Year: 2015

Modeling the effect of HIV coinfection on clearance and sustained virologic response during treatment for hepatitis C virus

Birger, Ruthie; Kouyos, Roger; Dushoff, Jonathan; Grenfell, Bryan

Abstract: Background: HIV/hepatitis C (HCV) coinfection is a major concern in global health today. Each pathogen can exacerbate the effects of the other and affect treatment outcomes. Understanding the within-host dynamics of these coinfecting pathogens is crucial, particularly in light of new, direct-acting antiviral agents (DAAs) for HCV treatment that are becoming available. Methods and findings: In this study, we construct a within-host mathematical model of HCV/HIV coinfection by adapting a previously published model of HCV monoinfection to include an immune system component in infection clearance. We explore the effect of HIV-coinfection on spontaneous HCV clearance and sustained virologic response (SVR) by building in decreased immune function with increased HIV viral load. Treatment is modeled by modifying HCV burst-size, and we use clinically-relevant parameter estimates. Our model replicates real-world patient outcomes; it outputs infected and uninfected target cell counts, and HCV viral load for varying treatment and coinfection scenarios. Increased HIV viral load and reduced CD4+ count correlate with decreased spontaneous clearance and SVR chances. Treatment efficacy/duration combinations resulting in SVR are calculated for HIV-positive and negative patients, and crucially, we replicate the new findings that highly efficacious DAAs reduce treatment differences between HIV-positive and negative patients. However, we also find that if drug efficacy decays sufficiently over treatment course, SVR differences between HIV-positive and negative patients reappear. Conclusions: Our model shows theoretical evidence of the differing outcomes of HCV infection in cases where the immune system is compromised by HIV. Understanding what controls these outcomes is especially important with the advent of efficacious but often prohibitively expensive DAAs. Using a model to predict patient response can lend insight into optimal treatment design, both in helping to identify patients who might respond well to treatment and in helping to identify treatment pathways and pitfalls.

DOI: 10.1016/j.epidem.2015.04.001

Epidemics 12 (2015) 1–10

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Modeling the effect of HIV coinfection on clearance and sustained virologic response during treatment for hepatitis C virus

Ruthie Birger[a,*], Roger Kouyos[b,c], Jonathan Dushoff[d], Bryan Grenfell[a,e]

[a] Department of Ecology and Evolutionary Biology, Princeton University, 106a Guyot Hall, Princeton, NJ 08544, USA
[b] Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zürich, University of Zürich, Rämistr. 100, CH-8091 Zürich, Switzerland
[c] Institute of Medical Virology, University of Zürich, Zürich, Switzerland
[d] Department of Biology, McMaster University, 1280 Main St. West, Hamilton, Ontario L8S 4K1, Canada
[e] Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 9 May 2014
Received in revised form 18 April 2015
Accepted 20 April 2015
Available online 27 April 2015

Keywords:
Mathematical model
HCV–HIV
Antiviral therapy
Immune response
Coinfection

ABSTRACT

Background: HIV/hepatitis C (HCV) coinfection is a major concern in global health today. Each pathogen can exacerbate the effects of the other and affect treatment outcomes. Understanding the within-host dynamics of these coinfecting pathogens is crucial, particularly in light of new, direct-acting antiviral agents (DAAs) for HCV treatment that are becoming available.
Methods and findings: In this study, we construct a within-host mathematical model of HCV/HIV coinfection by adapting a previously published model of HCV monoinfection to include an immune system component in infection clearance. We explore the effect of HIV-coinfection on spontaneous HCV clearance and sustained virologic response (SVR) by building in decreased immune function with increased HIV viral load. Treatment is modeled by modifying HCV burst-size, and we use clinically-relevant parameter estimates.

Our model replicates real-world patient outcomes; it outputs infected and uninfected target cell counts, and HCV viral load for varying treatment and coinfection scenarios. Increased HIV viral load and reduced $CD4^+$ count correlate with decreased spontaneous clearance and SVR chances. Treatment efficacy/duration combinations resulting in SVR are calculated for HIV-positive and negative patients, and crucially, we replicate the new findings that highly efficacious DAAs reduce treatment differences between HIV-positive and negative patients. However, we also find that if drug efficacy decays sufficiently over treatment course, SVR differences between HIV-positive and negative patients reappear.
Conclusions: Our model shows theoretical evidence of the differing outcomes of HCV infection in cases where the immune system is compromised by HIV. Understanding what controls these outcomes is especially important with the advent of efficacious but often prohibitively expensive DAAs. Using a model to predict patient response can lend insight into optimal treatment design, both in helping to identify patients who might respond well to treatment and in helping to identify treatment pathways and pitfalls.

1. Introduction and background

HIV–HCV coinfection is a whole greater than the sum of its parts, due to the potentiating effect each virus can have on the other. It is an increasing concern in certain populations including people who inject drugs (PWID) and men who have sex with men (MSM). Understanding the within-host dynamics of coinfection is crucial for designing treatment strategies that will avoid complications such as hepatotoxicity and treatment failure, while minimizing the cost of treatment. There is a rich literature on monoinfection with each pathogen (e.g. Ho et al., 1995; Neumann et al., 1998; Perelson, 1999; Dixit et al., 2004; Perelson et al., 2005; Biafore and D'Attellis, 2006; Reluga et al., 2009; Debroy et al., 2011) but to the best of our knowledge, within-host HIV–HCV coinfection has not yet been modeled.

HIV and HCV are both viral infections that can be blood-borne. They are often transmitted together, especially among PWID (Alter, 2006; Vickerman et al., 2013). The infections can interact synergistically: broadly, HIV causes deterioration of the immune system, which can lead to poorer control and clearance rates of HCV as well as reduced probability of treatment success (Kim and Chung, 2009), while HCV may increase progression rates of HIV through

* Corresponding author. Tel.: +1 347 429 0986.
E-mail address: rbirger@princeton.edu (R. Birger).

http://dx.doi.org/10.1016/j.epidem.2015.04.001

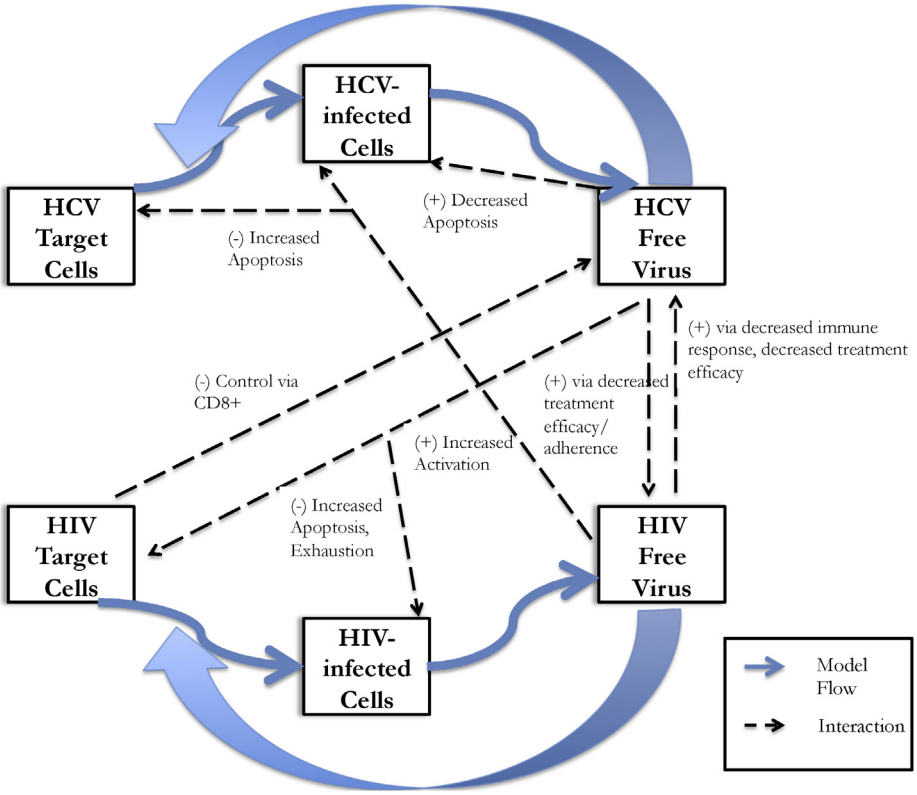

Fig. 1. Within-host HIV–HCV interactions. Dashed black arrows represent mechanisms of HIV–HCV interaction described in the literature. Solid blue arrows represent population-biological effects taken into account in our model. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

chronic immune activation or increased CD4 apoptosis (Gonzalez et al., 2010). Treatment success for HCV is defined as achieving sustained virologic response (SVR), i.e. HCV RNA is undetectable during treatment and for 6 months beyond treatment end (Feld and Hoofnagle, 2005).

We approach clinical implications of coinfection with a dynamic-static mathematical model, based on a previously published dynamical model of HCV monoinfection (Dahari et al., 2005; Reluga et al., 2009; Debroy et al., 2011) to include an explicit element of immune control. We then perturb the system by adding HIV infection as a static parameter, which erodes immune control and thus changes the HCV dynamics. Lastly, we explore how this loss of control impacts HCV treatment outcomes.

Understanding phenomena that may impact treatment outcomes is especially important with the advent of new direct-acting antiviral agents (DAAs) such as Sofosbuvir that are becoming available for HCV treatment. These new drugs are highly efficacious, but still very expensive, so thoughtful treatment design and administration is necessary (NatMed, 2014; Guedj et al., 2010; Ahlén et al., 2013).

1.1. Immune/HCV interactions

The immune response to HCV is complex and involves both innate and adaptive components. The adaptive response to HCV is mostly T-cell dependent. Virus-specific $CD4^+$ and $CD8^+$ responses have been detected during acute infection, and it is thought that these cells may clear virus by lysing infected cells or by cytokine/chemokine-mediated effects (Kim and Chung, 2009).

HCV may be responsible for immune dysregulation itself; some studies indicate an inverse correlation between HCV viral load and $CD4^+$ count (Mohsen et al., 2002). HCV may also downregulate proliferation of T cells or increase apoptosis. Increased immune activation in coinfected versus monoinfected patients has been noted, which also may speed HIV progression (Gonzalez et al., 2009). A schematic summary of HIV–HCV interaction effects is shown in Fig. 1.

1.1.1. Empirical evidence for effect of HIV infection on HCV clearance and treatment response

Patients who are able to clear HCV spontaneously have been noted to mount intense multispecific $CD4^+$ and $CD8^+$ responses, in particular with HCV-specific $CD4^+$ Th1 responses (Roe and Hall, 2008). Complementarily, some studies show that lower $CD4^+$ counts are associated with reduced probability of clearing (Kim and Chung, 2009). However, HCV can avoid these responses through mutation and inhibition of dendritic cell activation and production of Th1 cytokines. This can prevent cytotoxic lymphocyte (CTL)-induced apoptosis of infected hepatocytes, which can in turn increase viral production (Roe and Hall, 2008).

Some HIV-positive patients do clear HCV, but in much lower proportions than HIV-negative individuals. The correlative evidence for mechanism is mixed. Higher rates of chronic HCV are inversely correlated with $CD4^+$ count according to some studies reviewed by Kim and Chung (2009). A study in chimpanzees showed reduced endurance of HCV-specific $CD8^+$ CTL response after depletion of $CD4^+$ cells before reinfection; viremia upon reinfection was persistent despite the presence of functional $CD8^+$ T-cells (Grakoui et al., 2003). Other studies have found more general negative correlation between HIV viral load and SVR (Thomas, 2006; Roe and Hall, 2008). The phenomenon of increased persistence of HCV among HIV-positive patients is related to and accompanied by an increased HCV viral load.

A number of empirical studies show elevated HCV viral load (0.1–1 logs higher) among HIV-positive as compared to HIV-negative patients (Di Martino et al., 2001; Danta et al., 2008; Mohsen et al., 2002; Roe and Hall, 2008). The cause is most likely reduced immune response: coinfection is associated with lack of critical $CD4^+$ response to HCV (Danta et al., 2008; Harcourt et al., 2006). Indeed, the study in chimpanzees mentioned above showed that $CD8^+$ T-cells had impaired control of viral replication with insufficient $CD4^+$ help (Grakoui et al., 2003), and there is evidence that broad $CD4^+$ responses play a major role in HCV clearance (Diepolder et al., 1995).

1.1.2. Role of HIV treatment

In clinical settings where HCV treatment is available, most coinfected patients will have been treated with anti-retroviral therapy (ART) for HIV prior to receiving treatment for HCV despite some risks of hepatotoxicity from ART (Soriano et al., 2007; Taylor et al., 2012). However, even when ART is successful and results in achievement of virological suppression, $CD4^+$ recovery is often incomplete. Many studies have shown that $CD4^+$ count at similar durations after ART initiation varies widely, and is correlated with a range of patient characteristics such as nadir $CD4^+$ count (Kaufmann et al., 2003; McKinnon et al., 2010; Takuva et al., 2014) (see Supplementary Fig. 1). Correspondingly, there is evidence that even coinfected patients who are treated for HIV have a lower probability of clearing HCV (Schnuriger et al., 2009) or achieving SVR (Laguno et al., 2004; Dore et al., 2007; Andreoni et al., 2012).

1.2. Previous models of HCV

Some of the first within-host models of HCV aimed to capture the dynamics of infection by pairing a mathematical model with patient data from a trial of varying doses of interferon (IFN) treatment (Neumann et al., 1998; Perelson, 1999). The viral load patterns upon treatment observed (i.e. rapid initial decline in viral load followed by extended slow decline) were consistent with the main mechanism of IFN treatment being reduction in production of new virus by infected cells (burst size). Higher doses were more effective, and lower diversity of quasi-species were associated with better response to treatment.

Extensions to this model take into account complexities surrounding treatment response, such as non-response, rebound in viral load (relapse), or treatment with other therapies (Perelson et al., 2005; Dixit et al., 2004).

1.2.1. Models of extended infection

The aforementioned models deal with acute HCV infection and treatment dynamics over the course of several days or weeks. HCV can be a long course infection, however, and models can capture longer term dynamics as well.

The model created for this study is based on previous works (Reluga et al., 2009; Debroy et al., 2011; Dahari et al., 2005) and explores treatment dynamics past initial infection in detail. The conditions for achievement of SVR can be inconsistent. For example, the "End-of-Treatment" response, defined as undetectable viral load (below 2 logs) at the end of a 24 or 48 week course of treatment, is necessary but not sufficient for SVR. Debroy et al. (2011) analyze medium- and long-term responses leading to either a viral endemic equilibrium or a disease-free equilibrium to establish mathematical criteria for each state. Depending on the initial conditions and biological parameter values, there exists a possibility of bistability for some patients (i.e. they have the capacity to clear infection, but only if treated adequately). The parameter values depend on patient immunological characteristics, as well as viral characteristics and interactions, which can vary by genotype (as explored by Smith et al., 2010). Our model aims to extend the analysis of these previous models in scenarios of HIV coinfection.

2. Methods

2.1. HCV monoinfection model

The model proposed in this study follows closely the above-referenced model (Dahari et al., 2005; Reluga et al., 2009; Debroy et al., 2011). Following a standard ODE model proposed in earlier work (Perelson and Nelson, 1999), with some variations such as inclusion of infected hepatocytes in density dependence, the basic form of the equations (without the immune system component) is as follows:

$$\frac{dT}{dt} = s + r_1 T\left(1 - \frac{T+I}{T_{\max}}\right) - dT - \beta TV$$

$$\frac{dI}{dt} = \beta TV + r_2 I\left(1 - \frac{T+I}{T_{\max}}\right) - \delta I$$

$$\frac{dV}{dt} = pI - cV$$

Here, T, I, and V are the state variables representing, respectively, uninfected **T**arget cells (hepatocytes), **I**nfected hepatocytes, and free HCV **V**irus, s is the recruitment rate for uninfected hepatocytes, r_1 is the reproduction rate of uninfected hepatocytes, $T_{\max}$ is the maximum number/carrying capacity of target cells, d is the death rate of uninfected target cells, β is the mass-action infection parameter, r_2 is the reproduction rate of infected hepatocytes, δ is the clearance rate of infected hepatocytes, p is the number of virions an infected cell produces in its lifetime (which can also be interpreted as burst size), and c is viral clearance rate. With this model of HCV monoinfection as a basis, we can build a new model of HCV that includes the role of the immune system – specifically, $CD4^+$ cells, denoted H in the model equations. Work by Grakoui et al. (2003) and others has illuminated to some extent the role of $CD4^+$ cells in HCV control, and activation of $CD4^+$ cells by HCV has been documented (Lechner et al., 2000; Bowen and Walker, 2005). The model proposed here thus incorporates a dependence of the HCV clearance rate on $CD4^+$ count (α) and a dependence of the activation rate of $CD4^+$ cells on HCV infected cell count (γ). The equations thus become

$$\frac{dT}{dt} = s + r_1 T\left(1 - \frac{T+I}{T_{\max}}\right) - dT - \beta TV$$

$$\frac{dI}{dt} = \beta TV + r_2 I\left(1 - \frac{T+I}{T_{\max}}\right) - \delta(1+\alpha H)I$$

$$\frac{dV}{dt} = pI - cV$$

$$\frac{dH}{dt} = s_H(1+\gamma I) - d_H H$$

where s_H is the recruitment rate of $CD4^+$ cells, and d_H their death rate.

2.2. Immunological impact of HIV coinfection on HCV

Introducing HIV infection into the system will have an impact on its dynamics. Rather than including the full complexity of within-host HIV dynamics in this model, we have chosen to take advantage of the differing time scales of asymptomatic HIV infection and HCV treatment. Therefore, we use HIV set-point viral load as a constant

parameter (rather than a state variable with its own dynamics) so it contributes as a mass-action depleter of the immune system compartment. Perturbing the system by adding a component of HIV-infection changes the stability dynamics. To maximize simplicity in the model, HIV infection was therefore modeled as a single viral load, denoted by V_H, representing the set-point viral load. The equation for H thus becomes

$$\frac{dH}{dt} = s_H(1+\gamma I) - d_H H - \beta_H V_H H$$

where β_H is the mass-action infection parameter for HIV. Due to the static nature of the incorporation of HIV into this model, we are unable to capture dynamically the process of immune recovery after ART for HIV. However, as immune recovery is often incomplete, we can use lower values of H (we can vary s_H to generate these values when $V_H \approx 0$) to simulate a depleted immune system and thus capture the dynamics of HCV in HIV patients on ART.

2.3. HCV treatment

Treatment efficacy was included in the model as a parameter ε controlling viral production rate as in previous work (Neumann et al., 1998), and following Snoeck et al. (2010) and Dixit et al. (2004), we have implemented a cure boundary such that virus stops being produced when infected cell count drops below 1. The equations become

$$\begin{aligned}
\frac{dT}{dt} &= s + r_1 T\left(1 - \frac{T+I}{T_{\max}}\right) - dT - \beta TV \\
\frac{dI}{dt} &= \beta TV + r_2 I\left(1 - \frac{T+I}{T_{\max}}\right) - \delta(1+\alpha H)I \\
\frac{dV}{dt} &= (1-\varepsilon)pI - cV \\
\frac{dH}{dt} &= s_H(1+\gamma I) - d_H H - \beta_H V_H H
\end{aligned}$$

This formulation allows for implementation of imperfect treatment for varying durations in this model. As explored in the next section, these combinations can reveal the uncertainty surrounding cure inherent in certain patients.

2.4. Bistability analysis

This model allows for cure in two types of patient systems. As explored by Snoeck et al. (2010), including the cure boundary allows the model to replicate viral dynamics in patients in whom infection is effectively cleared (<1 infected hepatocyte in the modeled population). These patients do not exhibit true bistability; if infected hepatocytes are not completely cleared, the viral load will bounce back even from undetectable levels. In some patients, however, the system can by truly bistable and when infected cell count drops below a certain non-zero level, the patient will achieve SVR even if virus is not initially eradicated.

To explore the stability dynamics of the model, it can be useful to make the quasi-steady state approximation. Because the viral dynamics happen on a faster time scale than the cell dynamics, we can simplify the equations as

$$\begin{aligned}
\frac{dT}{dt} &= s + r_1 T\left(1 - \frac{T+I}{T_{\max}}\right) - dT - (1-\varepsilon)\tilde{\beta}TI \\
\frac{dI}{dt} &= (1-\varepsilon)\tilde{\beta}TI + r_2 I\left(1 - \frac{T+I}{T_{\max}}\right) - \delta(1+\alpha H)I \\
\frac{dH}{dt} &= s_H(1+\gamma I) - d_H H - \beta_H V_H H \\
V &= \frac{p}{c}I
\end{aligned}$$

where $\tilde{\beta} = (p/c)\beta$.

Following Debroy et al. (2011), we calculate the within-host R_0 by setting $dI/dt > 0$ at the start of the infection (before treatment, so the ε term disappears), when $I \approx 0$:

$$\frac{dI}{dt} = \tilde{\beta}TI + r_2 I\left(1 - \frac{T+I}{T_{\max}}\right) - \delta(1+\alpha H)I > 0$$

$$\tilde{\beta}T + r_2\left(1 - \frac{T}{T_{\max}}\right) > \delta(1+\alpha H)$$

$$R_0 = \frac{\tilde{\beta}T_0 + r_2(1-(T_0/T_{\max}))}{\delta(1+\alpha H_0)} > 1$$

where T_0, H_0 are the initial values of uninfected hepatocytes and activated CD4$^+$ cells in the absence of infection.

$$T_0 = \frac{T_{\max}}{2r_1}\left((r_1 - d) + \sqrt{(r_1-d)^2 + 4s\frac{r_1}{T_{\max}}}\right)$$

and

$$H_0 = \frac{s_H}{d_H}$$

Bistability of a viral endemic equilibrium (EE) and a disease-free equilibrium (DFE) can occur under certain circumstances (Debroy et al., 2011). In this monoinfection model, bistability occurs when the within-host R_0 is close to or less than 1, and $r_2 > \tilde{\beta}T_{\max}$, $r_2 > \delta(1+\alpha H_0)$. There is some evidence that HCV can increase the reproduction rate of infected cells to replace cells that were targeted successfully by immune response (Roe and Hall, 2008; Kim and Chung, 2009; Block et al., 2003; Erhardt et al., 2002; Hu et al., 2013), so stability of an endemic equilibrium given this condition has some clinical basis. The role of r_2 in the bistability in this system has an intuitive basis as well: the infected cell growth rate receives contributions both from infected replication and from virion infection of healthy cells. More basically, when $r_2 > r_1$, i.e. the maximum proliferation rate of the infected cells is greater than the maximum proliferation rate of infected cells, the infection can invade even at a stable, disease-free equilibrium. Interestingly, HIV-coinfection impacts greatly the stability of the DFE, but does not impact invasion probability at the stable DFE. Derivation of these conditions can be found in Appendix A.

The stability surrounding R_0 divides patients into four types: never achieving SVR ($R_0 > 1$), always achieving SVR ($R_0 < R_C$ where R_C is the critical bifurcation value), or in the bistable region, either experiencing spontaneous cure or experiencing viremia but with the ability to be pushed into the clearance area by treatment. With this formulation, it is possible to analyze numerically which values of duration and efficacy can push a patient from one basin of attraction to the other (i.e. endemic equilibrium to clearance). SVR is thus dependent on a combination of critical efficacy and time. When the immunological impact of HIV-coinfection is included, however, the stability dynamics change, reducing the probability of achieving SVR (Andreoni et al., 2012).

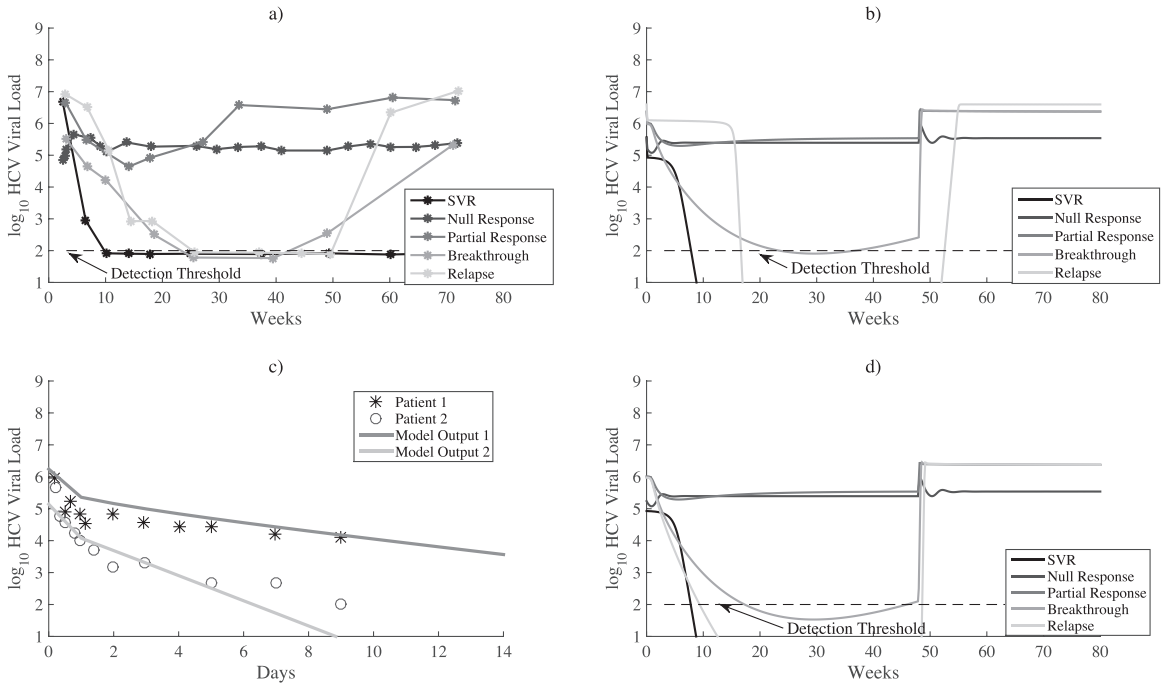

Fig. 2. Model comparison with data. Panel a shows patient data redrawn from Snoeck et al. (2010), displaying the five types of long-term treatment outcome: SVR, null response, partial response, breakthrough, and relapse. Panel b shows model scenarios from the model including free virus displaying these same five outcomes. Panel c shows short-term treatment dynamics over the first two weeks of treatment; model outputs are paired with data redrawn from Neumann et al. (1998). Panel d shows the same scenarios as b, using a version of the model wherein the quasi-steady state assumption has been implemented, demonstrating that the long-term dynamics can be recovered. Parameter values for each simulation are listed in Supplementary Table 3.

3. Results

The model can qualitatively replicate viral dynamics observed in HCV patients after treatment and described in previous studies such as Neumann et al. (1998) and Snoeck et al. (2010). Fig. 2 demonstrates this replication, showing both the initial biphasic decline (model outputs paired with data redrawn from Neumann et al., 1998 in panel c), and longer-term dynamics paired with data redrawn from Snoeck et al. (2010) (panels a and b). The model outputs shown are not explicitly fitted to the data presented, but nonetheless replicate the viral trajectories. When the quasi-steady state assumption is made, these longer-term dynamics can be similarly qualitatively recovered, as seen in panel d of Fig. 2. Using an example patient (Patient I) who exhibits true bistability of endemic- and disease-free equilibria allows us to visualize the impact of HIV infection. Simulating different levels of the depletion in CD4 count that might occur during the asymptomatic phase of HIV infection shows that the zone of bistability shrinks with decreasing $CD4^+$ count. The region of bistability is a region wherein the within-host R_0 is less than or close to 1 but greater than a certain critical reproductive number, R_C (see Appendix for calculation of R_C). In this region, there are three distinct equilibria: the stable endemic equilibrium (EE), the disease-free equilibrium (DFE) and a third, unstable EE. This unstable endemic equilibrium divides viral load measures into two basins of attraction: toward the DFE and toward the stable EE. Fig. 3 shows how this region of bistability encroaches farther into the region of spontaneous clearance the lower the $CD4^+$ count, and eventually erases the possibility of spontaneous clearance for realistic values of δ. The presence of HIV depletes the immune system component (even after successful treatment of HIV with ART) thus decreasing the probability of spontaneous clearance of HCV for this patient. The patient represented has values for parameters drawn from the realistic distributions described in Debroy et al. (2011) (and Supplementary Table 1). HIV parameters are adapted from Biafore and D'Attellis (2006). The set-point viral load values tested are derived from the estimates of the variability of HIV set-point viral load by Fraser (2007). The co-infection influence parameters are theoretical estimates chosen such that model reproduces viral load levels and relationships; while much empirical work has demonstrated qualitative relationships indicated by these parameters (e.g. Grakoui et al., 2003; Lechner et al., 2000; Bowen and Walker, 2005), this work does not allow for their precise determination in this context.

The bifurcation diagram demonstrates how spontaneous clearance can become non-clearance in a patient for whom the bistability criteria hold, but using this model we can also demonstrate differential treatment responses. Fig. 4 shows two sample patients who are both able to achieve SVR in a non-immunosuppressed state. Panel a shows Patient I, the same bistable patient as in the bifurcation diagram. Panel b shows Patient II, who does not demonstrate true bistability, but is able to achieve SVR with the cure boundary (i.e. when the infected hepatocyte count drops below 1). For both patients, when HCV-mononinfected, SVR is achievable after 24 weeks of treatment at levels of ~80% efficacy. However, for both patients, when $CD4^+$ is depleted partially (as in a state where HIV viral load is controlled but $CD4^+$ count has not fully recovered), 24 weeks of treatment is insufficient and relapse occurs: the patient must be treated for 48 weeks to achieve SVR. In the case when each patient is profoundly immunosuppressed (as in untreated HIV, or no immunologic response to treatment after very low nadir $CD4^+$ count), SVR cannot be achieved even with 48 weeks of treatment. This time series illustrates the sensitivity of treatment prognosis to HIV status, as well as the phenomenon that early treatment response is necessary but not sufficient to predict whether SVR will be achieved.

However, when treatment efficacy is high enough, as it can be with the new direct-acting drugs that have recently been approved (Jacobson et al., 2013; Lawitz et al., 2013; Keating and Vaidya,

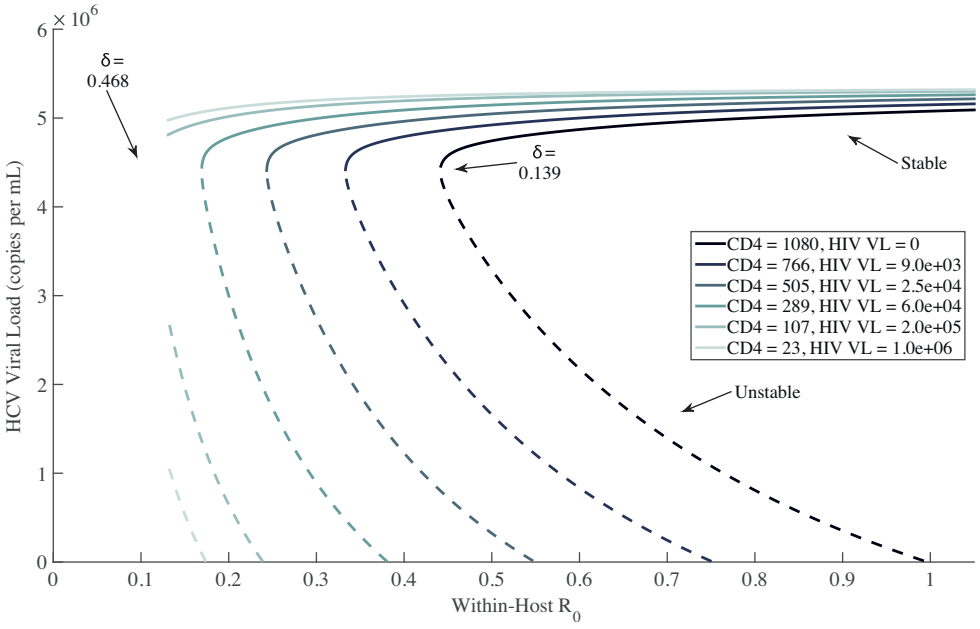

Fig. 3. Bifurcation diagram of stable and unstable equilibrium HCV viral loads with varying CD4$^+$ count. This figure shows the growing bistable region and corresponding shrinking region of spontaneous clearance for a parameter set with varying δ and within-host R_0. The x-axis represents the within-host R_0 in the HIV-free scenario with the given clearance rate parameters. The y-axis represents equilibrium HCV viral load. To the left of the bifurcation points is the zone of spontaneous clearance. If viral load can be pushed below the dotted lines (unstable equilibria), with sufficient treatment, the patient will then be in the region of stable DFE and will be able to achieve SVR. $\delta \times (1+\alpha H)$ ranges from d to 3 for varying CD4$^+$ counts*. The other parameters are as follows: $s = 4365$, $T_{max} = 4.016 \times 10^6$, $d = 1.06 \times 10^{-3}$, $\beta_c = 7.3 \times 10^{-8}$, $p = 13.48$, $c = 10.06$, $r_1 = 2.7$, $r_2 = 7.52$, $s_H = 9$, $\beta_H = 4.1 \times 10^{-6}$, $d_H = 9 \times 10^{-3}$, $\alpha = 5 \times 10^{-3}$, $\gamma = 2 \times 10^{-8}$. *Note: For lower CD4$^+$ counts/higher HIV viral loads, the tips of the bifurcation trees could not be reached with clinically realistic values of δ. This fact implies that there would be no realistic zone of spontaneous clearance for this patient when CD4$^+$ count falls below a certain point, though SVR might still be possible with sufficient treatment duration and efficacy.

2014), HIV coinfection with incomplete CD4$^+$ recovery no longer compromises SVR chances to the same extent. Sofosbuvir has been shown to effect SVR within 12–24 weeks in both HIV-positive and HIV-negative HCV patients (Fernández-Montero et al., 2013; Sulkowski et al., 2014a,b; Rodriguez-Torres et al., 2015), and our model replicates this result for the above theoretical patients I and II (Fig. 6, panels a and b), (we still predict treatment failure for short-duration treatment when the patients are severely immunocompromised, but most trials of Sofosbuvir in coinfected patients have been among patients on ART with stable CD4$^+$, e.g. Sulkowski et al., 2014a,b; Rodriguez-Torres et al., 2015). Fig. 5 shows the pairs of treatment efficacies and durations that lead to SVR for Patients I and II with and without depleted CD4$^+$ count from HIV coinfection. Each point on each line represents the minimum treatment duration necessary to achieve SVR for the corresponding treatment efficacy. In each of these scenarios, the model was run

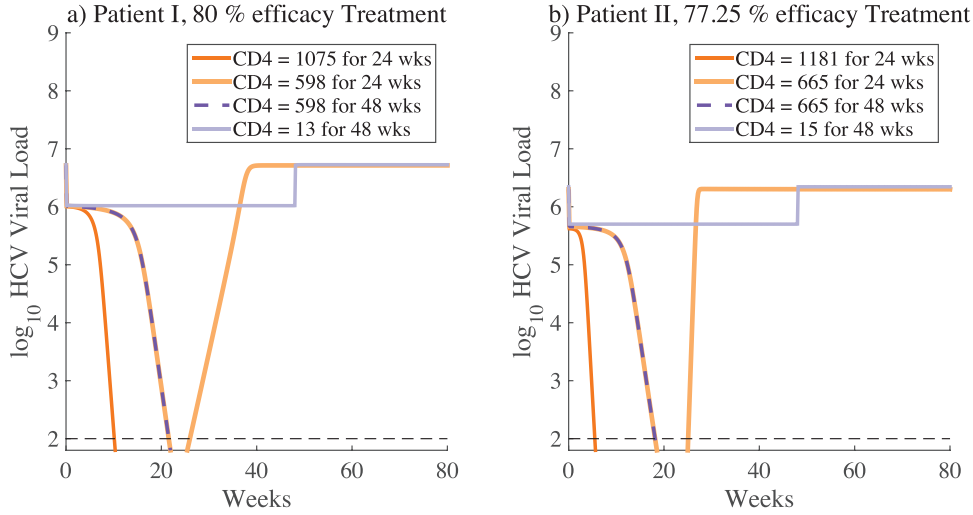

Fig. 4. Effect of depleted CD4$^+$ on infection clearance. This figure shows HCV viral load trajectories for two sample patients with different treatment efficacies and durations under initial conditions of normal CD4$^+$ count (~1000 per μL, HIV negative), and depleted CD4$^+$ count (~600 per μL, suppressed HIV with incomplete immunologic recovery), and very low CD4$^+$ count (~10 per μL, unsuppressed HIV) for treatment courses of 24 and 48 weeks. It can be seen that a treatment course of 24 weeks that is sufficient to achieve SVR when the patient has a normal CD4$^+$ count is no longer sufficient for either HIV positive scenario, even when CD4$^+$ count has partially recovered. However, when treatment is extended to 48 weeks, the patients are able to achieve SVR when CD4$^+$ count has partially recovered. Panel a shows these scenarios for Patient I, a theoretical patient exhibiting classic bistability, while panel b shows Patient II, a theoretical patient who requires the cure boundary condition to achieve SVR.

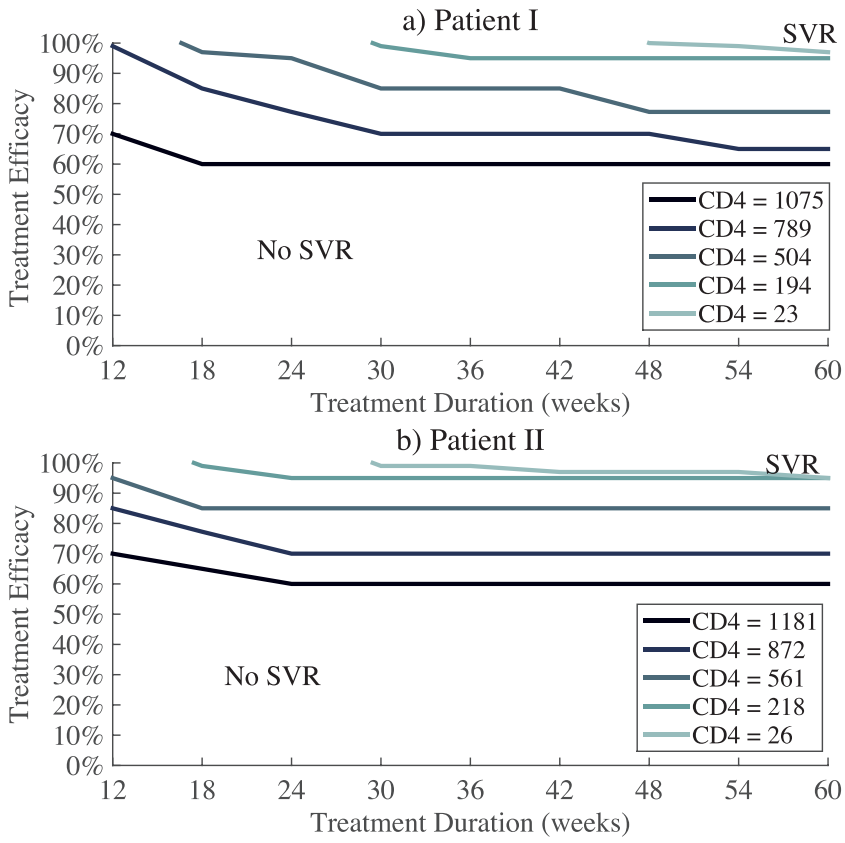

Fig. 5. Treatment and efficacy combinations for (a) Patient I and (b) Patient II. Each point on each line denotes the minimum treatment duration necessary to achieve SVR for the corresponding efficacy, for varying initial CD4$^+$ counts. For any combination above a line, SVR is achieved, while for any combination below the line, SVR is not achieved. All scenarios were run for 96 weeks to assure that any potential relapse was captured.

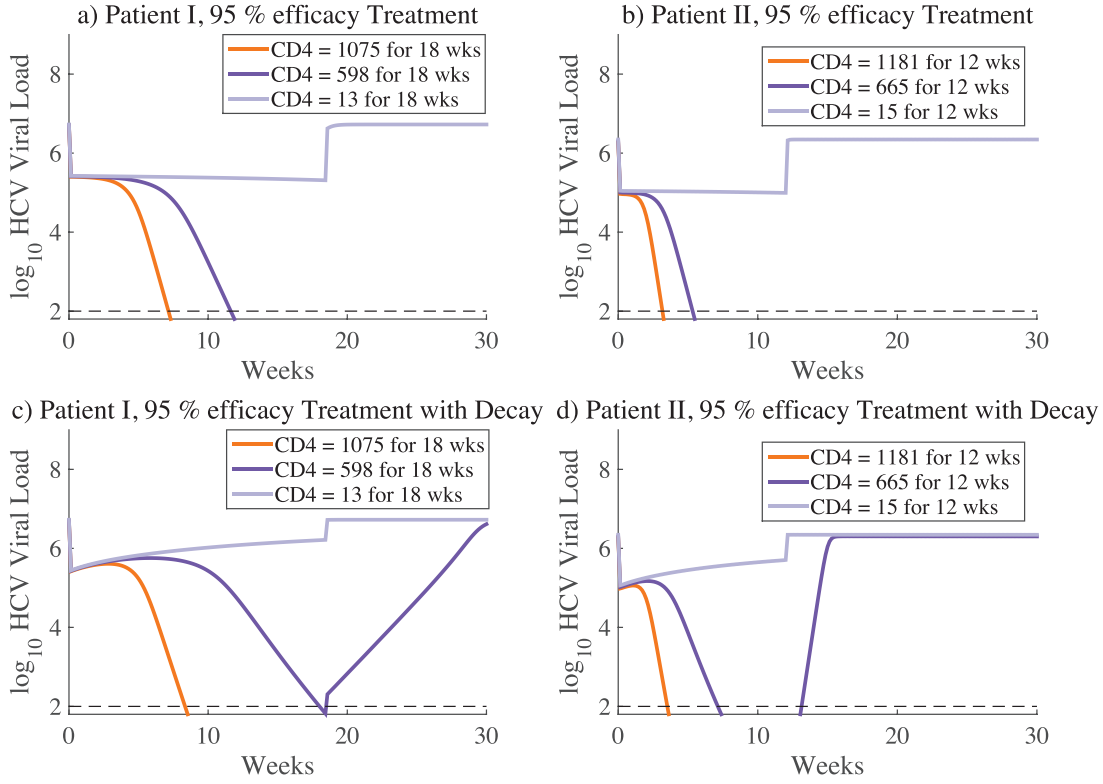

Fig. 6. High-efficacy treatment with short-term cure. Panels a and b demonstrate that high efficacy treatment, as with DAAs, can result in SVR over a short duration (12–24 weeks) for Patients I and II, respectively, even with incomplete CD4$^+$ recovery (though when each patient is severely immunocompromised, short-term cure is still unlikely). However, panels c and d show the same scenarios, but with treatment efficacy declining from 95% to 70–75% efficacy over the course of 12–16 weeks. When the CD4$^+$ count is depleted or low (HIV-positive), the patients respond initially, but relapse after treatment efficacy falls below a certain level.

for 96 weeks (well past the maximum treatment duration tested) in order to capture any relapse that might occur. This figure demonstrates how the minimum acceptable treatment efficacies and durations depend strongly on HIV status. It can be seen in this figure that duration/efficacy pairs that will result in SVR for the patients when they are HIV-negative fall in the "No SVR" region when the patient has a depleted $CD4^+$ count. As $CD4^+$ drops, the minimum treatment efficacy necessary for SVR increases, as does minimum duration for a given efficacy in some cases. When the patients are severely immunocompromised, only very high efficacy treatment will result in SVR. Lastly, as Fig. 5 suggests and Fig. 6 shows in panels c and d, in the likely event that treatment efficacy declines over time due to non-adherence, drug resistance, or concentration decay, the differences between monoinfected and coinfected patients may reappear, wherein coinfected patients relapse after treatment.

4. Discussion and conclusion

In this study, we propose a model of within-host HCV infection that is able to capture broadly the impact of concurrent treated or untreated HIV infection on clearance and long-term cure of HCV in coinfected patients. To the best of our knowledge, it is the first within-host model of HIV–HCV coinfection; it builds on previous models of HCV monoinfection (Debroy et al., 2011; Reluga et al., 2009) and HIV monoinfection (Biafore and D'Attellis, 2006; Perelson and Nelson, 1999) and allows for an explicit role of the immune system in HCV disease course. Our model qualitatively replicates results of empirical research showing that HIV-coinfected HCV patients have reduced probability of spontaneous clearance of HCV as well as reduces rates of achieving sustained virologic response (Kim and Chung, 2009; Mohsen et al., 2002; Di Martino et al., 2001). Similarly, we replicate newer empirical findings indicating that highly efficacious direct-acting antiviral agents (DAAs) reduce treatment differences between HIV-positive and HIV-negative HCV patients (Fernández-Montero et al., 2013).

This study adds to the literature a way of capturing HCV within-host dynamics while accounting for the role of the immune system under conditions of HIV infection. It contains the flexibility and tractability necessary for testing hypotheses about clearance and treatment. We provide a framework which may be useful for assessing a patient's chance of responding to treatment, given certain virologic, immunologic and therapeutic parameters. Our choice to model HIV statically allows our model capture how an immunocompromised patient can respond differently to HCV infection and subsequent treatment, while avoiding the problem of parameter proliferation.

There are several limitations of the model related to the complexity of the system. First, the bistability criterion that the proliferation rate of infected cells must be greater than the proliferation rate of uninfected cells only has partial support in the literature. Some studies report that HCV core protein can induce proliferation in hepatocytes (Erhardt et al., 2002; Hu et al., 2013; Kim and Chung, 2009; Roe and Hall, 2008) and inhibit immune-mediate cell killing (Block et al., 2003), while others report slowed proliferation in HCV-infected cells (Kannan et al., 2011). However, there are may be other mechanism of bistability, such as interferon refractoriness of some cells as proposed by Padmanabhan et al. (2014) that would yield similar impacts under the HIV coinfection conditions proposed in this model. Second, the model assumes very simplified within-host HIV dynamics by only including HIV viral load as a static parameter, so may miss some of the subtleties of CD4 decay and viral load changes through the course of infection. However, this simplification is appropriate for the shorter relative time-courses of the HCV dynamics explored here. Similarly, while we cannot model the explicit dynamics of treatment of HIV with ART, we are able to manually replicate them by using lower equilibrium values of $CD4^+$ count. Third, the way we model HCV treatment does not take into account pharmacokinetic/pharmacodynamic complexities beyond simple, exponential decay of treatment efficacy over time, but it is useful for making baseline calculations. It has been used in the past for modeling interferon (IFN) treatment (Debroy et al., 2011; Reluga et al., 2009; Perelson, 1999), but may in fact be a better representation of the mechanisms of DAAs (Guedj et al., 2010). IFN works by creating an antiviral environment inside susceptible cells, thereby decreasing their chances of getting infected (Feld and Hoofnagle, 2005), while ribavirin can act as a mutagen and cause some proportion of virions to be non-infectious (Dixit et al., 2004). Empirical evidence suggests that response is not directly dependent on concentration over time, but maximum drug effectiveness is correlated with treatment response. DAAs, however, mainly work to inhibit HCV replication thereby having a more direct effect on viral burst-size and infectiousness (Ahlén et al., 2013).

DAAs offer very promising prognoses for HCV patients, but are still prohibitively expensive for many (Mehta and Asch, 2014; NatMed, 2014). It is therefore crucial to assure that the drugs are being administered properly. Using a model to predict patient response may lend insight into pre-treatment estimation of treatment success, and could be helpful in monitoring effectiveness of therapy over the course of treatment. For example, if a patient requires or takes drug holidays, a model of this type may be helpful in predicting the maximum drug holiday allowable without compromising treatment. As Fig. 6 shows, HIV has the potential to alter treatment dynamics even in optimistic scenarios, underscoring further the importance of understanding this system.

The model results presented here give a theoretical demonstration of the effect that HIV coinfection can have on the course of HCV infection. While the system of HCV-HIV coinfection has many layers of complexity, we are able to use a model with relatively simple assumptions about pathogen and immune system interaction to qualitatively describe patient outcomes. Not only is an HIV-positive patient less likely to clear HCV spontaneously, but also less likely to respond to HCV treatment when treatment efficacy is below a certain level (Kim and Chung, 2009; Mohsen et al., 2002; Di Martino et al., 2001). Understanding what drives these treatment differences can help spare difficult treatment and side effects for patients who are unlikely to respond to treatment, as well as informing strategies to maximize treatment adherence. HIV-HCV coinfection is a growing issue not just among injecting drug users, but also among HIV-positive Men who have sex with Men (MSM) who may experience both increased transmissibility of HCV due to higher viral load and also increased susceptibility to sexually transmitted HCV due to incomplete restoration of mucosal immunity (Kim and Chung, 2009). It is thus vital to understand the within-host dynamics of these coinfecting pathogens in order to better assess treatment strategies and preempt shortfall and potential resistance acquisition.

Acknowledgments

We thank Professors Andrea Graham and Simon Levin, Department of Ecology and Evolutionary Biology, Princeton University for their helpful comments and insights. R.B. was supported by the Princeton University, Department of Ecology and Evolutionary Biology. R.D.K. was supported by the Swiss National Science Foundation # PZ00P3-142411. B.G. was supported by the Bill and Melinda Gates Foundation and the RAPIDD program of the Science and Technology Directorate, U.S. Department of Homeland Security, and the Fogarty International Center, NIH.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2015.04.001.

All code for model and figures can be found and downloaded at https://github.com/rbirger/HCVHIVWithinHostModel

References

Ahlén, G., Frelin, L., Brenndörfer, E.D., Brass, A., Weiland, O., Chen, M., Sällberg, M., 2013. Containing "The Great Houdini" of viruses: combining direct acting antivirals with the host immune response for the treatment of chronic hepatitis C. Drug Resist. Updat. 16, 60–67, http://dx.doi.org/10.1016/j.drup.2013.06.001, URL: http://www.sciencedirect.com/science/article/pii/S1368764613000253

Alter, M., 2006. Epidemiology of viral hepatitis and HIV co-infection. J. Hepatol. 44 (Suppl.), S6–S9, http://dx.doi.org/10.1016/j.jhep.2005.11.004, URL: http://www.sciencedirect.com/science/article/pii/S0168827805007269 http://pdn.sciencedirect.com/science?_ob=MiamiImageURL&_cid=272181&_user=1082852&_pii=S0168827805007269&_check=y&_origin=article&_zone=toolbar&_coverDate=31-Dec-2006&view=c&originContentFamily=serial&wchp=dGLbVlk-zSkzk&md5=193f443dc896d42da99a7df818b57313&pid=1-s2.0-S0168827805007269-main.pdf&sqtrkid=0.9442319773052815 http://ukpmc.ac.uk/abstract/MED/16352363

Andreoni, M., Giacometti, A., Maida, I., Meraviglia, P., Ripamonti, D., Sarmati, L., 2012. HIV–HCV co-infection: epidemiology, pathogenesis and therapeutic implications. Eur. Rev. Med. Pharmacol. Sci. 16, 1473–1483, URL: http://www.ncbi.nlm.nih.gov/pubmed/23111959

Biafore, F., D'Attellis, C., 2006. Exact linearisation and control of a HIV-1 predator–prey model. In: Proceedings of the 2005 IEEE Engineering in Medicine and Biology 27th Annual Conference, Shanghai, China, September 1–4, 2005. IEEE, pp. 2367–2370, http://dx.doi.org/10.1109/IEMBS.2005.1616942

Block, T.M., Mehta, A.S., Fimmel, C.J., Jordan, R., 2003. Molecular viral oncology of hepatocellular carcinoma. Oncogene 22, 5093–5107, http://dx.doi.org/10.1038/sj.onc.1206557, URL: http://www.ncbi.nlm.nih.gov/pubmed/12910247

Bowen, D., Walker, C., 2005. Adaptive immune responses in acute and chronic hepatitis C virus infection. Nature 436, 946–952, http://dx.doi.org/10.1038/nature04079, URL: http://www.nature.com/nature/journal/v436/n7053/pdf/nature04079.pdf http://www.nature.com/nature/journal/v436/n7053/abs/nature04079.html

Dahari, H., Feliu, A., Garcia-Retortillo, M., Forns, X., Neumann, A.U., 2005. Second hepatitis C replication compartment indicated by viral dynamics during liver transplantation. J. Hepatol. 42, 491–498, http://dx.doi.org/10.1016/j.jhep.2004.12.017, URL: http://www.ncbi.nlm.nih.gov/pubmed/15763335

Danta, M., Semmo, N., Fabris, P., Brown, D., Pybus, O.G., Sabin, C.A., Bhagani, S., Emery, V.C., Dusheiko, G.M., Klenerman, P., 2008. Impact of HIV on host–virus interactions during early hepatitis C virus infection. J. Infect. Dis. 197, 1558–1566, http://dx.doi.org/10.1086/587843, URL: http://www.ncbi.nlm.nih.gov/pubmed/18419344

Debroy, S., Bolker, B.M., Martcheva, M., 2011. Bistability and long-term cure in a within-host model of hepatitis C. J. Biol. Syst. 19, 533, http://dx.doi.org/10.1142/S0218339011004135, URL: http://www.worldscinet.com/jbs/19/1904/S0218339011004135.html

Di Martino, V., Rufat, P., Boyer, N., Renard, P., Degos, F., Martinot-Peignoux, M., Matheron, S., Le Moing, V., Vachon, F., Degott, C., Valla, D., Marcellin, P., 2001. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology 34, 1193–1199, http://dx.doi.org/10.1053/jhep.2001.29201, URL: http://onlinelibrary.wiley.com/doi/10.1053/jhep.2001.29201/abstract http://onlinelibrary.wiley.com/store/10.1053/jhep.2001.29201/asset/510340618_ftp.pdf?v=1&t=ha4sw1os&s=9858b849f3379ed24f625ee2d3c8335f0c09c558

Diepolder, H.M., Zachoval, R., Hoffmann, R.M., Wierenga, E.A., Santantonio, T., Jung, M.C., Eichenlaub, D., Pape, G.R., 1995. Possible mechanism involving T-lymphocyte response to non-structural protein 3 in viral clearance in acute hepatitis C virus infection. Lancet 346, 1006–1007, URL: http://www.ncbi.nlm.nih.gov/pubmed/7475549

Dixit, N.M., Layden-Almer, J.E., Layden, T.J., Perelson, A.S., 2004. Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. Nature 432, 922–924, http://dx.doi.org/10.1038/nature03153, URL: http://www.ncbi.nlm.nih.gov/pubmed/15602565

Dore, G.J., Torriani, F.J., Rodriguez-Torres, M., Bräu, N., Sulkowski, M., Lamoglia, R.S., Tural, C., Clumeck, N., Nelson, M.R., Mendes-Correa, M.C., Godofsky, E.W., Dieterich, D.T., Yetzer, E., Lissen, E., Cooper, D.A., 2007. Baseline factors prognostic of sustained virological response in patients with HIV-hepatitis C virus co-infection. AIDS 21, 1555–1559, http://dx.doi.org/10.1097/QAD.0b013e328216f2c7, URL: http://www.ncbi.nlm.nih.gov/pubmed/17630550

Erhardt, A., Hassan, M., Heintges, T., Häussinger, D., 2002. Hepatitis C virus core protein induces cell proliferation and activates ERK, JNK, and p38 MAP kinases together with the MAP kinase phosphatase MKP-1 in a HepG2 Tet-Off cell line. Virology 292, 272–284, http://dx.doi.org/10.1006/viro.2001.1227, URL: http://www.ncbi.nlm.nih.gov/pubmed/11878930

Feld, J.J., Hoofnagle, J.H., 2005. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. Nature 436, 967–972, http://dx.doi.org/10.1038/nature04082

Fernández-Montero, J.V., Vispo, E., Barreiro, P., Mendoza, C., Labarga, P., Soriano, V., 2013. Treatment of hepatitis C in HIV patients in the new era of direct-acting antivirals. Curr. Hepat. Rep. 12, 269–275, http://dx.doi.org/10.1007/s11901-013-0179-1, URL: http://link.springer.com/10.1007/s11901-013-0179-1

Fraser, C., 2007. Variation in HIV-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis. Proc. Natl. Acad. Sci. U. S. A. 104, 17441–17446, http://dx.doi.org/10.1073/pnas.0708559104, URL: http://www.pnas.org/content/104/44/17441.abstract http://www.pnas.org/content/104/44/17441 http://www.pnas.org/content/104/44/17441.short

Gonzalez, V., Landay, A., Sandberg, J., 2010. Innate immunity and chronic immune activation in HCV/HIV-1 coinfection. Clin. Immunol. 135, 12–25, http://dx.doi.org/10.1016/j.clim.2009.12.005, URL: http://cat.inist.fr/?aModele=afficheN&cpsidt=22560257

Gonzalez, V.D., Falconer, K., Blom, K.G., Reichard, O., Mørn, B., Laursen, A.L., Weis, N., Alaeus, A., Sandberg, J.K., 2009. High levels of chronic immune activation in the T-cell compartments of patients coinfected with hepatitis C virus and human immunodeficiency virus type 1 and on highly active antiretroviral therapy are reverted by alpha interferon and ribavirin treatment. J. Virol. 83, 11407–11411, http://dx.doi.org/10.1128/JVI.01211-09, URL: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2772767&tool=pmcentrez&rendertype=abstract

Grakoui, A., Shoukry, N., Woollard, D., 2003. HCV persistence and immune evasion in the absence of memory T-cell help. Science 302, 659–662, http://dx.doi.org/10.1126/science.1088774, URL: http://www.sciencemag.org/content/302/5645/659 http://www.sciencemag.org/content/302/5645/659.full.pdf http://www.sciencemag.org/content/302/5645/659.short

Guedj, J., Rong, L., Dahari, H., Perelson, A.S., 2010. A perspective on modelling hepatitis C virus infection. J. Viral Hepat. 17, 825–833, http://dx.doi.org/10.1111/j.1365-2893.2010.01348.x, URL: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3070361&tool=pmcentrez&rendertype=abstract

Harcourt, G., Gomperts, E., Donfield, S., Klenerman, P., 2006. Diminished frequency of hepatitis C virus specific interferon gamma secreting CD4+ T cells in human immunodeficiency virus/hepatitis C virus coinfected patients. Gut 55, 1484–1487, http://dx.doi.org/10.1136/gut.2005.083758, URL: http://gut.bmj.com/content/55/10/1484.short

Ho, D.D., Neumann, A.U., Perelson, A.S., Chen, W., Leonard, J.M., Markowitz, M., 1995. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373, 123–126, http://dx.doi.org/10.1038/373123a0

Hu, W.T., Li, H.C., Lee, S.K., Ma, H.C., Yang, C.H., Chen, H.L., Lo, S.Y., 2013. Both core and F proteins of hepatitis C virus could enhance cell proliferation in transgenic mice. Biochem. Biophys. Res. Commun. 435, 147–152, http://dx.doi.org/10.1016/j.bbrc.2013.04.059, URL: http://www.sciencedirect.com/science/article/pii/S0006291X13006980

Jacobson, I.M., Gordon, S.C., Kowdley, K.V., Yoshida, E.M., Rodriguez-Torres, M., Sulkowski, M.S., Shiffman, M.L., Lawitz, E., Everson, G., Bennett, M., Schiff, E., Al-Assi, M.T., Subramanian, G.M., An, D., Lin, M., McNally, J., Brainard, D., Symonds, W.T., McHutchison, J.G., Patel, K., Feld, J., Pianko, S., Nelson, D.R., 2013. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N. Engl. J. Med. 368, 1867–1877, http://dx.doi.org/10.1056/NEJMoa1214854, URL: http://www.ncbi.nlm.nih.gov/pubmed/23607593

Kannan, R.P., Hensley, L.L., Evers, L.E., Lemon, S.M., McGivern, D.R., 2011. Hepatitis C virus infection causes cell cycle arrest at the level of initiation of mitosis. J. Virol. 85, 7989–8001, http://dx.doi.org/10.1128/JVI.00280-11, URL: http://jvi.asm.org/content/85/16/7989.abstract?sid=c85ed6b2-b3fe-46a1-b3fd-dc14984cb40b

Kaufmann, G.R., Perrin, L., Pantaleo, G., Opravil, M., Furrer, H., Telenti, A., Hirschel, B., Ledergerber, B., Vernazza, P., Bernasconi, E., Rickenbach, M., Egger, M., Battegay, M., 2003. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch. Intern. Med. 163, 2187–2195, http://dx.doi.org/10.1001/archinte.163.18.2187, URL: http://archinte.jamanetwork.com/article.aspx?articleid=216131

Keating, G.M., Vaidya, A., 2014. Sofosbuvir: first global approval. Drugs 74, 273–282, http://dx.doi.org/10.1007/s40265-014-0179-7, URL: http://www.ncbi.nlm.nih.gov/pubmed/24442794

Kim, A., Chung, R., 2009. Coinfection with HIV-1 and HCV – a one-two punch. Gastroenterology 137, 795–814, http://dx.doi.org/10.1053/j.gastro.2009.06.040, URL: http://www.ncbi.nlm.nih.gov/pubmed/19549523 http://www.sciencedirect.com/science/article/pii/S0016508509009974

Laguno, M., Murillas, J., Blanco, J.L., Martínez, E., Miquel, R., Sánchez-Tapias, J.M., Bargallo, X., García-Criado, A., de Lazzari, E., Larrousse, M., León, A., Loncá, M., Milinkovic, A., Gatell, J.M., Mallolas, J., 2004. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS 18, F27–F36, URL: http://www.ncbi.nlm.nih.gov/pubmed/15316335

Lawitz, E., Mangia, A., Wyles, D., Rodriguez-Torres, M., Hassanein, T., Gordon, S.C., Schultz, M., Davis, M.N., Kayali, Z., Reddy, K.R., Jacobson, I.M., Kowdley, K.V., Nyberg, L., Subramanian, G.M., Hyland, R.H., Arterburn, S., Jiang, D., McNally, J., Brainard, D., Symonds, W.T., McHutchison, J.G., Sheikh, A.M., Younossi, Z., Gane, E.J., 2013. Sofosbuvir for previously untreated chronic hepatitis C infection. N. Engl. J. Med. 368, 1878–1887, http://dx.doi.org/10.1056/NEJMoa1214853, URL: http://www.ncbi.nlm.nih.gov/pubmed/23607594

Lechner, F., Wong, D.K., Dunbar, P.R., Chapman, R., Chung, R.T., Dohrenwend, P., Robbins, G., Phillips, R., Klenerman, P., Walker, B.D., 2000. Analysis of successful

immune responses in persons infected with hepatitis C virus. J. Exp. Med. 191, 1499–1512, http://dx.doi.org/10.1084/jem.191.9.1499, URL: http://jem.rupress.org/content/191/9/1499.abstract

McKinnon, L.R., Kimani, M., Wachihi, C., Nagelkerke, N.J., Muriuki, F.K., Kariri, A., Lester, R.T., Gelmon, L., Ball, T.B., Plummer, F.A., Kaul, R., Kimani, J., 2010. Effect of baseline HIV disease parameters on CD4+ T cell recovery after antiretroviral therapy initiation in Kenyan women. PLoS ONE 5, e11434, http://dx.doi.org/10.1371/journal.pone.0011434, URL: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0011434#pone-0011434-g001

Mehta, S.J., Asch, D.A., 2014. When are effective medications just too expensive? Clevel. Clin. J. Med. 81, 173–175, http://dx.doi.org/10.3949/ccjm.81a.14010, URL: http://www.ccjm.org/content/81/3/173.short

Mohsen, A., Easterbrook, P., Taylor, C., Norris, S., 2002. Hepatitis C and HIV-1 coinfection. Gut 51, 601–608, http://dx.doi.org/10.1136/gut.51.4.601, URL: http://gut.bmj.com/content/51/4/601 http://gut.bmj.com/content/51/4/601.abstract http://gut.bmj.com/content/51/4/601.full.pdf

NatMed, 2014. The price of good health. Nat. Med. 20, 319, http://dx.doi.org/10.1038/nm.3538

Neumann, A.U., Lam, N.P., Dahari, H., Gretch, D.R., Wiley, T.E., Layden, T.J., Perelson, A.S., 1998. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science 282, 103–107, URL: http://www.ncbi.nlm.nih.gov/pubmed/9756471

Padmanabhan, P., Garaigorta, U., Dixit, N.M., 2014. Emergent properties of the interferon-signalling network may underlie the success of hepatitis C treatment. Nat. Commun. 5, 3872, http://dx.doi.org/10.1038/ncomms4872, URL: http://www.ncbi.nlm.nih.gov/pubmed/24834957

Perelson, A.S., 1999. Viral kinetics and mathematical models. Am. J. Med. 107, 49S–52S, URL: http://www.ncbi.nlm.nih.gov/pubmed/10653457

Perelson, A.S., Herrmann, E., Micol, F., Zeuzem, S., 2005. New kinetic models for the hepatitis C virus. Hepatology 42, 749–754, http://dx.doi.org/10.1002/hep.20882, URL: http://www.ncbi.nlm.nih.gov/pubmed/16175615

Perelson, A.S., Nelson, P.W., 1999. Mathematical analysis of HIV-1 dynamics in vivo. SIAM Rev. 41, 3–44, http://dx.doi.org/10.1137/S0036144598335107

Reluga, T.C., Dahari, H., Perelson, A.S., 2009. Analysis of hepatitis C virus infection models with hepatocyte homeostasis. SIAM J. Appl. Math. 69, 999–1023, http://dx.doi.org/10.1137/080714579

Rodriguez-Torres, M., Gaggar, A., Shen, G., Kirby, B., Svarovskaia, E., Brainard, D., Symonds, W.T., McHutchison, J.G., Gonzalez, M., Rodriguez-Orengo, J., 2015. Sofosbuvir for chronic hepatitis C virus infection genotype 1-4 in patients coinfected with HIV. J. Acquir. Immune Defic. Syndr. 68, 543–549, http://dx.doi.org/10.1097/QAI.0000000000000516, URL: http://www.ncbi.nlm.nih.gov/pubmed/25622055

Roe, B., Hall, W.W., 2008. Cellular and molecular interactions in coinfection with hepatitis C virus and human immunodeficiency virus. Expert Rev. Mol. Med. 10, e30, http://dx.doi.org/10.1017/S1462399408000847, URL: http://www.ncbi.nlm.nih.gov/pubmed/18928579

Schnuriger, A., Dominguez, S., Guiguet, M., Harfouch, S., Samri, A., Ouazene, Z., Slama, L., Simon, A., Valantin, M.A., Thibault, V., Autran, B., 2009. Acute hepatitis C in HIV-infected patients: rare spontaneous clearance correlates with weak memory CD4 T-cell responses to hepatitis C virus. AIDS 23, 2079–2089, http://dx.doi.org/10.1097/QAD.0b013e328330ed24, URL: http://www.ncbi.nlm.nih.gov/pubmed/19710595

Smith, J.A., Aberle, J.H., Fleming, V.M., Ferenci, P., Thomson, E.C., Karayiannis, P., McLean, A.R., Holzmann, H., Klenerman, P., 2010. Dynamic coinfection with multiple viral subtypes in acute hepatitis C. J. Infect. Dis. 202, 1770–1779, http://dx.doi.org/10.1086/657317, URL: http://jid.oxfordjournals.org/content/202/12/1770.short

Snoeck, E., Chanu, P., Lavielle, M., Jacqmin, P., Jonsson, E.N., Jorga, K., Goggin, T., Grippo, J., Jumbe, N.L., Frey, N., 2010. A comprehensive hepatitis C viral kinetic model explaining cure. Clin. Pharmacol. Ther. 87, 706–713, http://dx.doi.org/10.1038/clpt.2010.35

Soriano, V., Puoti, M., Sulkowski, M., Cargnel, A., Benhamou, Y., Peters, M., Mauss, S., Bräu, N., Hatzakis, A., Pol, S., Rockstroh, J., 2007. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV–HIV International Panel. AIDS 21, 1073–1089, http://dx.doi.org/10.1097/QAD.0b013e3281084e4d, URL: http://www.ncbi.nlm.nih.gov/pubmed/17502718

Sulkowski, M.S., Gardiner, D.F., Rodriguez-Torres, M., Reddy, K.R., Hassanein, T., Jacobson, I., Lawitz, E., Lok, A.S., Hinestrosa, F., Thuluvath, P.J., Schwartz, H., Nelson, D.R., Everson, G.T., Eley, T., Wind-Rotolo, M., Huang, S.P., Gao, M., Hernandez, D., McPhee, F., Sherman, D., Hindes, R., Symonds, W., Pasquinelli, C., Grasela, D.M., 2014a. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N. Engl. J. Med. 370, 211–221, http://dx.doi.org/10.1056/NEJMoa1306218, URL: http://www.ncbi.nlm.nih.gov/pubmed/24428467

Sulkowski, M.S., Naggie, S., Lalezari, J., Fessel, W.J., Mounzer, K., Shuhart, M., Luetkemeyer, A.F., Asmuth, D., Gaggar, A., Ni, L., Svarovskaia, E., Brainard, D.M., Symonds, W.T., Subramanian, G.M., McHutchison, J.G., Rodriguez-Torres, M., Dieterich, D., 2014b. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA 312, 353–361, http://dx.doi.org/10.1001/jama.2014.7734, URL: http://jama.jamanetwork.com/article.aspx?articleid=1889138

Takuva, S., Maskew, M., Brennan, A.T., Long, L., Sanne, I., Fox, M.P., 2014. Poor CD4 recovery and risk of subsequent progression to AIDS or death despite viral suppression in a South African cohort. J. Int. AIDS Soc. 17, 18651, URL: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3942566&tool=pmcentrez&rendertype=abstract

Taylor, L.E., Swan, T., Mayer, K.H., 2012. HIV coinfection with hepatitis C virus: evolving epidemiology and treatment paradigms. Clin. Infect. Dis. 55 (Suppl. 1), S33–S42, http://dx.doi.org/10.1093/cid/cis367, URL: http://cid.oxfordjournals.org/content/55/suppl_1/S33.full

Thomas, D.L., 2006. Options for treatment of hepatitis C in HIV-infected persons. J. Hepatol. 44, S40–S43, http://dx.doi.org/10.1016/j.jhep.2005.11.011, URL: http://www.journal-of-hepatology.eu/article/S0168-8278(05)00733-6/abstract

Vickerman, P., Martin, N.K., Roy, A., Beattie, T., Jarlais, D.D., Strathdee, S., Wiessing, L., Hickman, M., 2013. Is the HCV–HIV co-infection prevalence amongst injecting drug users a marker for the level of sexual and injection related HIV transmission? Drug Alcohol Depend. 132, 172–181, http://dx.doi.org/10.1016/j.drugalcdep.2013.01.020, URL: http://www.sciencedirect.com/science/article/pii/S0376871613000331