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The cost-effectiveness of improved HCV therapies in HIV/HCV co-infected individuals

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Abstract

Objectives—To evaluate the effectiveness and cost-effectiveness of strategies to treat hepatitis C virus (HCV) in HIV/HCV co-infected patients in the U.S.

Subjects—Simulated cohort of HIV/HCV genotype 1 co-infected, non-cirrhotic, HCV treatment-naïve individuals enrolled in U.S. HIV guideline-concordant care.

Design/Interventions—Monte Carlo simulation comparing 5 strategies: no treatment; “dual therapy" with pegylated-interferon (PEG) and ribavirin (RBV); starting all patients (“PEG/RBV trial”) or some patients (“IL28B triage”) on PEG/RBV and advancing those with treatment failure to PEG/RBV and telaprevir (TVR), and “triple therapy” PEG/RBV/TVR for all patients. Sensitivity analyses varied efficacies and costs and included a scenario with interferon (IFN)-free therapy.

Main Measures—SVR, life expectancy (LE), discounted quality-adjusted life expectancy (QALE) and lifetime medical cost, and incremental cost-effectiveness ratios (ICERs) in $/QALY gained.

Results—“PEG/RBV trial,” “IL28B triage,” and “triple therapy” each provided 72% sustained virologic response (SVR) and extended QALE compared to “dual therapy” by 1.12, 1.14, and 1.15 QALY respectively. The ICER of “PEG/RBV trial” compared to “dual therapy” was $37,500/

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QALY. “IL28B triage” and “triple therapy” provided little benefit compared to “PEG/RBV trial” and had ICERs exceeding $300,000/QALY. In sensitivity analyses, IFN-free treatment attaining 90% SVR had an ICER <$100,000/QALY compared to “PEG/RBV trial” when its cost was ≤ $109,000 (125% of the cost of PEG/RBV/TVR).

Conclusion—HCV protease inhibitors are most efficiently used in HIV/HCV co-infection after a trial of PEG/RBV, sparing protease inhibitor for those who attain RVR and SVR. The cost-effectiveness of IFN-free regimens for HIV/HCV will depend on the cost of these therapies.

Keywords

HIV/HCV co-infection; cost-effectiveness; telaprevir; interferon-free

Introduction

HCV co-infection is a leading cause of morbidity and mortality among HIV-infected individuals [1]. Newer HCV therapies utilizing HCV protease inhibitors were licensed for the treatment of HCV mono-infection in the U.S. and Europe in 2011 [2]. Phase 2 clinical trials in HIV/HCV co-infected patients demonstrate sustained virologic response (SVR) rates as high as 74% in those with HCV genotype 1 infection [3, 4]. Clinical trial results for oral interferon (IFN)-free regimens for HCV mono-infected patients have been presented at national conferences, and the first IFN-free regimen for the treatment of HCV genotypes 2 and 3 in HCV mono-infected patients was submitted to the FDA in April 2013 [5]. These regimens attain 90% or greater SVR, with little toxicity and only 12 weeks of therapy [6–9].

The improved efficacy and toxicity profiles of new treatments are accompanied by higher costs [1, 10, 11]. Because many HIV/HCV co-infected patients rely on publicly-funded health insurance (or other public payers such as the prison healthcare system), treatment for HIV/HCV co-infection often occurs in resource-constrained settings [12]. In such environments, efficient use of HCV therapy could increase the number of people treated for HCV, maximizing the population-level benefits of HCV treatment.

Genome-wide association studies have discovered that those with homozygosity at a single nucleotide polymorphism (rs12979860) related to the interleukin-28 beta subunit (IL28B) gene, the “CC” genotype, have better treatment response to peginterferon (PEG) and ribavirin (RBV) than non-CC genotypes [13–16]. Using IL28B to triage CC genotype patients to initiate PEG/RBV without an HCV protease inhibitor could control costs. Another potential strategy is to initiate all patients on PEG/RBV, adding an HCV-protease inhibitor only for those who experience virologic failure. The comparative- and cost-effectiveness of such approaches in HIV/HCV co-infection are unknown.

To inform strategies for use of new therapies for HIV/HCV co-infected patients, we investigated the cost-effectiveness of alternative treatment options and identified approaches that would efficiently use scarce budgetary resources, potentially expanding access to HCV treatment.

Methods

Analytic Overview

We used the Hepatitis C Cost-Effectiveness (HEP-CE) model, a Monte Carlo simulation of screening and treatment of HCV, to estimate the effectiveness and cost-effectiveness of strategies for treating HIV/HCV co-infection. The model is summarized below and details are available elsewhere [17] and in the supplemental materials. We considered 5 HCV treatment strategies (Figure 1):

1. No treatment
2. "Dual therapy" – 48 weeks of response-guided PEG/RBV.
3. "PEG/RBV trial" – 48 weeks of response-guided PEG/RBV. Individuals who fail PEG/RBV at any time during therapy advance to triple therapy (strategy 5).
4. "IL28B triage" – Individuals are triaged to commence either PEG/RBV or triple therapy (strategy 5) based on IL28B genotype. Those with "CC" alleles initiate PEG/RBV, while all others start triple therapy. Patients who fail PEG/RBV advance to triple therapy.
5. "Triple therapy"—Treatment with 48 weeks of PEG/RBV in combination with the HCV protease inhibitor telaprevir (TVR).

All analyses simulated a cohort of 10 million hypothetical HIV/HCV co-infected individuals chronically infected with HCV genotype 1, non-cirrhotic, HCV treatment-naïve, and enrolled in U.S. HIV guideline-concordant care. Per these guidelines, individuals were either on suppressive antiretroviral therapy (ART) or were HIV-treatment-naïve with CD4 >500/ml (Table 1).

We projected outcomes including the percent attaining sustained virologic response (SVR), life expectancy (LE), discounted quality-adjusted life expectancy (QALE), discounted lifetime medical costs, and the incremental cost effectiveness ratio (ICER) of each strategy compared to its next costliest alternative. We conducted one-way and multi-way sensitivity analyses on these results.

We also considered scenarios using an oral, IFN-free regimen that was more effective and less toxic than PEG/RBV/TVR. We considered a range of IFN-free regimen efficacies and costs, and we identified cost/efficacy combinations leading to IFN-free therapy having an ICER <$100,000/QALY when compared to the preferred treatment strategy without an IFN-free regimen. To explore cost-reducing strategies in cost-constrained environments, we considered scenarios similar to the base case where patients initiate a trial of PEG/RBV, but instead of switching to triple therapy upon a failed course of PEG/RBV, they switch to IFN-free therapy.

Model structure

HCV Disease Progression—The model simulates HCV disease progression through 3 stages of liver disease: mild to moderate fibrosis, cirrhosis, and decompensated cirrhosis. Consistent with previous studies, all disease stages of HCV-infection are associated with

increased resource utilization and decreased quality of life (QoL) [18–24]. When individuals become cirrhotic, they are subject to increased mortality attributable to liver disease [25, 26]. With successful treatment (SVR), HCV-related mortality, resource utilization, and QoL revert to those of HIV mono-infected individuals.

HIV Disease Progression—We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model to estimate the cohort's HIV-related outcomes and costs [27]. CEPAC simulates HIV disease progression through CD4 count and HIV RNA levels. We used the CEPAC model to assess the cohort's progression of HIV disease across a range of CD4 and viral load categories. CEPAC provided sex-stratified estimates of monthly HIV-related mortality conditional upon being alive at the beginning of the month (life table), mean monthly medical costs related to HIV-disease, and QoL related to HIV-infection. We used these CEPAC outputs as HEP-CE model inputs, such that in every month, individuals in the HEP-CE model were exposed to sex and time-dependent HIV-attributable mortality, costs, and QoL changes (see supplemental materials).

HCV Therapy

1. "Dual therapy": All individuals initiate a planned 48-week course of weekly PEG alfa-2a 180 mcg subcutaneously in combination with twice daily oral RBV 600 mg (average cohort weight 80kg). Simulated patients undergo routine HCV RNA testing at the end of treatment week 4. Those with detectable viremia stop HCV therapy, while those with suppressed HCV RNA (rapid virologic response—RVR) continue a planned 48-week treatment course [3].

While taking HCV medications, all patients experience a monthly QoL decrement related to adverse therapy symptoms. Additionally, a proportion of patients on therapy experience non-treatment ending toxicities, including moderate anemia managed by RBV dose reduction and moderate neutropenia managed with PEG dose reduction and twice weekly filgrastim 300 mcg subcutaneously. Patients with non-treatment ending toxicities accrue cost adjustments related to dosing changes and additional therapies, but they remain on HCV treatment and are eligible to attain SVR. In every month, patients also risk treatment discontinuation due to non-adherence or major toxicity, including severe anemia or rash. Major toxicity is associated with additional costs and an additional QoL decrement.

2. "PEG/RBV trial": All patients initiate the same PEG/RBV regimen as in the "dual therapy" strategy. Those who fail to attain virologic suppression at week 4 (RVR) subsequently add telaprevir to their regimen for 12 weeks as described below ("triple therapy"). Patients who attain RVR on PEG/RBV at week 4 but do not achieve SVR at treatment completion, are re-treated with PEG/RBV/TVR. Patients who stop PEG/RBV therapy due to non-adherence or major toxicity are ineligible to advance to PEG/RBV/TVR.

3. "IL28B triage": IL28B genotyping is used to triage patients to start either PEG/RBV (CC genotype), or PEG/RBV/TVR (non-CC genotypes). The approach to modeling PEG/RBV therapy and the addition of TVR to failing regimens is the same as that for "PEG/RBV trial."

The efficacy of protease-based therapy among those who fail PEG/RBV is lower than its efficacy as first-line therapy [28]. Exposure to PEG/RBV, however, does not compromise protease efficacy if the individual simply started treatment with PEG/RBV/TVR [28]. We therefore assume that non-responders to PEG/RBV are more likely to be non-responders to PEG/RBV/TVR when retreated in all strategies, and we assume that in the "PEG/RV trial" strategy exposure of patients to PEG/RBV ahead of adding a protease inhibitor does not reduce the overall percentage of the cohort who ultimately attain SVR.

4. "Triple therapy": All patients initiate a regimen of PEG/RBV/TVR for 12 weeks followed by 36 weeks of PEG/RBV alone for a 48-week total therapy course. Patients receive 750 mg three times daily of TVR in combination with the same dosage of PEG/RBV as described above. Patients undergo routine HCV RNA monitoring at treatment weeks 4 and 12. Those with HCV RNA >1,000 copies/ml at either time point stop therapy. We did not specifically model TVR dose increases required when using efavirenz, but effectively included such dose changes in drug cost sensitivity analyses. The approach to modeling adherence, toxicity, and therapy disutility was the same as for dual therapy, but we included rash as potential treatment toxicity.

5. "Interferon-free regimen": Patients initiate a 12-week course of an HCV protease inhibitor, a polymerase inhibitor, and RBV [6, 7, 29]. The regimen has lower toxicity and higher adherence, QoL while on therapy, and SVR rate than IFN-containing regimens. Individuals face a risk of treatment ending toxicity and non-adherence, but we assumed there are no early stopping criteria for IFN-free therapy.

Costs—We assessed costs in the model from the health system perspective. In each simulation month, individuals accrue "background costs" associated with non-HIV/HCV-related healthcare. In addition to these costs, there are HCV- and HIV-specific costs. HCV-associated costs include those of HCV medications, physician visits, laboratory tests for monitoring and safety, emergency department visits, and hospitalizations for liver-related events (Table 1). HIV-associated costs include costs of ART, laboratory monitoring, and hospital admissions associated with AIDS-related events [30–38].

To reflect increased resource utilization among those with HIV/HCV co-infection compared to HIV mono-infection, all costs except those of HIV and HCV medications and HIV-related testing are 70% greater in co-infected individuals than in HIV mono-infected [19, 39].

QoL—QoL estimates include independent effects related to HIV- and HCV-infection integrated in the model using a multiplicative assumption [20, 22, 40–43]. HIV-related QoL is a function of current CD4 count and acute AIDS-related events. HCV-related QoL is a function of fibrosis stage, HCV treatment status, and treatment-related toxicity (Table 1).

Base case parameters

The cohort was 66% male [44–47], mean age 45 years (S.D. 6 years) [44–48], mean CD4 count 520/μl (S.D. 100/μl) [49–51], and 32% CC genotype prevalent [14] (Table 1). The median time to cirrhosis from HCV infection (mean age of infection 26 years [52]) was 25

years [53], and the rate of liver-related deaths with cirrhosis was 2.73 per 100 person-years [25, 26].

The total SVR probability for PEG/RBV among those with CC genotype was 55% [16, 54–57] and 20% for CT or TT [16, 54–56]. The total SVR probability with PEG/RBV/TVR was 74% [3] and ranged from 80–100% with an IFN-free regimen [6, 7]. The probability of withdrawal due to toxicity or non-adherence was 11% for triple therapy [3], 23% for dual therapy [57], and 3% for IFN-free therapy [6, 7]. The cost of a complete course of dual and triple therapy, including the cost of managing toxicities, was $43,000 and $87,300 respectively. The cost of a complete course of IFN-free therapy ranged from $87,300-$175,000 [31, 33]. Those with mild to moderate fibrosis, cirrhosis, and decompensated cirrhosis had a QoL of 0.89, 0.62, and 0.48 respectively [20, 22, 43].

Analyses

We calculated the incremental cost-effectiveness ratio (ICER) of each treatment strategy as the additional cost divided by the additional quality-adjusted life years (QALY) gained compared to the next less expensive strategy [58, 59]. Strategies were considered inefficient and excluded from ICER calculations if they resulted in higher costs but fewer QALYs gained or had a higher ICER than a more effective strategy [59, 60]. QALYs and costs were both discounted at 3% annually [59]. We assumed a societal willingness-to-pay of $100,000 per QALY where strategies below the threshold were considered “cost-effective” [61, 62].

Results

Base case

Without HCV treatment, undiscounted LE was 13.24 years, QALE was 6.76 QALYs, and discounted lifetime medical costs were $198,700 (Table 2). “Dual therapy” yielded 30.8% attaining SVR, increased LE by 0.52 years to 13.76 years, QALE by 0.84 QALY to 7.60 QALY, and lifetime medical costs by $23,200. The ICER for treating patients with dual therapy compared to no treatment was $27,700/QALY gained.

The “PEG/RBV trial” strategy was the least costly approach to using an HCV protease-inhibitor. “PEG/RBV trial” increased SVR to 72% and LE and QALE compared to “dual therapy” by 0.70 years and 1.13 QALY, a larger gain than that provided by “dual therapy” compared to “no treatment.” “PEG/RBV trial” increased lifetime medical cost compared to “dual therapy” by $42,300 to $264,200, resulting in an ICER for “PEG/RBV trial” compared to “dual therapy” of $37,500/QALY.

The “IL28B triage” and “triple therapy” scenarios both increased SVR by <1% compared to “PEG/RBV trial.” As a result, LE and QALE increased by less than 0.01 QALY, resulting in ICERs >$300,000/QALY (Table 2).

Sensitivity analysis

“PEG/RBV trial” remained the preferred (<$100,000/QALY) treatment strategy when we varied treatment efficacy for both PEG/RBV and PEG/RBV/TVR regimens. Across all

efficacy assumptions, the ICERs of “IL28B triage” compared to “PEG/RBV trial” and of “triple therapy” compared to “IL28B triage” remained more than $250,000/QALY.

Total treatment costs had the greatest impact on cost-effectiveness conclusions (Figure 2). With a higher cost of PEG/RBV therapy, the “PEG/RBV trial” and “dual therapy” strategies became less efficient than “IL28B triage.” With higher PEG/RBV costs, “triple therapy” remained economically unattractive with an ICER >$500,000/QALY.

When we reduced the cost of PEG/RBV/TVR by 50%, the “triple therapy” strategy was most efficient, with an ICER compared to no treatment of $20,500/QALY. This remained the preferred strategy at a threshold of $100,000/QALY as long as the cost of PEG/RBV/TVR was less than $50,000 (57% of base case cost). When we increased the cost of PEG/RBV/TVR by 50%, the “PEG/RBV trial” strategy was preferred with an ICER of $55,600/QALY compared to “dual therapy.”

“PEG/RBV trial” remained the preferred treatment strategy with an ICER <$100,000/QALY across a broad range of other sensitivity analyses including HIV therapy efficacy, time to cirrhosis, QoL, and costs of routine medical care, ARTs and laboratory tests (Figure 2).

IFN-free scenario

Treating individuals with an “IFN-free” regimen achieving 90% SVR extended discounted QALE by 2.56 years compared to no treatment, by 0.59 years compared to “PEG/RBV trial,” and by 0.57 years compared to “triple therapy.” In a two-way sensitivity analysis comparing “IFN-free” therapy to “PEG/RBV trial,” an IFN-free regimen that provided a 90% SVR rate had an ICER <$100,000/QALY when the cost of the IFN-free regimen was ≤ 125% of the cost of a complete course of PEG/RBV/TVR, or approximately $109,000 (Figure 3). An IFN-free regimen that attained 95% SVR had an ICER <$100,000/QALY when the cost of the IFN-free regimen was ≤ 150% of the cost of a complete course of PEG/RBV/TVR, or $131,000.

When we considered potential intermediate strategies for using IFN-free therapy, a strategy in which all patients initiated PEG/RBV and only those with treatment failure advanced to an IFN-free regimen, was preferred with an ICER compared to “dual therapy” of $51,800/QALY (Supplemental Table 4). In this scenario, providing IFN-free therapy to all patients was cost-effective (ICER <$100,000/QALY) only when the cost of a course of IFN-free treatment was less than $88,000 (base case $131,000), or when the QoL of being on PEG/RBV was less than 0.3 (similar to having compensated cirrhosis).

Discussion

We assessed the cost-effectiveness of new therapies to treat HIV/HCV genotype 1 co-infected individuals and found that although new HCV therapies improve life expectancy in co-infected patients, they substantially increase costs and are most efficiently used after an initial trial of PEG/RBV to determine protease inhibitor necessity. Furthermore, the economic efficiency of future IFN-free regimens will depend greatly on their cost. In highly

cost-constrained environments, initiating treatment with PEG/RBV, or using IL28B genotyping to triage patients to IFN-free therapy, may be economically attractive.

It is not surprising that we found that initiating all patients on “triple therapy” is not cost-effective. The REALIZE study demonstrates that using a lead-in of PEG/RBV before adding TVR is efficacious and does not compromise overall SVR [28]. Extrapolating this finding to naïve patients, in HIV/HCV co-infected patients, there is little disadvantage to the “PEG/RBV trial” approach as patients who do not attain RVR with PEG/RBV alone can add TVR to their regimen without extending the treatment course or decreasing treatment efficacy. Those who attain RVR with PEG/RBV have a >95% chance of ultimately attaining SVR [57, 63].

Several important observations explain the greater economic efficiency of the “PEG/RBV trial” strategy compared to “IL28B triage.” First, the efficacy of PEG/RBV in non-CC genotypes is approximately 20%; thus, the “IL28B triage” strategy forgoes substantial cost savings without additional clinical benefits when it assigns the 20% of patients who would have attained SVR on PEG/RBV instead to triple therapy. Second, the negative predictive value of failing to attain RVR as a predictor of attaining SVR is approximately 98% [57, 63], while that of IL28B CC is only 80% [64–66]. Therefore, the “PEG/RBV trial” strategy functions as a more specific “diagnostic test” than IL28B testing to prioritize patients to triple therapy.

A cost-effectiveness analysis in HCV mono-infection has reported that protease inhibitor-based therapy for all HCV mono-infected patients is cost-effective when compared to the “IL28B triage” strategy [67]. In the base case analysis, however, that study did not consider retreatment with a protease-based regimen for patients who were triaged to PEG/RBV. When the authors did consider re-treatment, the ICER of “triple therapy” was approximately $100,000/QALY, and for some subgroups, IL28B–triage was a dominant strategy. A critical difference between HCV mono- and co-infection is that in mono-infection, the overall treatment course of protease-based therapy is usually 6 months, while that of PEG/RBV is 12 months. As a result, strategies that assign some mono-infected patients to initiate PEG/RBV have a greater negative impact on QoL. Simultaneously, protease-based regimens are relatively less costly because using a protease inhibitor often saves the expense of 6 additional months of PEG/RBV. There may be greater disadvantage of the “PEG/RBV trial” approach in HCV-mono infection than in HIV/HCV co-infection, where response-guided therapy to shorten therapy is not yet proven. Finally, even in HCV mono-infection, the cost-effectiveness of initiating all patients on triple therapy is not entirely clear, as at least one cost-effectiveness analysis has found that “IL28B–triage” is preferred [68].

In two-way sensitivity analysis, we demonstrated the range of costs and efficacies across which future IFN-free regimens would be cost-effective compared to the “PEG/RBV trial” approach using TVR. We found that total therapy costs remained the critical factor determining cost-effectiveness. Assuming an IFN-free regimen that attains 90% SVR, treating all patients with IFN-free therapy will be cost-effective compared to protease-based regimens only if the IFN-free regimen costs are approximately $109,000 or less.

We also explored strategies to reduce the cost of IFN-free therapy by triaging such medications to a proportion of the population. In that case, initiating PEG/RBV and advancing to IFN-free treatment for failure was the preferred strategy. Importantly, a trial of PEG/RBV was cost-effective despite the fact that in the base case scenario, QoL while taking therapy was 10 times worse for an IFN-containing regimen than for IFN-free (0.10 QALY lost vs. 0.01 QALY). Only when the QoL while taking IFN was similar to that of having decompensated cirrhosis did initiating IFN-free therapy for all patients become cost-effective.

Concern that failing an initial course of PEG/RBV could compromise the efficacy of future treatment might limit enthusiasm for the "PEG/RBV trial" approach. Phase 2 trials of IFN-free regimens in HCV mono-infection demonstrate a lower efficacy among treatment-experienced patients [8, 9]. Such findings, however, likely demonstrate that failing PEG/RBV is a marker for having difficult to treat HCV. No data exist to suggest that first-line PEG/RBV itself decreases the efficacy of IFN-free treatment. Routine use of IFN-free regimens in budget-constrained settings will therefore require price negotiations for IFN-free therapy to provide acceptable value for money compared to using those funds to treat a larger number of patients with a strategy that initiates some or all patients on PEG/RBV.

There are several limitations to this analysis. First, we based efficacy estimates for protease-based therapy on phase 2 clinical trials and developed estimates for an IFN-free regimen using trials in HCV mono-infected patients. Nonetheless, the findings that the ICERs of universal triple therapy and IFN-free therapy strategies were >$100,000/QALY at base case therapy costs were consistent across a plausible range of efficacy assumptions. Second, many HCV providers may be inclined to treat HIV/HCV co-infected cirrhotic patients with currently available therapies, but wait for the improved toxicity-profile of IFN-free regimes for patients without cirrhosis [69, 70]. **Given the importance of therapy costs in determining the cost-effectiveness of treatment, it might also be economically attractive to defer HCV therapy for those with early-stage fibrosis until such time that a generic HCV protease inhibitor is available. Such questions of "treat now or defer", while interesting, are outside the scope of this analysis, as they are critically dependent on still unknown relative efficacies of current and future therapies in early-stage and cirrhotic patients, as well as on the relative prices of multiple future drugs**.

In summary, this analysis informs strategies for maximizing the population-level benefits of new HCV therapies in HIV/HCV co-infected patients. We found that in the era of "triple therapy," initiating PEG/RBV and adding TVR when patients fail to attain RVR or SVR maximizes the benefits attainable from constrained healthcare budgets. IFN-free regimens with improved efficacy may provide reasonable value, but this will depend on the cost of these regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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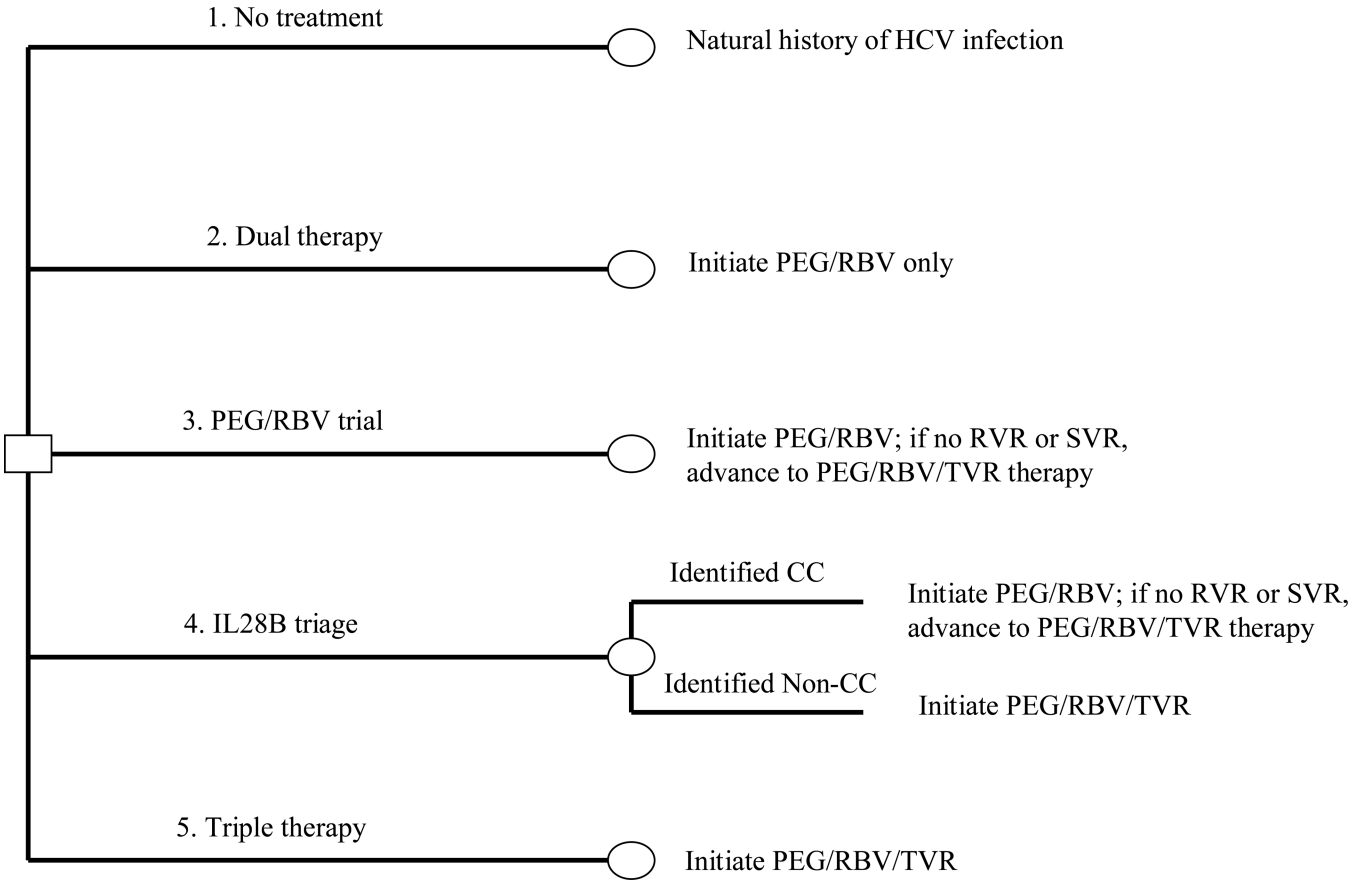

Figure 1. Treatment strategy schematic

Simplified decision tree depicting the treatment strategies considered for treating HCV infection of HIV/HCV co-infected patients without cirrhosis. Note: figure layout was modeled after a similar figure by Liu et al. 2012 [67].

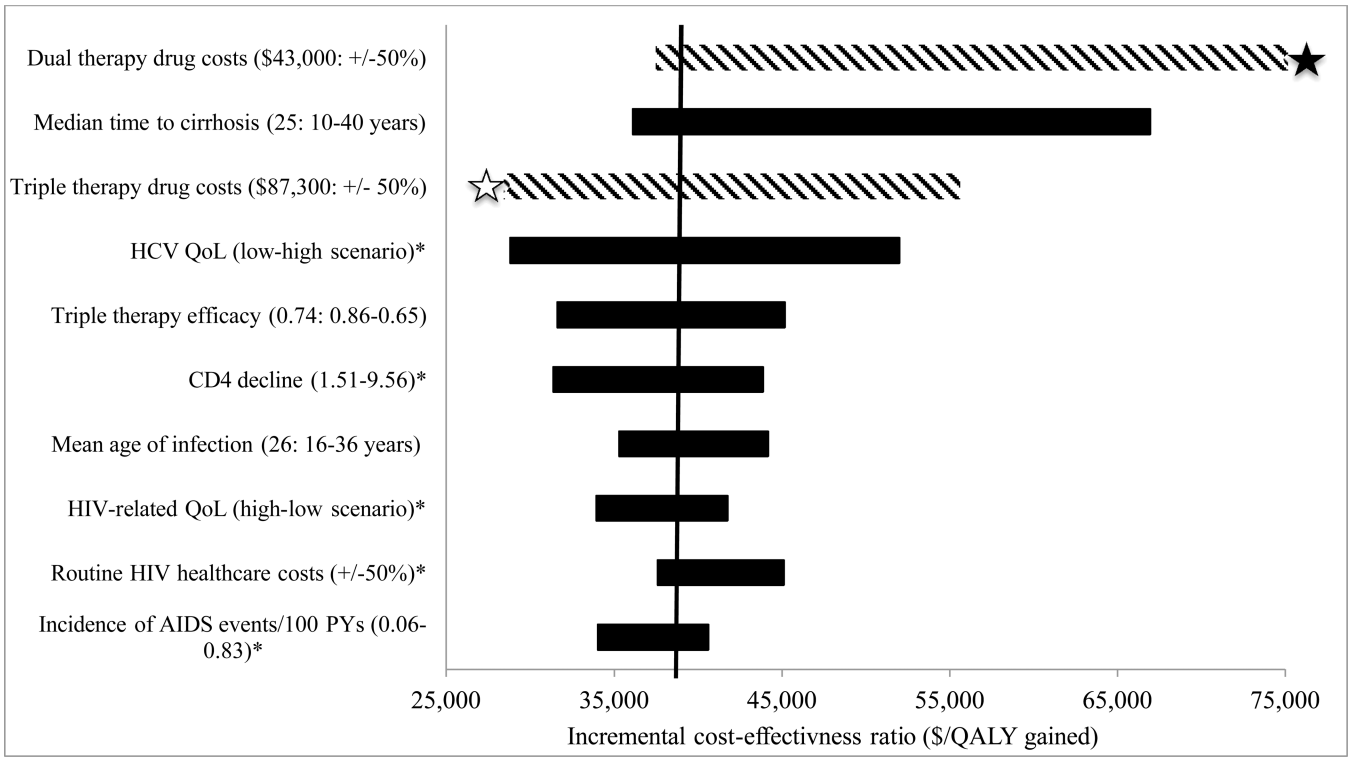

Figure 2. Tornado diagram "PEG/RBV trial" one-way sensitivity analyses

Tornado diagram illustrating the incremental cost effectiveness ratio (ICER) of the "PEG/RBV trial" strategy compared to its next best alternative when varying model input parameters through plausible ranges. Long bars demonstrate parameters that have a large impact on ICERs. Bars with a striped pattern illustrate parameters that led to the "PEG/RBV trial" strategy becoming dominated by either "IL28B triage" or "triple therapy", meaning that the other option provided greater life expectancy at a lower cost per QALY gained. The white star indicates that the "PEG/RBV trial" strategy became dominated by "triple therapy." The black star indicates that the "PEG/RBV trial" strategy became dominated by "IL28B triage." The asterisk refers to Table 1 for base case values. (QALY= quality-adjusted life years; QoL= quality of life).

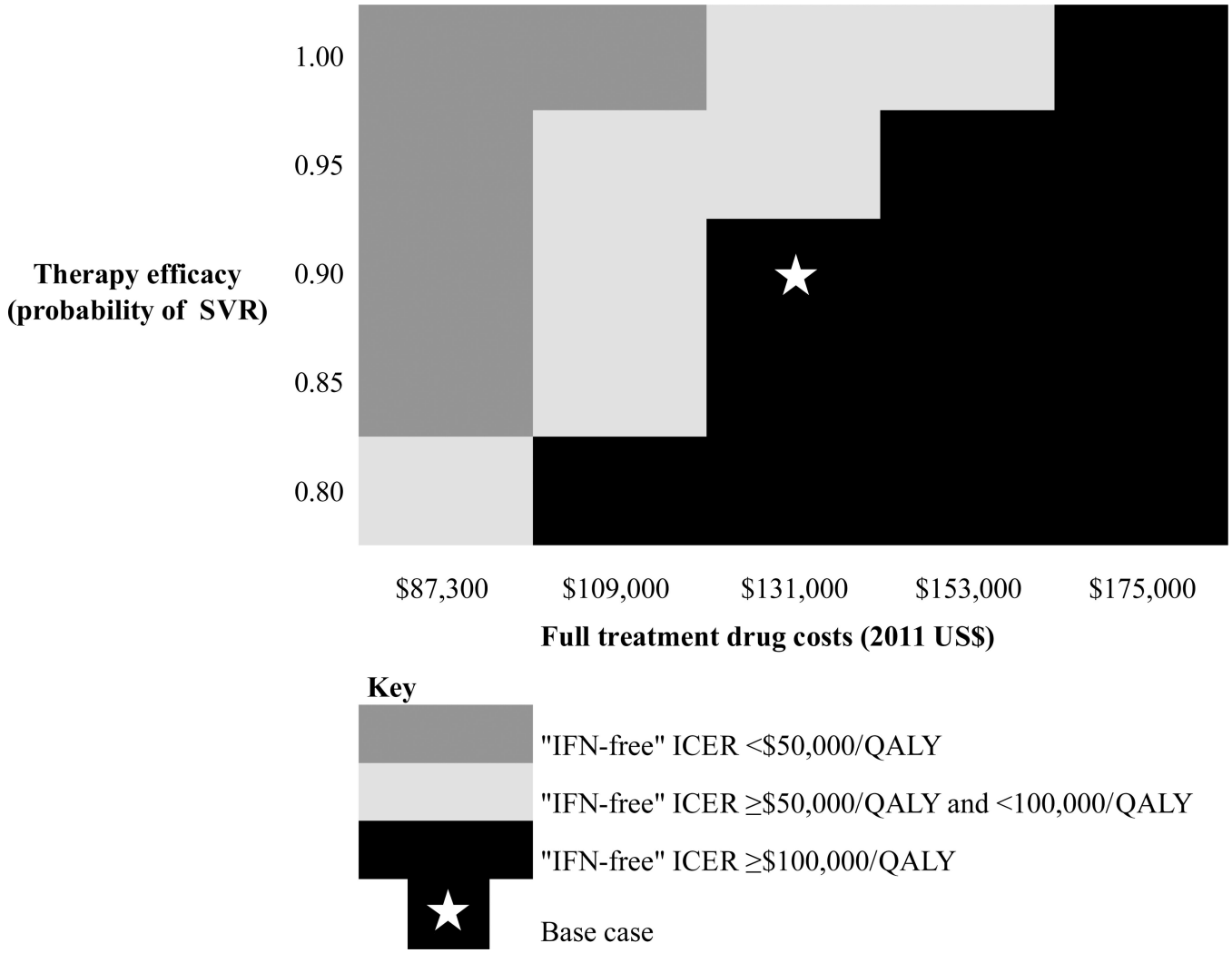

Figure 3. Two-way sensitivity analysis varying costs and efficacy of IFN-free therapy as an alternative to "PEG/RBV trial" strategy

Two-way sensitivity analysis comparing an IFN-free regimen as an alternative to the "PEG/RBV trial" strategy at various cost multipliers of the base case cost of PEG/RBV/TVR ($87,000-$175,000) and efficacies (80% SVR rate – 100% SVR rate). The striped boxes reflect an incremental cost effectiveness ratio (ICER) of "IFN-free" compared to "PEG/RBV trial" <$100,000/QALY, making "IFN-free" the preferred strategy. In contrast, the black boxes reflect an ICER of "IFN-free" compared to "PEG/RBV trial" > $100,000/QALY, making "PEG/RBV trial" the preferred strategy.

Table 1

Model inputs for an analysis of the cost-effectiveness of HCV therapies in HIV/HCV co-infected patients

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses	Source(s)
Cohort characteristics			
Average age, years (S.D.)*	45 (6)	35–55	[44–48]
Proportion male	0.66	0–1.0	[44–47]
Average age at HCV infection (years)*	26 (20–30)	16–36	[52]
Prevalence of IL28B CC genotype	0.32	0.26–0.39	[14]
Mean CD4 count, cells/μl (S.D.)*	520 (100)	350–700	[49–51]
Proportion with CD4 > 500 at baseline on ART	0.756	0.5–1.0	[49–51, 71]
Standardized mortality ratio (SMR)[a]			[72, 73]
Men	4.69	1.00–6.01	
Women	7.80	1.00–14.14	
IL28B test characteristics			
Sensitivity	0.99	0.95–1.00	[74–76]
Specificity	0.99	0.96–1.00	[74–76]
HCV disease progression			
Median years to cirrhosis from age of infection (10%–90%)*	25 (23–27)	10–40	[53]
Median years first liver-event after developing cirrhosis (10%–90%)*	10.8 (9.2–14.3)	5.6–19.3	[25, 77]
Liver-related mortality with cirrhosis (deaths/100 PYs)	2.73	1.38–4.08	[25, 26]
HIV disease progression			
Rate of CD4 decline (cells/μl/month)[b]	3.03–6.38	1.51–9.56	[78]
Incidence of AIDS events (events/100 PYs)[c]	0.12–0.55	0.06–0.83	[79–86]
HCV therapy efficacy			
PEG/RBV therapy			
CC genotype at rs12979860			
Probability of RVR	0.80	0.74–0.91	[16, 57]
Probability of SVR given RVR	0.91	0.77–0.94	[16, 57]
Probability of withdrawal (toxicity or non-adherence)	0.23	0.19–0.29	[57]
Probability of withdrawal due to toxicity	0.10	0.08–0.13	[87]
Total probability of SVR	**0.55**	**0.40–0.69**	**[16, 54–57]**
Non-CC allele (TT or TC)			
Probability of RVR	0.42	0.33–0.52	[16, 57]
Probability of SVR given RVR	0.64	0.57–0.73	[16, 57]
Probability of withdrawal (toxicity or non-adherence)	0.23	0.19–0.29	[57]
Probability of withdrawal due to toxicity	0.10	0.08–0.13	[87]
Total probability of SVR	**0.20**	**0.13–0.30**	**[16, 54–57]**
PEG/RBV/TVR			
Probability of having treatment failure (HCV viremia >1,000/ml)	0.18	0.02–0.21	[88]
Probability of withdrawal (toxicity or non-adherence)	0.18	0.06–0.23	[3]

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses	Source(s)
Probability of withdrawal due to toxicity	0.08	0.03–0.10	[88, 89]
Total probability of SVR	**0.74**	**0.65–0.86**	**[3]**
IFN-free therapy			
Probability of withdrawal	0.03	0.02–0.04	[6, 7]
Probability of withdrawal for toxicity	0.006	0.004–0.009	See text
Total probability of SVR	**0.90**	**0.80–0.95**	**[6, 7]**
Probability of death due to toxicity for all strategies	0	0–0.029	[57, 88, 90]
HIV therapy efficacy			
ART efficacy (proportion HIV RNA < 400 copies/ml at 24 weeks)[d]	0.15–0.86	0.13–0.99	[91–95]
ART efficacy (proportion HIV RNA < 50 copies/ml at 24 weeks)[d]	0.15–0.65	0.12–0.75	[91–95]
CD4 rise on suppressive ART (cells/μl/month)[d]	26–90	13–135	[91–95]
HIV loss to follow-up (rate/100 PYs)[e]	24.17	12.09–36.26	[96]
Costs			
Costs of screening tests and ART			
IL28B assay test	$80	$40-$120	[31]
ART costs[d]	$1,600-$4,800	$800-$7,700	[33, 34, 38]
Healthcare costs			
Without HCV (HIV only)[f]	$300- $20,600	$150-$30,900	[31, 32, 35–37]
With HCV[f]	$370-$23,300	$190-$35,000	[19, 31, 39]
HCV therapy costs/month			
TVR	$15,200	$7,600-$23,000	[33]
PEG[g]	$2,100	$1,100-$3,200	[33]
RBV[h]	$1,400	$700-$2,100	[33]
Filgrastim[i]	$1,900	$900-$2,700	[33]
Clobetasol propionate[j]	$160	$80-$320	[33]
Total costs of dual therapy[l]	$43,000	$21,500-$64,500	[31, 33]
Total costs of triple therapy[k]	$87,300	$43,700-$131,000	[31, 33]
Total costs of IFN-free therapy	$131,000	$98,200-$196,500	See text
Cost of treatment ending toxicity for triple and IFN-free therapy	$360	$180-$540	[30, 31, 33, 97, 98]
Cost of treatment ending toxicity for dual therapy	$420	$210-$630	[30, 31, 33, 57, 97]
Provider visit costs[m]	$120	$60–180	
Quality of life			
HCV-related quality of life			
No fibrosis to moderate fibrosis	0.89	0.75–0.95	[20, 22, 43]
Cirrhosis	0.62	0.55–0.75	[20, 22, 43]
Decompensated cirrhosis	0.48	0.40–0.60	[20, 22, 43]
On IFN (applied to appropriate HCV-attributable QoL)	0.90	0.84–0.96	[42]
On IFN-free therapy (applied to appropriate HCV-attributable QoL)[n]	0.95	0.90–0.99	See text

Variable	Base Case Value	Range Evaluated in Sensitivity Analyses	Source(s)
Major toxicity decrement (monthly)[o]	0.16	0.09–0.25	[99]
HIV-related quality of life (CD4 cells/μl)			
>500	0.87	0.78–0.96	[41]
351–500	0.86	0.77–0.95	[41]
251–350	0.86	0.77–0.95	[41]
101–250	0.85	0.76–0.94	[41]
51–100	0.85	0.76–0.94	[41]
≤50	0.83	0.74–0.92	[41]
With acute AIDS-related event[p]	0.69–0.78	0.69–0.78	[40]

SD: standard deviation; IL28B: interleukin-28B; ART: anti-retroviral therapy; PYs: person-years; PEG: peginterferon; RBV: ribavirin; TVR: telaprevir; SVR: sustained virologic response; RVR: rapid virologic response; IFN: interferon; OI: opportunistic infection; MSM: men who have sex with men; IDU: injection drug user

Note: all costs are in 2011 U.S. dollars.

[*] These parameters are entered into the model as distributions rather than point estimates, allowing for first-order Monte Carlo variance. Numbers in parentheses next to the base case value represent either the standard deviation (if normally distributed) or the tenth and ninetieth percentile values (if non-normally distributed) of the distribution. The ranges provided in the sensitivity analysis column provide the range of central measure (mean or median) that we tested in sensitivity analyses.

[a] The SMR captures elevated non-HIV and non-HCV mortality among those who are HIV/HCV co-infected. It reflects competing risks of death from substance use and other co-morbidities. To determine the SMR for the entire cohort, we first identified risk-group specific SMRs (MSM, IDU, heterosexual risk) by sex, and then took the weighted average of these estimates, using the proportion of each risk-factor among HIV/HCV co-infected patients.

[b] Depending on HIV RNA.

[c] Depending on CD4, OI history and event type.

[d] Depending on ART regimen.

[e] Beginning in month 18 (we assumed no HIV-related loss to follow-up during HCV treatment).

[f] Depending on age, sex, duration of HIV infection, and CD4 count.

[g] 13% of patients received a reduced weekly dose of 135 mcg in response to non-treatment ending neutropenia [100].

[h] Assumed to be 1,200 mg/day for a 75 kg person; 36% of patients on triple therapy and 17% of patients on dual therapy receive a reduced dose RBV = 600 mg/day in response to non-treatment ending anemia [100].

[i] 13% of patients developed non-treatment ending neutropenia (absolute neutrophil count < 750/ml) and received filgrastim 300 mcg/two times weekly [100].

[j] 28% of patients on triple therapy during the first 3 months of therapy receive 150 g per month for treating mild rash [100].

[k] Includes an additional cost of a nursing visit for patients who have adverse events.

[l] Depending on treatment month.

[m] Treatment visit costs are higher in the first month compared to other months.

[n] The multiplier is applied for 3 months instead of 12 months for IFN-free therapy, resulting in 0.5 quality-adjusted life months saved compared to being on PEG/RBV therapy.

[o] This utility “toll” was subtracted from a patient’s health state utility during the month of a major toxicity event.

[p] Depending on type of OI event.

Table 2

Incremental cost effectiveness ratios of HIV/HCV telaprevir-based treatment strategies

		Undiscounted	Discounted		Incremental		
Strategy	**% Attaining SVR**	**Life Expectancy**	**Cost ($)**	**QALE**	**Cost ($)**	**QALY**	**CER ($/QALY)**
No treatment	0	13.240	198,700	6.760	---	---	---
Dual therapy	30.8	13.761	221,900	7.600	23,200	0.839	27,700
PEG/RBV trial	72.1	14.459	264,200	8.728	42,300	1.128	37,500
IL28B triage	72.3	14.463	269,200	8.743	5,000	0.016	319,400
Triple therapy	72.5	14.462	277,700	8.750	8,500	0.007	1,240,000

QALY: quality-adjusted life year; CER: cost-effectiveness ratio; PEG/RBV: Peginterferon and Ribavirin; IL28B: interleukin-28B

Note: all costs and QALYs are lifetime and discounted at an annual rate of 3%. Costs are in 2011 US dollars and rounded to the nearest $100. All life-years and QALYs are rounded to the nearest thousandth.

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