without ribavirin

Sofosbuvir/velpatasvir, a second generation of NS5AI, fixed dose combination for 12 week is the first IFN-free pan-genotypic DAA regimen, with SVR rate of 95% for HCV-3 and 97%-100% for the other genotypes with compensated liver diseases(61, 62). Sofosbuvir/velpatasvir plus ribavirin for 12 weeks was also effective and safe in the treatment of Child-Turcotte-Pugh B decompensated cirrhotic patients of all HCV genotypes with an SVR rate of 94%(63).

Resource-guided therapy in the transition era from IFN-based to IFN-free therapy

Although the IFN-free DAA regimens have very high efficacy with simpler dosing, shorter treatment duration and are well tolerated, most of the regimens are currently unavailable or unaffordable in most areas of Asia-Pacific region(64). For example in naïve Taiwanese patients, the cost per SVR achieved ranges from USD $18,000 to $52,000 with IFN-free DAA regimens, compared to only $7,627 and $4,799 for HCV-1 and HCV-2, respectively, with PegIFN/ribavirin therapy(65). Therefore, the policy of reimbursement in Taiwan is based on both of the cost-effectiveness and the affordability in the nation level. It is, therefore, necessary to develop resource-guided therapy for CHC patients with strategy based on the availability, cost-effectiveness, national affordability and individual affordability of anti-HCV agents until the IFN-free DAA regimens become available and affordable, either national level or patient level, in resource-constrained areas.

- *IFN-ineligible/intolerant patients*

All IFN-ineligible/intolerant patients, including those with decompensated liver disease, should wait and be treated with IFN-free DAA regimens.

- *IFN-eligible/tolerant naïve patients (Figure 1a)*

IFN "easy-to-cure" population: Around 40% of HCV-1/4/6 naïve patients had a LVL (<400,000-800,000 IU/ml) and carrying IL28B CC genotype. Treatment could be initiated for these easy-to-cure HCV-1 super-responders with 24-week PegIFN/ribavirin, which had a positive predictive value of 80% in predicting an SVR, and even higher for those with a RVR(13, 66). Adding NS3/4A PI to PegIFN/ribavirin should not be used for the HCV-1 super-responders because of no benefit in improving efficacy.(67) Around 85% of non-cirrhotic HCV-2 naïve patients could achieve a RVR. Treatment could be initiated for these "easy-to-cure" HCV-2 super-responders with 16-week PegIFN/RBV, which had an SVR rate of > 93%(14, 68).

IFN "hard-to-cure" population HCV-1 patients with high VL and carrying IL28B non-CC genotype should not be treated with IFN-based regimens, because of a high negative predictive value of 91%(66). HCV-2/3 patients with cirrhosis had only 30%-62% SVR rates to 24 weeks of PegIFN/ribavirin(31). DAA regimens are recommended for the "hard-to-cure" population.

For the patients between the two groups, treatment could be initiated with either PegIFN/ribavirin or DAA regimens based on the cost-effectiveness of the DAA regimens.

- *IFN-eligible/tolerant IFN-experienced patients (Figure 1b)*

For HCV-1 IFN-experienced patients, retreatment with 48 weeks of PegIFN/ribavirin could be advised if the patients were prior relapsers and carry IL28B CC genotype, because an acceptable SVR rate of 76% for this group.(69, 70) However, treatment should be stopped if HCV RNA decline < 1 log at treatment week 4 or < 2 logs at treatment week 12 during the retreatment.

For HCV-2 IFN-experienced patients, retreatment with 24 weeks of PegIFN/ribavirin could be advised if the patients were prior relapsers, because an acceptable SVR rate at 79% for this group(71). However, treatment should be stopped if HCV RNA decline < 2 logs at treatment week 12 during the retreatment.

All the other IFN-experienced patients should be treated with DAA-containing regimens to ensure the treatment efficacy.

Prioritization of HCV therapy

All of the patients with chronic HCV infection should be treated, except those with expected short life expectancies, which can not be reversed by treating HCV or liver transplantation.(19) However, the impact of IFN-free DAA regimens is not only on financial level but also on manpower resource for the patient-care level. Once the IFN-fee DAA regimens become available and affordable, prioritization of HCV patients according to the factors associated with HCC development after SVR might be justified, at least in a short term. Age and pretreatment hepatic fibrosis stage have been associated with HCC risk even after achieving an SVR. And the risk increases overtime, the time-degenerative factors.(72) In a 15-year follow-up, for CHC patients' age < 40 years old, the risk of HCC development did not differ between patients with and without SVR; by contrast for those with age > 40 years old, the risk of HCC was significantly higher among non-SVR than SVR. Similarly, a significantly higher risk of HCC among patients without SVR than those with SVR was only observed in CHC patients with hepatic fibrosis score of 2 or more, but not in those with fibrosis score of 0 or 1.(72) The results suggested to treat the older patients and/or patients with significant fibrosis as early as possible.

Perspectives

The World Health Organization has called a mission on combating hepatitis C with a goal of HCV elimination by 2030.(73) The universal affordability of DAAs is the key to achieve the goal worldwide. The manufacturing cost of a 12-week IFN-free DAA regimen was estimated USD 122-192 per person.(74) Gilead Sciences has announced generic licensing agreement of their products to increase the treatment accessibility in developing countries. Further cost down from the competition of pharmaceutical companies or extended generic licensing of DAA will help for the ultimate goal of HCV elimination in the future.

Conclusions

The new advance in the treatment with IFN-free DAA regimens greatly improves the treatment efficacy with high safety profile for CHC. Resource-guided therapy with strategy of prioritization based on time-degenerative factors is justified before all of the IFN-free DAA regimens are available and affordable.

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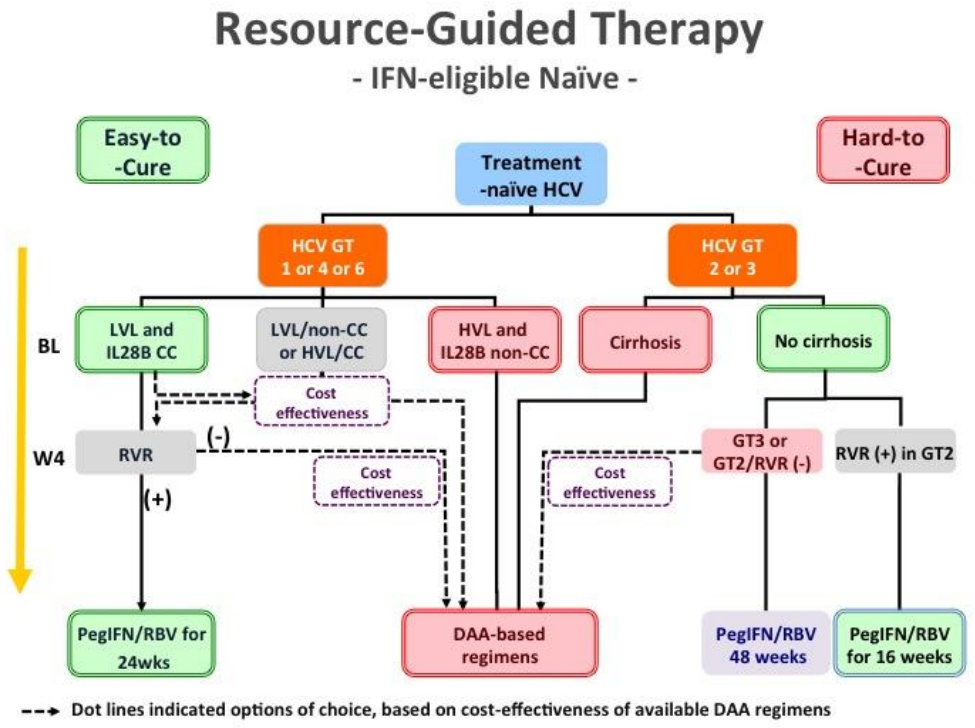

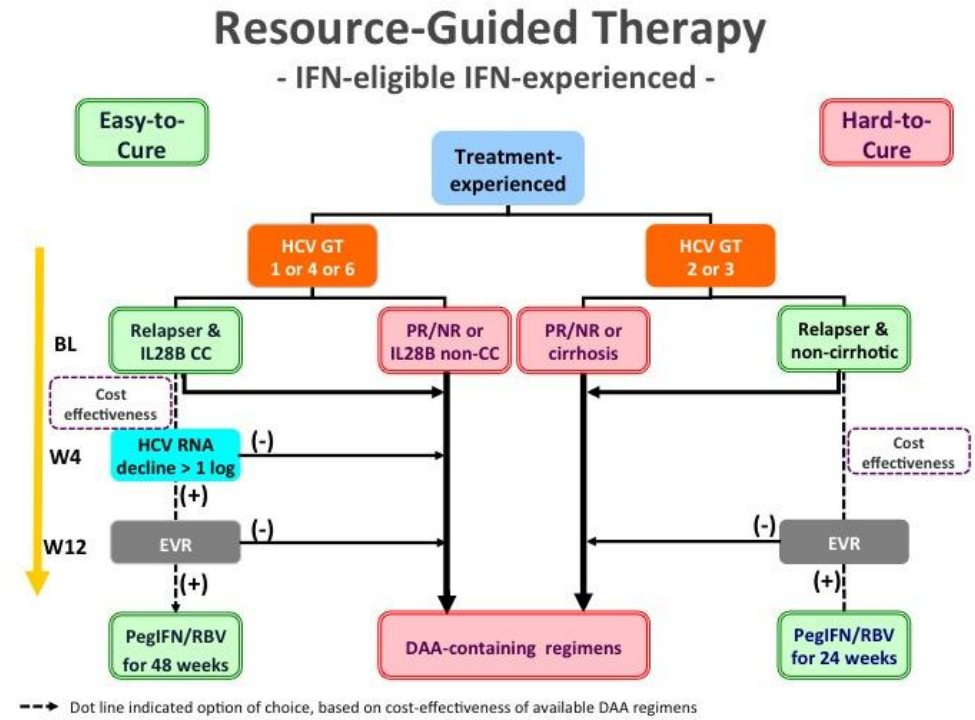

Figure 1. Resource-guided therapy for chronic hepatitis C in the transition era from IFN-based to IFN-free DAA regimens in resource-constrained areas. (1a) IFN-eligible naïve patients; (1b) IFN-eligible IFN-experienced patients.

HCV, hepatitis C virus; GT, genotype; DAA, directly-acting antiviral agents; BL, baseline; W, treatment week; LVL, low HCV viral loads (< HVL, high HCV viral loads; RVR, rapid virological response, HCV RNA undetectable at week 4; EVR, early virological response, HCV RNA decline > 2 logs at week 12; cEVR, complete EVR, HCV RNA undetectable at week 12; pEVR, partial EVR, HCV RNA decline > 2 logs but detectable at week 12; PegIFN, peginterferon; RBV, ribavirin. IL28B CC, interleukin-28B CC genotype; PR, partial responders; NR, null responders.