Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2014-06-01-D-113 Simeprevir

Stand: März 2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Simeprevir (2014-B-018)
Zur Behandlung der chronischen Hepatitis C Patienten in Kombination mit anderen Arzneimitteln

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	– Ribavirin (als Teil einer Kombinationstherapie) – Interferon alfa 2a – Peginterferon alfa 2a – Interferon alfa 2b – Peginterferon alfa 2b – Boceprevir (Genotyp 1) – Telaprevir (Genotyp 1) – Sofosbuvir
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	– Nicht medikamentöse Maßnahmen kommen nicht in Betracht
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Boceprevir (Beschluss nach § 35a SGB V vom 01.03.2012) - Telaprevir (Beschluss nach § 35a SGB V vom 29.03.2012) - Sofosbuvir (Verfahren nach § 35a SGB V hat am 01.02.2014 begonnen)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	⇨ *siehe systhematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

<table>
<tr><th>Wirkstoff
ATC-Code
Handelsname</th><th>Anwendungsgebiet
(Text aus Fachinformation/SmPC)</th></tr>
<tr><td colspan="2">Zu bewertendes Arzneimittel:</td></tr>
<tr><td>Simeprevir
ATC-Code und Handelsname liegen nicht vor</td><td>Simeprevir ist in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C bei erwachsenen Patienten indiziert.

<table>
<tr><th>Patientenpopulation[1]</th><th>Behandlung</th><th>Dauer</th></tr>
<tr><td>Genotyp 1, 4 naiv</td><td>Simeprevir in Kombination mit Peginterferon alfa und Ribavirin</td><td>12/24 Wochen</td></tr>
<tr><td>Genotyp 1, 4 erfahren</td><td>Simeprevir in Kombination mit Peginterferon alfa und Ribavirin</td><td>12/48 Wochen</td></tr>
<tr><td>Genotyp 1 Patienten mit Interferon Kontraindikation oder Interferonunverträglichkeit</td><td>Simeprevir in Kombination mit Sofosbuvir (Sovaldi®)</td><td>12 Wochen</td></tr>
<tr><td colspan="3">[1] Einschließlich Patienten mit HIV Ko-Infektion und Patienten mit oder ohne Zirrhose.</td></tr>
</table>

Zum Zeitpunkt der Einreichung des G-BA Antrages lag noch keine Fachinformation auf Deutsch vor. Der hier dargestellte Text entspricht dem Text des pUs in der Beratungsanforderung.</td></tr>
<tr><td colspan="2">Systemische Therapie</td></tr>
<tr><td>Ribavirin
Copegus®
(J05AB04)</td><td>Copegus ist indiziert zur Behandlung der chronischen Hepatitis C und darf nur als Teil einer Kombinationstherapie mit Peginterferon alfa-2a oder mit Interferon alfa-2a angewendet werden. Copegus darf nicht als Monotherapie angewendet werden.

Die Kombination von Copegus mit Peginterferon alfa-2a oder Interferon alfa-2a ist indiziert bei erwachsenen Patienten, die Serum-HCV-positiv sind, einschließlich Patienten mit kompensierter Zirrhose. Die Kombination mit Peginterferon alfa-2a ist auch indiziert bei Patienten mit einer klinisch stabilen HIV-Begleitinfektion, einschließlich Patienten mit kompensierter Zirrhose. Die Kombination von Copegus und Peginterferon alfa-2a ist indiziert bei unvorbehandelten Patienten und bei Patienten, bei denen eine vorhergehende Therapie mit Interferon alfa (pegyliert oder nicht pegyliert) alleine oder in der Kombinationstherapie mit Ribavirin versagt hat.</td></tr>
</table>

	Bitte beachten Sie die Fachinformation von Peginterferon alfa-2a oder Interferon alfa-2a für Informationen zur Anwendung des jeweiligen Arzneimittels. (Stand 07/2012)
Peginterferon alfa 2a Pegasys® (L03AB11)	Pegasys ist indiziert zur Behandlung *erwachsener Patienten* mit chronischer Hepatitis C, deren Serum HCV-RNA-positiv ist, einschließlich Patienten mit kompensierter Zirrhose und/oder mit einer klinisch stabilen HIV-Begleitinfektion. Pegasys wird bei Patienten mit chronischer Hepatitis C am besten in Kombination mit Ribavirin angewendet. Die Kombination von Pegasys und Ribavirin ist indiziert bei unvorbehandelten Patienten und bei Patienten, bei denen eine vorhergehende Therapie mit Interferon alfa (pegyliert oder nicht pegyliert) alleine oder in der Kombinationstherapie mit Ribavirin versagt hat. Die Monotherapie ist hauptsachlich bei einer Intoleranz oder Kontraindikationen gegen Ribavirin indiziert. (Stand 10/2013)
Interferon alfa 2a Roferon® (L03AB04)	– Histologisch nachgewiesene chronische Hepatitis C bei *erwachsenen Patienten*, bei denen HCV-Antikörper oder HCVRNA und erhöhte Serumspiegel der Alaninaminotransferase (ALT) ohne Leberdekompensation vorliegen. – Die Wirksamkeit von Interferon alfa-2a bei der Behandlung der Hepatitis C wird durch die Kombination mit Ribavirin erhöht. Roferon-A sollte als Monotherapie nur bei Intoleranz oder Kontraindikationen gegen Ribavirin angewendet werden. (Stand 07/2013)
Ribavirin Rebetol® (J05AB04)	3-fach-Kombinationstherapie: Rebetol ist, in Kombination mit Boceprevir und Peginterferon alfa-2b, bestimmt zur Behandlung der chronischen Hepatitis- C(CHC)-Infektion vom Genotyp 1 bei erwachsenen Patienten (18 Jahre und älter) mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Bitte beachten Sie die Fachinformationen zu Peginterferon alfa-2b und Boceprevir, wenn Rebetol in Kombination mit diesen Arzneimitteln angewendet wird. Therapie mit zwei Arzneimitteln (Duale Therapie): Rebetol ist bestimmt zur Behandlung der chronischen Hepatitis-C-Virusinfektion bei Erwachsenen, Kindern ab dem Alter von 3 Jahren und Jugendlichen und darf nur als Teil eines Kombinations-Dosierungsschemas mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden. Eine Rebetol Monotherapie darf nicht angewendet werden. Bitte beachten Sie die Fachinformationen zu Interferon alfa-2b und Peginterferon alfa-2b, wenn Rebetol in Kombination mit diesen Arzneimitteln angewendet wird. Es liegen keine Informationen zur Sicherheit oder Wirksamkeit für die Anwendung von Rebetol mit anderen Formen von Interferon (d. h. kein alfa-2b) vor.

	Naive Patienten *Erwachsene* Patienten (18 Jahre und älter): Rebetol ist bestimmt für die • 3-fach-Kombinationstherapie – in Kombination mit Peginterferon alfa-2b und Boceprevir zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis- C-Infektion vom Genotyp 1 mit kompensierter Lebererkrankung. • Duale Therapie – in Kombination mit Interferon alfa-2b oder Peginterferon alfa-2b zur Behandlung von erwachsenen Patientenmit chronischer Hepatitis C, die nicht vorbehandelt sind, ohne Leberdekompensation sind, erhöhte Alanin-Aminotransferase- Werte (ALT-Werte) haben und die Hepatitis-C-Virus-Ribonukleinsäure(HCV-RNA)-positiv sind. •Duale Therapie – in Kombination mit Peginterferon alfa-2b zur Behandlung einer CHC-Infektion bei Patienten mit kompensierter Zirrhose und/oder klinisch stabiler HIV-Co-Infektion. Vorbehandelte Patienten *Erwachsene* Patienten: Rebetol ist bestimmt für die • 3-fach-Kombinationstherapie – in Kombination mit Peginterferon alfa-2b und Boceprevir zur Behandlung von erwachsenen Patienten mit CHC-Infektion vom Genotyp 1 mit kompensierter Lebererkrankung. • Duale Therapie – in Kombination mit Peginterferon alfa-2b zur Behandlung von Patienten mit chronischer Hepatitis C, die auf eine vorangegangene Therapie mit Interferon alfa (pegyliert oder nicht-pegyliert) alleinoder inKombination mit Ribavirin nicht angesprochen bzw. einen Rückfall erlitten haben (siehe Abschnitt 5.1). • Duale Therapie – in Kombination mit Interferon alfa-2b zur Behandlung von Patienten mit chronischer Hepatitis C, die zunächst auf eine Interferon-alfa-Monotherapie angesprochen haben (mit Normalisierung der ALT-Werte am Ende der Behandlung), jedoch später einen Rückfall erlitten haben. (Stand 11/2013)
Peginterferon alfa 2b Pegintron® (L03AB10)	*Erwachsene (3-fach-Kombinationstherapie):* PegIntron ist, in Kombination mit Ribavirin und Boceprevir (3-fach-Kombinationstherapie), indiziert zur Behandlung der chronischen Hepatitis-C(CHC)-Infektion vom Genotyp 1 bei erwachsenen Patienten (18 Jahre und älter) mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Bitte beachten Sie die Fachinformationen zu Ribavirin und Boceprevir, wenn Sie PegIntron in Kombination mit diesen Arzneimitteln anwenden. *Erwachsene (Duale Therapie und Monotherapie):* PegIntron ist indiziert zur Behandlung erwachsener Patienten (18 Jahre und älter) mit CHC, die Hepatitis-C-Virus-RNA(HCVRNA)-positiv sind, einschließlich Patienten mit kompensierter Zirrhose und/oder Patienten, die klinisch stabil mit HIV co-infiziert sind.

	PegIntron in Kombination mit Ribavirin (Duale Therapie) ist indiziert zur Behandlung der CHC-Infektion bei nicht vorbehandelten erwachsenen Patienten, einschließlich Patienten, die klinisch stabil mit HIV co-infiziert sind, und bei erwachsenen Patienten, die nicht auf eine vorangegangene Kombinationstherapie mit Interferon alfa (pegyliert oder nicht-pegyliert) und Ribavirin oder auf eine Interferon alfa-Monotherapie angesprochen bzw. einen Rückfall erlitten haben. Die Interferon-Monotherapie, einschließlich PegIntron, ist hauptsächlich indiziert im Fall einer Intoleranz oder einer Gegenanzeige gegenüber Ribavirin. Bitte beachten Sie die Fachinformation zu Ribavirin, wenn PegIntron in Kombination mit Ribavirin angewendet wird. (Stand 05/2013)
Interferon alfa 2b IntronA® (L03AB05)	Vor Behandlungsbeginn mit IntronA sollten die Ergebnisse von klinischen Studien zum Vergleich von IntronA mit pegyliertem Interferon berücksichtigt werden. *Erwachsene* IntronA ist indiziert zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die erhöhte Transaminasenwerte ohne Leberdekompensation haben und die Hepatitis C-Virus-RNA (HCV-RNA)-positiv sind. Die beste Art, IntronA bei dieser Indikation anzuwenden, ist die Kombination mit Ribavirin. (Stand 03/2013)
Ribavirin Ribavirin-ratiopharm® (J05AB04)	Ribavirin-ratiopharm ® ist indiziert zur Behandlung der chronischen Hepatitis-C-Virusinfektion (HCV-Infektion) bei Erwachsenen und darf nur als Teil eines Kombinations- Dosierungsschemas mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden. Eine Ribavirin-ratiopharm ®-Monotherapie darf nicht angewendet werden. Es liegen keine Informationen zur Unbedenklichkeit oder Wirksamkeit für die Anwendung von Ribavirin-ratiopharm ® mit anderen Formen von Interferon (d.h. kein alfa-2b) vor. <u>Vorbehandelte Patienten</u> <u>Erwachsene</u> Ribavirin-ratiopharm ® ist in Kombination mit Interferon alfa-2b indiziert zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die zunächst auf eine Interferon-alfa-Monotherapie angesprochen haben (mit Normalisierung der ALT-Werte am Ende der Behandlung), jedoch später einen Rückfall erlitten haben. Ribavirin-ratiopharm® ist indiziert in Kombination mit Peginterferon alfa-2b zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die auf eine vorangegangene Therapie mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin nicht angesprochen, bzw. einen Rückfall erlitten haben. (Stand 05/2012)
Boceprevir Victrelis® (J05AE12)	Victrelis ist indiziert zur Behandlung der chronischen Hepatitis C(CHC)-Infektion vom Genotyp 1 in Kombination mit Peginterferon alfa und Ribavirin bei erwachsenen Patienten mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Siehe Abschnitte 4.4 und 5.1. (Stand 03/2014)

<table>
<tr><td>Telaprevir
Incivo®
(J05AE11)</td><td>INCIVO ist in Kombination mit Peginterferon alfa und Ribavirin zur Behandlung der chronischen Hepatitis C vom Genotyp 1 bei erwachsenen Patienten mit kompensierter Lebererkrankung (einschließlich Zirrhose) indiziert:
– die nicht vorbehandelt sind;
– die entweder mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin vorbehandelt wurden, einschließlich Patienten, die einen Rückfall (Relaps) erlitten haben, Patienten mit partiellem Ansprechen oder Patienten mit fehlendem Ansprechen (Null-Responder) (siehe Abschnitte 4.4 und 5.1). (Stand 12/2013)</td></tr>
<tr><td>Sofosbuvir
Sovaldi®
(noch nicht zugewiesen)</td><td>Sovaldi wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet (siehe Abschnitte 4.2, 4.4 und 5.1).

Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV) siehe Abschnitte 4.4 und 5.1.

Abschnitt 4.2 der Fachinformation:
Tabelle 1: Empfohlene(s) gleichzeitig angewendete(s) Arzneimittel und Behandlungsdauer für die Kombinationstherapie mit Sovaldi
<table>
<tr><th>Patientengruppe* Behandlung Dauer</th><th>Behandlung</th><th>Dauer</th></tr>
<tr><td rowspan="2">Patienten mit CHC vom Genotyp 1, 4, 5 oder 6</td><td>Sovaldi + Riba virin + Peginterferon alfa</td><td>12 Wochen [a, b]</td></tr>
<tr><td>Sovaldi + Ribavirin

Nur zur Anwendung bei Patienten, die für eine Therapie mit Peginterferon alfa ungeeignet sind oder eine Unverträglichkeit gegenüber Peginterferon alfa haben

(siehe Abschnitt 4.4)</td><td>24 Wochen</td></tr>
<tr><td>Patienten mit CHC vom Genotyp 2</td><td>Sovaldi + Ribavirin</td><td>12 Wochen[b]</td></tr>
<tr><td></td><td>Sovaldi + Ribavirin + Peginterferon alfa</td><td>12 Wochen[b]</td></tr>
<tr><td>Patienten mit CHC vom Genotyp 3</td><td>Sovaldi + Ribavirin</td><td>24 Wochen</td></tr>
<tr><td>Patienten mit CHC, die auf eine Lebertransplantation warten</td><td>Sovaldi + Ribavirin</td><td>Bis zur Lebertransplantation[c]</td></tr>
</table>
</td></tr>
</table>

	* Einschließlich Patienten mit Koinfektion mit dem humanen Immundefizienzvirus (HIV). [a] Für vorbehandelte Patienten mit einer HCV-Genotyp 1 Infektion liegen keine Daten zur Kombination von Sovaldi mit Ribavirin und Peginterferon alfa vor (siehe Abschnitt 4.4). [b] Es ist zu erwägen, die Dauer der Therapie möglicherweise über 12 Wochen hinaus auf bis zu 24 Wochen verlängern; dies gilt insbesondere für Subgruppen mit einem oder mehreren der negativen prädiktiven Faktoren, die in der Vergangenheit mit niedrigeren Ansprechraten auf Interferon-haltige Therapien (z. B. fortgeschrittene Fibrose/Zirrhose, hohe Ausgangsviruslast, schwarze Hautfarbe, IL28B-Non-CC-Genotyp, früheres Nichtansprechen auf Peginterferon alfa und Ribavirin) assoziiert waren. [c] Siehe unten: „Besondere Patientengruppen – Patienten, die auf eine Lebertransplantation warten“. (Stand 04/2014)

Quellen: at-Datenbank, Fachinformationen

Synoptische Evidenzübersicht zur Ermittlung der zweckmäßigen Vergleichstherapie:

Inhalt

Indikation für die Recherche von Simeprevir

"Simeprivir ist in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C bei erwachsenen Patienten indiziert."

Geplantes erweiteretes (Teil-) Anwendungsgebiet:

Zur Behandlung der chronischen Infektion mit dem Hepatitis-C-Virus (HCV) bei erwachsenen Patienten vom Genotyp 1 mit einer Interferon-Kontraindikation oder Interferonunverträglichkeit.

Berücksichtigte Wirkstoffe/Therapien: Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet".

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenzbasierten systematischen Leitlinien zur Indikation „chronische Hepatitis C " durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 18.12.2013 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab insgesamt 460 Treffer, welche anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Die erste Durchsicht ergab 154 eingeschlossene Quellen, die anschließend im Volltext überprüft wurden. Daraus konnten 55 Referenzen, in die synoptische Evidenz-Übersicht aufgenommen werden.

Abkürzungen	
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BOC	Boceprevir
BW	Body weight
CI	Confidence interval
DAHTA	Deutsche Agentur für Health Technology Assessment
EVR	Early virological response
FLT	Fixed-length treatment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
OR	Odds ratio
PegIFN	Pegyliertes Interferon
PI	Protease Inhibitor
PR	peginterferon alpha and ribarivin
RBV	Ribavirin
RGT	response-guided treatment
RVR	Rapid virological response
RR	Relative risk
SVR	Sustained response rate
TRIP	Turn Research into Practice Database
TVR	Telaprevir

G-BA	
Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) Telaprevir. Berlin (Ger): G-BA; 2012. Stand: **29.03.2012**	**Telaprevir** Zugelassenes Anwendungsgebiet: Incivo® ist in Kombination mit Peginterferon alfa und Ribavirin zur Behandlung der **chronischen Hepatitis C vom Genotyp 1** bei erwachsenen Patienten mit kompensierter Lebererkrankung (einschließlich Zirrhose) indiziert: – die nicht vorbehandelt sind; – die entweder mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin vorbehandelt wurden, einschließlich Patienten, die einen Rückfall (Relaps) erlitten haben, Patienten mit partiellem Ansprechen oder Patienten mit fehlendem Ansprechen (Null-Responder). 1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie a) In Kombination mit Peginterferon + Ribavirin gegenüber Peginterferon + Ribavirin bei therapienaiven Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Telaprevir, Ausmaß nicht quantifizierbar. b) In Kombination mit Peginterferon + Ribavirin gegenüber Peginterferon + Ribavirin bei therapieerfahrenen Patienten mit chronischer HCV-Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon plus Ribavirin: Hinweis auf einen Zusatznutzen von Telaprevir, Ausmaß nicht quantifizierbar.
Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) Boceprevir. Stand: **01.03.2012**	**Boceprevir** Zugelassenes Anwendungsgebiet: VictrelisR ist indiziert zur Behandlung der **chronischen Hepatitis C (CHC)-Infektion vom Genotyp 1** in Kombination mit Peginterferon alfa und Ribavirin bei erwachsenen Patienten mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. 1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie a) In Kombination mit PegInterferon + Ribavirin gegenüber PegInterferon + Ribavirin bei therapienaiven Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon plus Ribavirin: *Hinweis auf einen Zusatznutzen von Boceprevir, Ausmaß nicht quantifizierbar.* b) In Kombination mit PegInterferon + Ribavirin gegenuber PegInterferon + Ribavirin bei therapieerfahrenen

	Patienten mit cHCV-Infektion (Genotyp 1) *Zweckmäßige Vergleichstherapie:* Peginterferon plus Ribavirin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenuber Peginterferon plus Ribavirin: *Hinweis auf einen Zusatznutzen von Boceprevir, Ausmaß nicht quantifizierbar.*

Cochrane Reviews

Brok 2009: Ribavirin monotherapy for chronic hepatitis C.	Systematische Literaturrecherche bis März 2009. Der Anteil der Patienten mit **Hepatitis-C-Virus-Genotyp 1** wurde in 8 Studien der 14 eingeschlossenen RCTs (Median 73%; range 40 bis 97%) berichtet. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To assess the beneficial and harmful effects of ribavirin monotherapy for patients with chronic hepatitis C. **Population:** Patients with chronic hepatitis C **Anzahl der Patienten:** 657 Patienten **Anzahl der Studien:** 14 Studien **Vergleiche:** • Ribavirin versus no intervention or placebo; • Ribavirin versus interferon. **Endpunkte:** Primäre Endpunkte: Failure of serum (or plasma) sustained virological response, Liver-related morbidity plus all-cause mortality All adverse events Sekundäre Endpunkte: Failure of end of treatment virological response, Failure of sustained biochemical response, Failure of end of treatment biochemical response, Failure of histological response, Quality of life **Ergebnisse (basierend auf 14 eingeschlossenen RCTs):** **Compared with placebo or no intervention:** • ribavirin had no significant effect on the sustained virological response (RD 0%, 95% CI -2% to 3%, five trials) or end of treatment virological response (RD 0% 95% CI -3% to 3%, ten trials). • Ribavirin had no significant effect on liver-related morbidity plus mortality (RD0%, 95%CI -2%to 3%, 11 trials). • Ribavirin significantly increased the risk of adverse reactions, including anaemia. • Ribavirin significantly improved end of treatment biochemical and histological response but not the sustained biochemical response. **Ribavirin versus interferon** • Compared with ribavirin, interferon significantly increased

	the number of patients with an end of treatment virological response (RD 17%; 95% CI 7% to 27%, five trials), but not the number with sustained virological response (RD 13%; 95% CI -4% to 29%, two trials). • Ribavirin was significantly inferior to interferon regarding virological and biochemical responses (five trials) • No liver-related morbidity or mortality was reported in any trial. • Compared with ribavirin, interferon increased the number with end of treatment and sustained biochemical responses. • no significant difference in adverse events or treatment discontinuations between ribavirin and interferon. • None of the trials reported histological response or quality of life. <u>Fazit der Autoren:</u> Ribavirin seems without beneficial effects on serum virological response and liver-related morbidity or mortality, and significantly increased the risk of adverse reactions. Ribavirin monotherapy seems significantly inferior to interferonmonotherapy. The total number of included patients is small, and more trials are perhaps needed. The use of ribavirin monotherapy for chronic hepatitis C cannot be recommended outside randomised trials. **Anmerkungen FBMed:** Der Anteil der Patienten mit Hepatitis-C-Virus vom Genotyp 1 wurde in acht Studien (Median 73%, von 40% auf 97%) berichtet.
Brok 2010: Ribavirin plus interferon versus interferon for chronic hepatitis C.	Systematische Literaturrecherche bis März 2009. Der Anteil der Patienten mit **Hepatitis-C-Virus-Genotyp 1** wurde in 72 Studien (Median 61%; range 0 bis 100%) berichtet. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To assess the beneficial and harmful effects of ribavirin and interferon combination therapy versus interferon monotherapy for chronic hepatitis C. **Population:** Patients with chronic hepatitis C. **Anzahl der Patienten:** 12,707 Patienten **Anzahl der Studien:** 83 Studien **Vergleiche:** Comparisons of any type, dose, or duration of ribavirin plus interferon alpha therapy versus interferon alpha monotherapy **Endpunkte:** <u>Primäre Endpunkte:</u> failure of serum (or plasma) sustained virological response (SVR); liver-related morbidity plus all-cause mortality; all adverse events <u>Sekundäre Endpunkte:</u> failure of end-of-treatment virological

	response; failure of histological response; quality of life. **Ergebnisse:** **Failure of serum sustained virological response** • Combination therapy significantly reduced the number with failure of SVR when all patients were combined (RR 0.75, 95% CI 0.71 to 0.79; 67 trials) • Combination therapy had a significant effect on the response in subgroups of naive (RR 0.72, 95% CI 0.68 to 0.75; 25 trials, I2 = 34%), relapsers (RR 0.62, 95% CI 0.54 to 0.70; 14 trials, I2 = 57%), and non-responders (RR 0.89, 95% CI 0.84 to 0.93; 22 trials, I2 = 63%) • Sensitivity analyses of trials with genotype 1 (RR 0.67, 95% CI 0.56 to 0.80, 7 trials) gave the same overall results showing that adding ribavirin significantly reduced the number with failure of SVR. **Liver-related morbidity plus all-cause mortality** • Few patients developed cirrhosis, hepatocellular carcinoma, or died • On combination therapy the number of outcomes was 16 out of 7482 patients, and on monotherapy the number of outcomes was 29 out of 5225 patients. • Combination therapy significantly reduced morbidity plus mortality (Peto OR 0.43, 95% CI 0.23 to 0.79, I2 = 0%). • The results were not significant for naive alone (Peto OR 0.55, 95% CI 0.20 to 1.55), relapsers alone (Peto OR 0.13, 95% CI 0.00 to 6.78), or non-responders alone (Peto OR 0.56, 95% CI 0.17 to 1.19). **Adverse events and reactions** • The most frequent adverse reaction was anaemia, which occurred in 727 out of 4448 patients (16%) on combination therapy and 43 out of 2944 (1%) on monotherapy (RR 9.45, 95% CI 7.42 to 12.05; 35 trials). • Combination therapy significantly increased the risk of leukopenia (RR 3.42, 95% CI 1.38 to 8.49; 3 trials), but not neutropenia or thrombocytopenia. • Combination therapy increased the risk of several dermatological adverse reactions, eg,dermatitis (RR 1.67, 95% CI 1.21 to 2.30; 3 trials), pruritus (RR 1.62, 95% CI 1.29 to 2.02; 18 trials), and rash (RR 1.74, 95%CI 1.17 to 2.61; 12 trials). • Combination therapy also led to a significant increase in gastrointestinal adverse reactions (dyspepsia and anorexia or nausea), insomnia, and miscellaneous adverse events (cough, dyspnoea, and fatigue). **Failure of end-of-treatment virological response** • Combination therapy significantly reduced the number of patients with failure of virological response (RR0.72, 95%CI 0.69 to 0.77; 78 trials). • Combination therapy also had a significant effect on virological response of naive patients, relapsers, and non-responders individually. **Failure of histological response**

	• All post-treatment biopsies were performed between 3 to 12 months after the end of treatment. Combination therapy significantly reduced the number of patients with failure on both inflammation score (grading) (RR 0.84, 95% CI 0.77 to 0.91; 11 trials) and fibrosis score (staging) (RR 0.95, 95% CI 0.92 to 0.97;9 trials). • Combination therapy also had a significant effect on liver histology of naive patients, relapsers, and non-responders individually. **Quality of life** • Only one trial with 257 relapsers reported data on quality of life. • Combination therapy had a significant beneficial effect on some subscales. These included scales on general health (MD 7.00, 95% CI 0.67 to 13.33), social functioning (MD 6.00, 95% CI 1.22 to 10.78), and mental health (MD 5.00, 95% CI 1.53 to 8.47). <u>Fazit der Autoren:</u> Compared with interferon alone, ribavirin plus interferon is more effective in clearing hepatitis C virus from the blood. Combination therapy may reduce liver-related morbidity and all-cause mortality, but we need more evidence. The number needed to treat to obtain a beneficial effect is considerable considering the increased risk of several severe adverse reactions and costs. **Anmerkungen FBMed:** Subgruppenanalysen für „Failure of serum sustained virological response“ für Patienten mit Genotyp 1 Patienten wurden durchgeführt.
Iorio 2010: Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus.	Systematische Literaturrecherche bis Mai 2009. The mean proportion of patients with hepatitis C genotype 1 ranged from 44% to 78%. Ansonsten vom Genotyp 2,3 und 4. Alles Patienten mit einer HIV/HCV-Koinfektion. **Fragestellung:** To assess the benefits and harms of antiviral treatment for **chronic hepatitis C in patients with HIV.** **Population:** Patients with chronic hepatitis C and stable HIV co-infection. **Anzahl der Studien:** 14 Studien **Anzahl der Patienten:** 2269 Patienten **Vergleiche:** • Randomised comparisons of peginterferon (any type, ie, alpha 2a or 2b) plus ribavirin versus peginterferon or interferon (any type, ie, alpha 2a or 2b) plus ribavirin • randomised comparisons of peginterferon plus ribavirin given for different doses or treatment durations **Endpunkte:** <u>Primäre Endpunkte:</u> Virologic response defined as loss of hepatitis C virus RNA: • at the end of treatment

	• at least six months after treatment (sustained virological response). Sekundäre Endpunkte: Mortality; Progression to acquired immunodeficiency syndrome (AIDS) related illness; Hospitalisation; Histological response; Biochemical response (normalisation of transaminases); Level of CD4-positive T-Lymphocytes; Level of HIV RNA; All adverse events; Withdrawals and dropouts **Ergebnisse (basierend auf 14 eingeschlossenen RCTs):** *Peginterferon plus ribavirin versus interferon plus ribavirin:* **Virologic response defined as loss of hepatitis C virus RNA from the blood** • Peginterferon plus ribavirin was more effective in achieving end of treatment and sustained virological response compared with interferon plus ribavirin (5 trials, 1340 patients). • the benefit of peginterferon plus ribavirin was seen irrespective of HCV genotype although patients with genotype 1 or 4 had lower response rates (27%) than patients with genotype 2 or 3 (56%). ➔ Peginterferon plus interferon increased the risk of achieving a sustained virological response for both subgroups (genotype 1 or 4 RR 3.36, 95% CI 2.33 to 4.86 and genotype 2 or 3 RR 1.70, 95% CI 1.36 to 2.12). **Mortality** • No significant difference was found between patients randomized to peginterferon plus ribavirin versus interferon plus ribavirin (RR 1.27, 95% CI 0.49 to 3.30; Chi2 statistic = 0.35). **Adverse events** • The most frequent adverse events were anaemia, flu-like symptoms, and depression • Fourteen per cent of patients randomised to peginterferon plus ribavirin developed anaemia and 64% flu-like symptoms. • Both anaemia and flu-like symptoms occurred significantly more frequently among patients randomized to peginterferon plus ribavirin (RR 1.57, 95%CI 1.16 to 2.14 and RR 1.16, 95% CI 1.07 to 1.26, respectively). • The risk of depression was not significantly different in the two treatment groups (RR 0.97, 95% 0.80 to 1.17). **Withdrawals and dropouts** • The proportion of patients who dropped out or were withdrawn for any reason was significantly lower among patients randomized to peginterferon plus ribavirin compared with interferon plus ribavirin (30% and 36%; RR 0.82, 95% CI 0.71 to 0.96). **Other secondary outcome measures** • No data were available allowing analysis of the outcomes progression to AIDS, hospitalisation, biochemical response, level ofCD4-positive lymphocytes, or levels of HIV RNA. *Peginterferon plus ribavirin versus peginterferon alone:*

	Virologic response defined as loss of hepatitis C virus RNA from the blood • Peginterferon plus ribavirin was more effective in achieving end of treatment and sustained virological response compared with peginterferon (2 trials, 714 patients). • The proportion of patients with a sustained virological response was highest among patients randomised to peginterferon plus ribavirin (131 of 359), versus peginterferon alone (64 of 355, RR 2.03, 95% CI 1.57 to 2.63). • The difference was seen for patients with genotype 1 or 4 (RR 1.71, 95% CI 1.24 to 2.38) **Mortality** • Five deaths were reported in the two treatment groups (RR 1.00, 95% CI 0.29 to 3.41) **Histological response** • The number of patients with improved histology and paired liver biopsies was 77 of 135 (57%) in the peginterferon plus ribavirin group and 52 of 134 (39%) in the peginterferon group. **Adverse events, withdrawals, and dropouts** • In total, 113 patients randomised to peginterferon plus ribavirin and 129 patients randomised to peginterferon were lost to follow up (RR 0.86, 95% CI 0.71 to 1.05) • Six patients in both treatments groups became anaemic (RR 1.00, 95% CI 0.33 to 3.05). • No significant differences were seen in occurrence of flu-like symptoms (RR 2.40, 95% CI 0.35 to 16.58) or depression (RR 0.76, 95% CI 0.57 to 1.03). **Other secondary outcome measures** • No data were available for any of the remaining outcomes. <u>Fazit der Autoren:</u> Peginterferon plus ribavirin may be considered a treatment for patients with chronic hepatitis C and stable HIV who have not received treatment for hepatitis C as the intervention may clear the blood of HCV RNA. Supporting evidence comes mainly from the analysis of this non-validated surrogate outcome assessed in comparisons against other antiviral treatments. There is no evidence on treatment of patients who have relapsed or did not respond to previous therapy. Careful monitoring of adverse events is warranted. **Anmerkungen FBMed:** Subgruppenanalysen für die anhaltende virologische Ansprechrate der Patienten mit Genotyp 1 und 4 Patienten wurden durchgeführt.
Katz 2012: Extended peginterferon plus ribavirin treatment for 72 weeks versus standard peginterferon plus ribavirin treatment for 48 weeks in	Systematische Literaturrecherche bis November 2011. The mean proportion of **genotype 1 was 79.9%** in the nine trials that reported the genotype. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen.

chronic hepatitis C genotype 1 infected slowresponder adult patients.	**Fragestellung:** To compare the therapeutic benefits and harms of different antiviral regimens in patients with hepatitis C re-infected grafts after liver transplantation. **Population:** Patients with hepatitis C viral re-infection of the liver graft irrespective of age, cadaveric or living donor transplant, indication for liver transplantation, first or retransplantation, and the immunosuppressive therapy used. **Anzahl der Studien:** 7 Studien **Anzahl der Patienten:** 1369 Patienten **Vergleiche:** Peginterferon (alfa-2a or alfa-2b) and ribavirin for 72 weeks versus peginterferon (alfa-2a or alfa-2b) and ribavirin for 48 weeks **Endpunkte:** Primäre Endpunkte: Overall mortality; HCV-related mortality; Liver-related morbidity Sekundäre Endpunkte: Number of participants with sustained virological response (SVR); Number of participants with end of treatment response (EOR); Number of participants who relapsed; Adherance to treatment; Reduction of treatment dose; Occurrence of adverse events **Ergebnisse (basierend auf 7 eingeschlossenen RCTs):** • None of the included trials mentioned primary outcomes. **Sustained virological response** • extension of the treatment period to 72 weeks increased the sustained virological response according to both definitions (71/217 (32.7%) versus 52/194 (26.8%); risk ratio (RR) 1.43, 95% CI 1.07 to 1.92, P = 0.02, I2 = 8%; and 265/499 (53.1%) versus 207/496 (41.7%); RR 1.27, 95% CI 1.07 to 1.50, P = 0.006, I2 = 38%), with a risk difference of 0.11 and calculated number needed to treat of nine. **End of treatment response and number of participants who experienced virological relapse after treatment** • The end of treatment response was not significantly different between the two treatment groups. • The number of participants who relapsed virologically was found to be lower in the groups that had been treated for 72 weeks using both definitions (27/84 (32.1%) versus 46/91 (50.5%); RR 0.59, 95% CI 0.40 to 0.86, P = 0.007, I2 = 18%, 3 trials; and 85/350 (24.3%) versus 146/353 (41.4%); RR 0.59, 95% CI 0.47, 0.73, P < 0.000001, I2 = 0%, 3 trials). **Adherence to treatment, reduction of treatment dose, and adverse events** • The length of treatment did not significantly affect the adherence (247/279 (88.5%) versus 252/274 (92.0%); RR 0.95, 95% CI 0.84 to 1.07, P = 0.42, I2 = 69%, 3 trials).

	• In the single trial that reported adverse events, no significant difference was seen between the two treatment groups. <u>Fazit der Autoren:</u> This review demonstrates higher a proportion of sustained virological response after extension of treatment from 48 weeks to 72 weeks in HCV genotype 1 infected patients in whom HCV RNA was still detectable but decreased by ≥ 2 log after 12 weeks and became negative after 24 weeks of treatment, and in patients with detectable HCV RNA after four weeks of treatment with peginterferon plus ribavirin. The observed intervention effects can be caused by both systematic error (bias) and random errors (play of chance). There was no reporting on mortality and the reporting of clinical outcomes and adverse events was insufficient.More data are needed in order to recommend or reject the policy of extending the treatment period for slow responders.
Koretz 2013 Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C	**Fragestellung:** To assess the benefits and harms of interferon monotherapy retreatment in chronic hepatitis C patients who are nonresponders and relapsers to previous interferon therapy. **Systematische Literaturrecherche im Suchzeitraum bis 2012** **Vergleich:** interferon monotherapy with no treatment **Population:** Patients with chronic Hep C, non-responder and relapsing **Endpunkte:** Mortality (all-cause and liver-related), Quality of life (however defined by authors), Adverse events **Ergebnisse (7 Studien)** • Based on all trials reporting the outcomes, no significant difference was observed in either all-cause mortality (78/843 (9.3%) versus 62/867 (7.2%); risk ratio (RR) 1.30, 95% confidence interval (CI) 0.95 to 1.79; 3 trials) or hepatic mortality (41/532 (7.7%) versus 40/552 (7.2%); RR 1.07, 95% CI 0.70 to 1.63; 2 trials); • When only the two trials at low risk of bias were combined, all-cause mortality was significantly higher in the recipients of the pegylated interferon (78/828 (9.4%) versus 57/848 (6.7%); RR 1.41, 95% CI 1.02 to 1.96) although trial sequential analysis could not exclude the possibility of random error. • There was less variceal bleeding in the recipients of the interferon (4/843 (0.5%) versus 18/867 (2.1%); RR 0.24, 95% CI 0.09 to 0.67; 3 trials), although again trial sequential analysis could not exclude the presence of a type I error and the effect could not be confirmed in a random-effects model meta-analysis.

	• No significant differences were seen with regard to the development of ascites, encephalopathy, hepatocellular carcinoma, or the need for liver transplantation. • The recipients of interferon had significantly more sustained viral responses (20/557 (3.6%) versus 1/579 (0.2%); RR 15.38, 95% CI 2.93 to 80.71; 4 trials) and a type I error was excluded by trial sequential analysis. <u>Fazit der Autoren:</u> The clinical data were limited to patients with histologic evidence of severe fibrosis who were retreated with pegylated interferon. In this scenario, retreatment with interferon did not appear to provide significant clinical benefit and, when only the trials at low risk of bias were considered, retreatment for several years may even have increased all-cause mortality. Such treatment also produced adverse events. On the other hand, the treatment did result in improvement in some surrogate outcomes, namely sustained viral responses and histologic evidence of inflammation. Interferon monotherapy retreatment cannot be recommended for these patients. No clinical data are available for patients with less severe fibrosis. The sustained viral response cannot be used as a surrogate marker for hepatitis C treatment in this clinical setting with low sustained viral response rates and needs to be validated in others in which higher sustained viral response rates are reported.

Systematische Reviews

<u>Hinweis:</u> Behandlung der chronischen Hepatitis C vom **Genotyp 1**

Canadian Agency for Drugs and Technologies in Health 2012: Boceprevir and Telaprevir for Chronic Hepatitis C Infection.	Health Canada recently approved boceprevir (Victrelis) and telaprevir (Incivek) for **treatment of chronic hepatitis C, genotype 1 infection**: • for previously treated patients, adding a protease inhibitor (PI) to standard therapy with peginterferon alfa and ribavirin (PR) can triple the likelihood of treatment success • there are no head-to-head trials to provide guidance on where each drug should be positioned with respect to the other Das Expertenkomitee empfiehlt die Ergänzung der Standardtherapie (Ribavirin plus Peginterferon) mit Boceprevir oder Telaprevir, wenn folgende Kriterien gelten: • reduzierter Preis • nachweisbare Viruslast (level of Hep. C Virus detectable) in den letzten 6 Monaten • ein mittels Biopsie nachgewiesenes Fibrosestadium von F2, F3 oder F4 • keine HIV- Ko-Infektion • nur eine Therapieoption (entweder 12 Wochen Telaprevir oder bis zu 44 Wochen Boceprevir) Bisher liegen lediglich umfassende Studien zum Endpunkt dauerhaftes virologisches Ansprechen (SVR) vor (vgl. siehe Abbildung).

	For boceprevir:[1] 	Trial	SVR for Patients Treated with Boceprevir plus PR	SVR for Patients Treated with Placebo plus PR
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SPRINT-2: Treatment-naive patients	63% to 66%	38%
RESPOND-2: Patients with a history of non-response or relapse on PR	59% to 66%	21%
Study 5685: Patients with a history of non-response or relapse on PR	64%	21% | *PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.* For telaprevir:[2] | Trial	SVR for Patients Treated with Telaprevir plus PR	SVR for Patients Treated with Placebo plus PR
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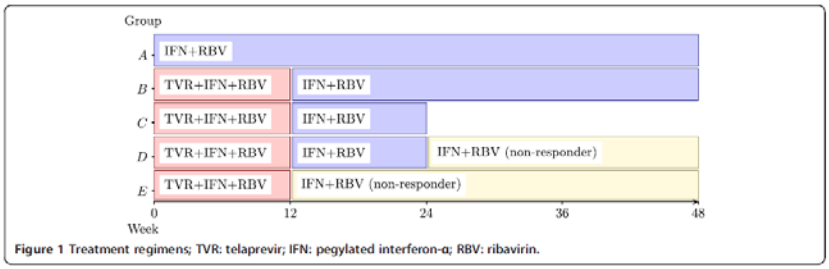
ADVANCE: Treatment-naive patients	75%	44%
REALIZE: Treatment-experienced patients	64% to 66%	16%	 *PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.*
Chou 2013: Comparative Effectiveness of Antiviral Treatment for Hepatitis C Virus Infection in Adults: A Systematic Review.	Systematischer Review mit Metaanalyse zum Vergleich der 2 Fach-Therapie und 3 Fach-Therapie. **Alle Genotypen.** The proportion of patients with HCV genotype-1 ranged from 44% to 78% **Fragestellung:** To compare benefits and harms of antiviral regimens for chronic HCV infection in treatment-naive adults. **Suchzeitraum:** 1947 bis 08/2012 **Vergleich:** • dual therapy with pegylated interferon alfa-2b plus ribavirin versus pegylated interferon alfa-2a plus ribavirin; • triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and either telaprevir or boceprevir versus dual therapy; • different doses or durations of dual or triple therapy. **Endpunkte:** SVR-Rate **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 90 Studien **Ergebnisse:** • Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower likelihood of SVR than was pegylated interferon alfa-2a plus ribavirin (absolute difference, 8 percentage points [95% CI, 3 to 14 percentage points]) on the basis of 7 poor- to fair-quality trials. • For genotype 1 infection, fair-quality trials found that triple therapy with pegylated interferon, ribavirin, and either boceprevir (2 trials) or telaprevir (4 trials) was associated with a higher likelihood of SVR than was dual therapy (absolute difference, 22 to 31 percentage points). • Compared with dual therapy, boceprevir triple therapy increased risk for hematologic adverse events and telaprevir triple therapy increased risk for anemia and rash. A large well-designed cohort study and 18 smaller cohort studies found that an SVR after antiviral therapy was associated with lower risk for all-cause mortality than was no SVR. <u>Fazit der Autoren:</u> SVR rates for genotype 1 infection are higher with triple therapy that includes a protease inhibitor than with standard dual therapy. Die SVR-Rate nach einer antiviralen Therapie scheint mit verbesserten klinischen

	Ergebnissen assoziiert.
Cooper 2012: Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1 infection: an indirect comparison meta-analysis. Therapeutics and Clinical Risk Management 2012; 8:105-130.	Systematischer Review mit Metaanalyse zur Wirksamkeit und Sicherheit von Boceprivir und Telaprevir in Kombination mit pegiliertem Interferon Alpha und Ribavirin. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen. **Fragestellung**: Das Ziel dieser Studie war es, die relative Wirksamkeit und Sicherheit von Boceprevir und Telaprevir in einem indirekten Vergleich / Meta-Analyse zu untersuchen, wenn sie in Kombination mit pegyliertem Interferon alpha und Ribavirin verwendet werden. **Suchzeitraum:** Beginn der jeweiligen DB bis 10/2011 **Vergleich:** telaprevir or boceprevir coadministered with peginterferon alpha plus ribavirin (intervention) and placebo coadministered with peginterferon alpha plus ribavirin (control). **Endpunkte:** Primäre Endpunkte: dauerhaftes virologisches Ansprechen, Rezidive und Therapieabbruch; Sekundäre Endpunkte: unerwünschte Ereignisse wie Anämie, Neutropenie, Ausschlag und Juckreiz **Anzahl der Patienten:** 5072 Patienten **Anzahl der Studien**: 10 Studien **Ergebnisse** (basierend auf 10 ***Phase II- und III- Studien*** *(alles RCTs), davon 4 zu BOC und 6 zu TVR):* • Im indirekten Vergleich ergaben sich weder für therapie-naive noch für vorbehandelte Patienten signifikante Unterschiede in Bezug auf die primären Endpunkte • Im direkten Vergleich ergaben sich signifikante Unterschiede für die Dreifachtherapie sowohl mit BOC als auch mit TVR versus Placebo+Ribavirin+PegIFN Alpha für therapie-naive als auch für vorbehandelte Patienten ▪ **SVR** naive Patienten: RR 1,91 [95%KI 1,65-2,21] ▪ **SVR** vorbehandelte Patienten: RR 3,09 [95%KI 2,24-4,28] ▪ **Relapse** naive Patienten: RR 0,24 [95%KI 0,06-1,0] ▪ **Relapse** vorbehandelte Patienten: RR 0,36 [95%KI 0,2-0,62] ▪ **Therapieabbruch** naive Patienten: RR 0,65 [95%KI 0,47-0,89] ▪ **Therapieabbruch** vorbehandelte Patienten: RR 0,54 [95%KI 0,45-0,65] • TVR war häufiger assoziiert mit Ausschlag und Juckreiz; bei therapie-naiven Patienten traten unter BOC häufiger Neutropenien auf (RR 1,46 (95%KI 1,09-1,95) Fazit der Autoren: Boceprevir und Telaprevir erscheinen vergleichbar in Bezug auf die anhaltende virologische Ansprechrate, Rückfall, oder Behandlungsabbruch für Patienten, welche mit der Standard-Dosis-Therapie und „response-guided“ Behandlungsdauer behandelt wurden.
Cure 2012: Efficacy of telaprevir and boceprevir in treatment-naive and treatment-experienced genotype 1 chronic	Systematischer Review zu Boceprevir und Telaprevir (ohne Meta-Analyse). Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: The objective of this study was to indirectly compare the efficacy of telaprevir and boceprevir combined with PR in achieving SVR in both treatment-naı¨ve and experienced patients infected with G1 chronic HCV, using a Bayesian network meta-analysis framework.

hepatitis C patients: an indirect comparison using Bayesian network meta-analysis.	**Suchzeitraum:** 01/2000 bis 07/2011 **Vergleich:** PR (alfa-2a or 2b) to another PR or TVR- or BOC-based therapy **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 11 Studien **Endpunkte:** SVR- Rate (defined as undetectable HCV RNA level 24 weeks after the end of therapy) **Anzahl der Patienten:** 5318 Patienten **Ergebnisse (basierend auf 11 Studien):** *Treatment-naive patients:* • for telaprevir (12 weeks+response guided treatment [RGT] 24/48 weeks PR) and boceprevir (24 weeks+RGT 28/48 weeks PR) versus PR were respectively 3.80 (2.78–5.22) and 2.99 (2.23–4.01). • The OR for telaprevir versus boceprevir was 1.42 (0.89–2.25), with a probability for telaprevir being more effective (P[OR41]) of 0.93. *Treatment-experienced patients:* • OR of telaprevir (12 weeksþ48 weeks PR) and boceprevir (32 weeksþRGT 36/48 weeks PR) versus PR were respectively 13.11 (7.30–24.43) and 5.36 (2.90–10.30). • The OR for telaprevir versus boceprevir was 2.45 (1.02–5.80), with telaprevir having a probability of 0.98 of being more effective. <u>Fazit der Autoren:</u> In the absence of direct comparative head-to-head studies between telaprevir and boceprevir for the treatment of chronic HCV genotype 1 patients, an indirect comparison based on Bayesian network meta-analysis suggests better efficacy for telaprevir than boceprevir in both treatment-naive and treatmentexperienced patients.
Dang 2012: Telaprevir for Chronic Hepatitis C with Genotype 1: A Meta-Analysis.	Systematischer Review zu Telaprevir (ohne Meta-Analyse). Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: We assessed its antiviral efficiency in untreated patients and in patients who did not have an SVR to previous therapy in order to identify an optimal regimen for each type of patient. **Suchzeitraum:** Bis 09/2010 **Vergleich:** telaprevir administered at any dose, duration and route administration, given separately or in combination *versus* no intervention, placebo or other intervention. **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 5 Studien **Endpunkte:** <u>Primäre Endpunkte:</u> SVR-Rate, end of treatment response (ETR); <u>Sekundäre Endpunkte:</u> Unerwünschte Ereignisse und Behandlungsabbruch **Ergebnisse** (basierend auf 5 Studien)**:** • Overall analysis revealed a significant effect of telaprevir in both naive patients (RR, 1.32; 95% CI, 1.08-1.60) and previously failed treated patients (p<0.0001). • Monotherapy and double therapy seemed to show no effect in naive patients. • Triple therapy followed with PegIFN-2a plus ribavirin seemed to be effective in both naive patients and previously failed treated patients. • Telaprevir was associated with a significantly higher incidence of

	serious adverse events (RR, 1.45; 95% CI, 1.00-2.10) and with discontinuation (RR, 2.23; 95% CI, 1.40-3.55) because of adverse events. • In naive patients, relapsers and non-responders, the regimen of telaprevir/PegIFN-2a/ribavirin for 12 weeks followed by PegIFN-2a/ribavirin for 12 weeks (T12PR24) was the optimal regimen regarding to efficiency and duration. Fazit der Autoren: Telaprevir combined with PegIFN-2a plus ribavirin may improve sustained response in genotype 1 chronic hepatitis C. Regimen T12PR24 may be the best regimen in this respect. New randomized controlled trials are required to confirm this meta-analysis.
Gu 2012: Telaprevir for genotype 1 chronic hepatitis C: a systematic review and meta-analysis.	Systematischer Review mit Meta-Analyse zu Telaprevir**.** Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: To assess the beneficial and harmful effects of telaprevir for patients with genotype 1 chronic hepatitis C. **Suchzeitraum:** 1980 bis 05/2012 **Vergleich:** telaprevir in combination with peginterferon alfa and ribavirin versus no intervention or placebo in combination with peginterferon alfa and ribavirin **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 6 Studien **Endpunkte:** Primäre Endpunkte: SVR-Rate, virologic response at the end of treatment; Sekundäre Endpunkte: relapse rate**,** severe adverse events, treatment discontinuations, commonly reported adverse events, including anemia, neutropenia, rash and pruritus. **Ergebnisse (basierend auf 6 Studien):** • Telaprevir in combination with peginterferon alfa and ribavirin seemed to show a significant effect on sustained virologic response, virologic response at the end of treatment and relapse rate in naive patients and previously unsuccessfully treated patients, except T12PR12 which seemed without beneficial effect on: o Sustained virologic response: OR=1.41; 95% CI 0.83 to 2.40) o relapse rate (Odds Ratio OR=1.55; 95% CI 0.71 to 3.36) in naive patients. • It also was associated with a significantly higher incidence of severe: o adverse events OR=2.15, 95% CI1.29 to 3.58) o treatment discontinuation OR=4.79, 95% CI1.72 to 13.37) because of adverse events in previously unsuccessfully treated patients, but not in naive patients. Fazit der Autoren: Telaprevir in combination with peginterferon alfa and ribavirin has been recommended as option for the treatment of genotype 1 chronic hepatitis C. It has been considered as effective to improve viral response and reduce relapse rate in patient who suffer genotype 1 chronic hepatitis C. However, the treatment should be monitored carefully as it may cause some severe adverse events. For further confirmation of its treatment effect and clarify its possible adverse events, more randomized clinical trials need to be carried out.
Goralcyk 2013:	1. Fragestellung

Treatment of chronic HCV genotype 1 infection with telaprevir: a Bayesian mixed treatment comparison of fixed-length and response-guided treatment regimens in treatment-naïve and –experienced patients.	This systematic review and Bayesian mixed-treatment-comparison (MTC) aimed to compare the efficacy and safety of standard-therapy with pegylated-interferon-α/ribavirin (Peg-IFN-α/RBV (48 weeks), group A), FLT with TVR, Peg-IFN-α/RBV for 12 weeks with a long (+36 weeks, group B) or short (+12 weeks, group C) tail of Peg-IFN-α/RBV treatment, and RGT with 12 weeks of TVR, Peg-IFN-α/RBV followed by 12 weeks of Peg-IFN-α/RBV (group D) or no therapy (group E).
	2. Methodik **Population:** Adult patients with chronic HCV genotype 1 **Vergleich:** Standardtherapie vs. TVR **Endpunkte:** sustained virologic response (SVR) **Suchzeitraum (Aktualität der Recherche):** bis 02/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7 studies (n=3505 patients)
	3. Ergebnisdarstellung Behandlungsgruppen:  Figure 1 Treatment regimens; TVR: telaprevir; IFN: pegylated interferon-α; RBV: ribavirin. • Compared to standard-treatment (group A), treatment-naïve patients allocated to groups B, C, and D were significantly more likely to achieve sustained-virological-response (SVR, odds ratios (OR): B vs. A 3.5 (credibility interval [CrI] 2.2-5.4), C vs. A 3.0 (CrI 1.8-4.9), D vs. A 3.4 (CrI 2.5-4.6)) • Treatment-experienced patients achieved increased SVR rates when they were treated in group B (OR: 8.2 (CrI 5.0-13.5)), C (OR 7.0 (CrI 3.9-12.8)), or simulated group D (OR 8.2 (CrI 4.3-15.3)). • Patients treated with short RGT (simulated group E) did also have a significant improvement when they were treatment-experienced (simulated OR 3.6 (CrI 1.6-8.2)), whereas the effect was not significant in treatment-naïve patients (OR E vs. A 1.6 (CrI 0.9-2.7))
	4. Anmerkungen/Fazit der Autoren Long FLT and RGT regimens are useful treatment options for HCV-genotype-1 in both treatment-naïve and -experienced patients. A short 24-weeks FLT regimen does not seem to be inferior and should further be evaluated in clinical trials to reduce side effects and costs of treatment.
Park 2013: Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype	1. Fragestellung The primary objective was to compare the efficacy and safety of triple therapies including either PI to dual therapy in patients with chronic hepatitis C genotype 1; the secondary objective was to conduct subgroup analyses to make comparisons based on patients' race.
	2. Methodik

1: a meta-analysis.	**Population:** Genotype 1 chronic hepatitis C patients **Intervention:** triple therapies (telaprevir or boceprevir + peg-interferon + ribavirin) **Komparator:** dual therapy (peg-interferon + ribavirin) **Endpunkte:** sustained virologic response (SVR) **Suchzeitraum (Aktualität der Recherche):** bis 11/2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 studies (n=4421 patients)
	3. Ergebnisdarstellung a. 10 der eingeschlossenen Studien speziell für Fragestellung bzw. Patientenpopulation) 4421 der eingeschlossenen Patienten speziell für Fragestellung b. Overall, triple therapy was significantly associated with a higher achievement of SVR than dual therapy: (i) telaprevir-based triple therapy in treatment-naïve patients (relative risk [RR] = 1,62; 95% confidence interval [CI], 1,47–1,78) (ii) telaprevir-based triple therapy in treatment-experienced patients (RR = 3,85; 95% CI, 3,03–4,90) (iii) boceprevir-based triple therapy in treatment-naïve patients (PR = 1,70; 95% CI, 1,56–1,86) and (iv) boceprevir-based triple therapy in treatment-experienced patients (RR = 2,98; 95% CI, 2,29–3,87) • Patients on triple therapies had the significantly increased incidences of treatment discontinuation attributable to adverse events and serious adverse events when compared to dual therapy, especially treatment-experienced patients.
	4. Anmerkungen/Fazit der Autoren Regarding achieving SVR, triple therapies including either PI are superior to dual therapy for both treatment-naïve and treatment-experienced patients.
Sitole 2013: Telaprevir Versus Boceprevir in Chronic Hepatitis C: A Meta-Analysis of Data From Phase II and III Trials.	Systematischer Review mit Meta-Analyse zu Teleprevir. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. Patienten von Genotyp 1. **Fragestellung:** This meta-analysis compared 24- and 48- week sustained viral responses (SVR) and drug-related adverse events (AEs) between telaprevir and boceprevir triple-therapy regimens in the treatment of chronic HCV infection. **Suchzeitraum:** 1995 bis 10/2012 **Vergleich:** telaprevir vs. boceprevir **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 8 Studien **Endpunkte:** SVR-Rate, AEs ((anemia, diarrhea, nausea, pruritis, and rash), discontinuations **Ergebnisse** (basierend auf 8 Studien)**:** • With telaprevir, the ORs (95% CI) for SVR at 24 weeks in treatment-naive and treatment-experienced patients were 3.31 (2.27– 4.82; *P* < 0.0001) and 4.21 (1.83–9.72; *P*<0.001), respectively.

	• Telaprevir triple therapy did not result in more drug related discontinuations but did cause additional rash, pruritis, and anemia. • With boceprevir, the ORs (95% CI) were improved in both treatment-naive and treatment experienced patients (3.55 [2.66-4.56; *P*< 0.0001] and 7.34 [3.92–13.9; *P* <0.0001]), but with more treatment-related anemia and dysgeusia. Fazit der Autoren: Based on the findings from this metaanalysis, telaprevir or boceprevir combined with Peg-IFN _ RBV had favorable short-term data on SVR while resulting in more drug-related AEs. Extended follow-up is required to determine whether these agents offer a reduction in the risk for chronic hepatitis C genotype 1–related mortality and/or hospitalization.
Smith 2011: Telaprevir: an NS3/4A protease inhibitor for the treatment of chronic hepatitis C. Ann Pharmacother **2011;** 45 (5): 639-48.	Review zu Telaprevir. Einzelne deskriptive Darstellung der verfügbaren Studien der Phasen I bis III. Patienten vom Genotyp 1. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To review the use of telaprevir for the treatment of chronic hepatitis C. **Suchzeitraum:** 1966 bis 01/2011 **Vergleich:** telaprevir with concomitant ribavirin treatment compared to 48 weeks of ribavirin treatment **Endpunkte:** SVR rates **Anzahl der Patienten:** k.A. **Ergebnisse:** • Telaprevir has activity against HCV genotype 1 infection in vitro and in vivo, but monotherapy results in rapid viral resistance. • In 3 Phase 2 and 3 Phase 3 randomized placebo-controlled trials, 12 weeks of telaprevir, along with varying durations of ribavirin treatment, induced higher sustained virologic response (SVR) compared with ribavirin alone. • SVR was approximately 70% in treatment-naïve patients, 50-60% for patients in whom • SVR had not occurred with prior ribavirin treatment, and 40-45% of those who received ribavirin alone. • There was a high incidence of maculopapular rash (52% in 1 trial) and anemia (27% in 1 trial) in telaprevir-treated patients. • The average dropout rate in Phase 3 trials as a result of adverse effects was 13%. Fazit der Autoren: “Twelve weeks of telaprevir with concomitant ribavirin treatment increases SVR for treatment-naïve and non-naïve patients with genotype 1 chronic HCV compared to 48 weeks of ribavirin treatment. Telaprevir may shorten the length of ribavirin therapy for some patients with extended rapid viral response, but viral mutations, adverse effects, and a high dropout rate may reduce the SVR see in clinical practice.”
Wilby 2012: Review of boceprevir and telaprevir for the treatment of chronic hepatitis C. Can J Gastroenterol 2012;	Systematischer Review zu Boceprevir und Telaprevir (ohne Meta-Analyse). All HCV genotypes and patient populations were included. **Fragestellung:** To summarize and evaluate the published literature pertaining to boceprevir and telaprevir, and to provide clinicians with suggestions for use in patients with chronic hepatitis C infection.

26 (4): 205-10.	**Suchzeitraum:** bis September 2011 **Vergleich:** boceprevir or telaprevir in combination with pegylated interferon and ribavirin compared with pegylated interferon and ribavirin alone **Anzahl der Patienten:** k.A. **Ergebnisse** Der Review enthält eine deskriptive Beschreibung von 4 Phase III Studien (je 2 RCTs für Boceprevir (SPRINT-2, RESPOND-2) und 2 für Telaprevir (ADVANCE, REALIZE), die bereits im Rahmen der frühen Nutzenbewertung bewertet wurden. <u>Fazit der Autoren:</u> Boceprevir and telaprevir will revolutionize the management of hepatitis C genotype 1 patients and will most likely decrease the burden of end-stage disease worldwide. However, current clinical limitations include establishing appropriate and cost-effective treatment durations, and use in special populations such as transplant patients and patients coinfected with HIV. Future research will need to clarify these clinical obstacles to clearly define the role of these agents in hepatitis C management.
Zhu 2013: Statin therapy improves response to interferon alfa and ribavirin in chronic hepatitis C: A systematic review and meta-analysis.	1. Fragestellung We conducted a systematic review and meta-analysis to explore the efficacy of adding statins to IFN-a and ribavirin therapy for chronic hepatitis C.
	2. Methodik Population: Participants chronically infected with HCV Intervention: PEG-IFNα + ribavirin + statin Komparator: PEG-IFNα + ribavirin Endpunkte: primary: SVR; secondary: RVR und EVR Suchzeitraum (Aktualität der Recherche): bis 10/2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 18 studies (n=k.A.)
	3. Ergebnisdarstellung a. 5 der eingeschlossenen Studien wurden metaanalytisch erfasst mit 454 Patienten (441 der Patienten mit HCV (Genotyp 1)) *b. SVR (5 Studien)* • In comparison with IFN-α and ribavirin dual anti-HCV therapy, statins increased the SVR rates when combined with IFN- α and ribavirin (OR = 2.02, 95% CI: 1.38–2.94). • No significant heterogeneity was observed between these studies • In order to exclude the possible confounding effect of non-genotype 1, sensitivity analysis was performed: • The addition of statins to the dual combination therapy still significantly increased the SVR rates compared with controls (OR = 2.11, 95% CI: 1.40–3.18). Heterogeneity was not significant *RVR (2 Studien)* • statins obviously increased the RVR rates when combined with IFN- α and ribavirin in comparison with IFN-a and ribavirin controls (OR = 3.51, 95% CI: 1.08–11.42). • There was no significant heterogeneity

	EVR (3 Studien) • Compared to the controls, statins, in combination with IFN- α and ribavirin, also obviously increased the EVR rates (OR = 1.89, 95% CI: 1.20–2.98). • No significant heterogeneity existed ➔ There were no significant increases in adverse events and withdrawals with the addition of statins
	4. Anmerkungen/Fazit der Autoren In conclusion, the addition of statins to IFN-a and ribavirin improves SVR, RVR, and EVR without additional adverse events and thus may be considered as adjuvant to IFN-a and ribavirin for chronic hepatitis C. Statins might also be used for HCV genotypes other than genotype 1, or in patients in whom the use of protease inhibitors is contraindicated or not indicated.

Systematische Reviews

Hinweis: Behandlung der chronischen Hepatitis C vom **Genotyp 4** (je nach Darstellung Studienergebnisse auch andere Genotypen mit extrahiert)

Bota 2011: Response to Standard of Care Antiviral Treatment in Patients with HCV Liver Cirrhosis – a Systematic Review.	Systematischer Review zu Pegylated Interferon alpha 2a, Pegylated Interferon alpha 2b und Ribavirin. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen. **Fragestellung:** The aim of this study was to establish the sustained virological response (SVR) rates in HCV patients with liver cirrhosis treated with standard of care therapy (Pegylated Interferon and Ribavirin for 48 weeks in genotypes 1 and 4 and 24 weeks in genotypes 2 and 3). **Suchzeitraum:** Bis 02/2011 ***Vergleich:*** Pegylated Interferon alpha 2a (doses ranging between 135-180 µg/week) or Pegylated Interferon alpha 2b (1 or 1.5 µg/kg/week) and Ribavirin (doses ranging between 800-1200 mg/day) **Endpunkte:** SVR-Rate **Anzahl der Patienten:** 1,149 Patienten **Anzahl der Studien:** 11 Studien **Ergebnisse** (basierend auf 11 Studien): • The overall SVR rate was 33.3% (95%CI-confidence interval=30.6-36.2%). • SVR was significantly higher in patients with genotypes 2 and 3 (422 patients) as compared to those with genotypes 1 and 4 (692 patients): 55.4% (95%CI=50.7-60.1) versus 21.7% (95%CI=18.7-25), p<0.0001. Fazit der Autoren: The overall SVR rate in cirrhotic patients treated with standard of care therapy is 33.3%, but lower in cases affected by genotypes 1 and 4 (21.6%) which makes them a priority regarding the development of more potent drugs for effective treatment.
Chan 2009: The utility of	Review der die Studien, die Ribavirin-Konzentration oder die Dosis und das Ansprechen auf die Behandlung gemessen haben wurden eingeschlossen. Patienten mit einer HIV/HCV-Koinfektion.

therapeutic drug monitoring for ribavirin in patients with chronic hepatitis C--a critical review**.**	**Fragestellung:** To evaluate the utility of therapeutic drug monitoring (TDM) for ribavirin in chronic hepatitis C. **Suchzeitraum:** Beginn der jeweiligen DB bis Juni 2009 **Endpunkte:** Rate of SVR achievement **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 12 Studien **Ergebnisse** (basierend auf 12 Studien für Hepatitis C–HIV Koinfektion) Patients with HCV infection who are co-infected with HIV: • The reported rate of SVR achievement with combination therapy in this patient group is 17–29% for genotypes 1 and 4. • In addition, these patients are also on concomitant antiretroviral therapy that may be involved in pharmacokinetic and pharmacodynamic drug interactions. As a result, it is paramount that HCV infection be adequately treated. • Attempts have been made to discern correlations between ribavirin and virologic response and toxicity in coinfected patients to help in optimizing treatment. • There is evidence that an opposite effect is seen in HCV–HIV coinfected patients. • Furthermore, although several trials showed a dose–response relationship, one study demonstrated no correlation between ribavirin dose and virologic response. Fazit der Autoren: There is conflicting evidence about the existence of a correlation between ribavirin concentrations and virologic response or development of toxicity. This inconsistent evidence, coupled with the currently employed effective strategies that maximize sustained virologic response and minimize development of anemia, precludes the utility of TDM for ribavirin.
Gluud 2009: Peginterferon Plus Ribavirin for Chronic Hepatitis C in Patients With Human Immunodefi ciency Virus.	Systematischer Review zu Peginterferon plus Ribavirin bei Patienten mit chronischer Hepatitis C und HIV-Koinfektion. The mean proportion of patients with hepatitis C genotype 1 ranged from 44 to 78 % . **Fragestellung:** The aim of this study was to assess the effects of peginterferon plus ribavirin for chronic hepatitis C in patients with human immunodefi ciency virus (HIV). **Suchzeitraum:** bis 07/2008 **Vergleich:** peginterferon plus ribavirin with other antiviral treatments **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 7 Studien ***Endpunkte:*** Primäre Endpunkte: virological response; Sekundäre Endpunkte: mortality (all cause), improvement in histology, losses to follow-up, and adverse events **Ergebnisse** (basierend auf 7 Studien): Patients with HCV infection who are co-infected with HIV: • The patients included had chronic hepatitis C and stable HIV and were not previously treated with interferon or ribavirin (treatment naive). • The treatment duration ranged from 24 to 48 weeks.

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Peginterferon plus ribavirin increased the proportion of patients with an end-of-treatment or sustained virological response compared with interferon plus ribavirin or peginterferon alone.
In subgroup analyses of trials comparing peginterferon plus ribavirin with interferon plus ribavirin, the proportion with a sustained virological response was 26 % (109 of 423) for patients with genotype 1 or 4 and 57 %.
Several adverse events occurred, including fatal lactic acidosis and liver failure, but there were no significant differences in mortality rates between treatment groups.

Subgroup meta-analyses of randomized trials on patients with HIV and hepatitis C genotype 1 or 4
<table>
<tr><td colspan="2">End-of-treatment virological response</td></tr>
<tr><td colspan="2">Peginterferon plus ribavirin vs. interferon plus ribavirin</td></tr>
<tr><td>Genotype 1 or 4</td><td>147 / 423 (35 %) vs. 37 / 419 (9 %); RR 3.92
(2.82 – 5.47); _ 2 = 0.27; I 2 = 23 %</td></tr>
<tr><td colspan="2">Peginterferon plus ribavirin vs. peginterferon</td></tr>
<tr><td>Genotype 1 or 4</td><td>73 / 213 (34 %) vs. 42 / 209 (20 %); RR 1.71
(1.24 – 2.38); _ 2 = 0.40; I 2 = 0 %</td></tr>
<tr><td colspan="2">Sustained virological response</td></tr>
<tr><td colspan="2">Peginterferon plus ribavirin vs. interferon plus ribavirin</td></tr>
<tr><td>Genotype 1 or 4</td><td>109 / 423 (26 %) vs. 32 / 419 (76 %); RR 3.36
(2.33 – 4.86); _ 2 = 0.78; I 2 = 0 %</td></tr>
<tr><td colspan="2">Peginterferon plus ribavirin vs. peginterferon</td></tr>
<tr><td>Genotype 1 or 4</td><td>55 / 213 (26 %) vs. 27 / 209 (13 %); RR 2.01
(1.33 – 3.05); _ 2 = 0.47; I 2 = 0 %</td></tr>
</table>
<u>Fazit der Autoren:</u> Peginterferon plus ribavirin may be considered for treatment-naive patients with HIV and chronic hepatitis C. Adverse events should be monitored carefully.
</td></tr>
<tr><td>Marcellin 2012:
Safety profile of standard- vs. high-dose peginterferon alfa-2a plus standard-dose ribavirin in HCV genotype 1/4 patients:
pooled analysis from 5 randomized studies.</td><td>Retrospective Analyse gepoolter Daten von 5 RCTs zur Behandlung von Patienten mit HCV vom Genotyp 1 und 4. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen.

Fragestellung: This analysis examines the safety profile of standard- versus high-dose peginterferon alfa-2a.
Suchzeitraum: k.A.
Vergleich: standard- vs. high-dose peginterferon alfa-2a plus standard-dose ribavirin
Endpunkte: adverse events, treatment discontinuations
Anzahl der Patienten: 2,940 Patienten
Anzahl der Studien: 5 Studien</td></tr>
</table>

	Ergebnisse (basierend auf 5 RCTs): • In standard and high-dose groups, similar frequencies of serious adverse events (SAEs, 3.2 and 4.2%, respectively) and treatment discontinuations for safety reasons (2.8 and 2.9%) were reported. • More patients reported weight decrease as an adverse event (AE) in the 360 µg/week group (7.7 vs.3.3%). • Significant ($p < 0.05$) independent predictors for discontinuation due to safety were older age, male gender, lower albumin and low neutrophil count, but not the starting dose of peginterferon alfa-2a. • Although more laboratory abnormalities were reported in patients receiving high-dose peginterferon alfa-2a, this was not reflected in AEs or discontinuations, suggesting these are adequately managed by dose modification. <u>Fazit der Autoren:</u> High-dose peginterferon alfa-2a for 12 weeks does not significantly increase the incidence of SAEs or discontinuations for safety reasons, beyond that of a standard dose regimen.

Leitlinien

Allgemeine Empfehlungen

EASL 2014: EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.

Leitlinie der European Association for the Study of the Liver (EASL)

Methodik

Grundlage der Leitlinie: The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2).

Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system):

Evidence quality	Notes	Grading
High	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	**Notes**	**Grading**
Strong	Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

Empfehlungen

Indications for treatment: Who should be treated?

- All treatment-naive patients with compensated disease due to HCV should be considered for therapy (recommendation A1)
- Treatment should be scheduled, not deferred, for patients with significant fibrosis (METAVIR score F3 to F4) (recommendation A1)
- In patients with less severe disease, the indication for and timing of therapy can be individualized (recommendation B1)

Drug dosing in HCV genotype 1 therapy:

- The combination of PegIFN/RBV and TVR or BOC is the approved standard of care for chronic hepatitis C genotype 1 (recommendation A1).
- There is no head to-head comparison to allow recommendation of TVR or BOC as preferred therapy
- Patients with cirrhosis should never receive abbreviated treatment in BOC or TVR treatment regimens (recommendation B1)
- Selected patients with high likelihood of SVR to PegIFN/ RBV or with contraindications to BOC or TVR can be treated with dual therapy
- When lead-in is used to identify patients with IFN-α- sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment (recommendation B2)
- Both pegylated IFN-α molecules, pegylated IFN-α2a (180 µg/wk)

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<tr><td></td><td>and pegylated IFN-α2b (1.5 µg/kg/wk), can be used in dual or triple therapy (recommendation B1)
• Ribavirin should be dosed following the pegylated IFN-α label for triple therapy (recommendation B2)
• Ribavirin should be given at a weight-based dose of 15 mg/kg in dual therapy (recommendation B2)</td></tr>
<tr><td rowspan="2">Ghany 2013: An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases.</td><td>AASLD Practice Guideline</td></tr>
<tr><td>Methodik
Grading System for Recommendations:
<table><tr><th>Classification</th><th>Description</th></tr><tr><td>Class 1</td><td>Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective</td></tr><tr><td>Class 2</td><td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment</td></tr><tr><td>Class 2a</td><td>Weight of evidence/opinion is in favor of usefulness/efficacy</td></tr><tr><td>Class 2b</td><td>Usefulness/efficacy is less well established by evidence/opinion</td></tr><tr><td>Class 3</td><td>Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful</td></tr><tr><td>Level of Evidence</td><td>Description</td></tr><tr><td>Level A</td><td>Data derived from multiple randomized clinical trials or meta-analyses</td></tr><tr><td>Level B</td><td>Data derived from a single randomized trial, or non-randomized studies</td></tr><tr><td>Level C</td><td>Only consensus opinion of experts, case studies, or standard-of-care</td></tr></table></td></tr>
<tr><td></td><td>Empfehlungen:
• The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin (Class 1, Level A).
• Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin (Class 1, Level A).</td></tr>
<tr><td rowspan="2">SIGN 2013: Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C. Edinburgh: SIGN; 2013.</td><td>SIGN guideline</td></tr>
<tr><td>Grundlage der Leitlinie: Methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/guidelines/fulltext/50/index.html.</td></tr>
</table>

	KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS LEVELS OF EVIDENCE 1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias 1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias 1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias 2++ High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal 2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3 Non-analytic studies, eg case reports, case series 4 Expert opinion GRADES OF RECOMMENDATION *Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.* A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+ C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++ D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ GOOD PRACTICE POINTS ✓ Recommended best practice based on the clinical experience of the guideline development group Empfehlungen *Treatment of chronic hepatitis C* • All treatment-naive patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy [A]. • All treatment-experienced patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy [A]. • Treatment-naive patients co-infected with HIV and HCV genotype 1 who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be considered for treatment with pegylated IFN and weight-based ribavirin for 48-72 weeks depending on viral response [B].
Wilkins 2013: British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013.	Leitlinie der British HIV Association (BHIVA) Methodik Grundlage der Leitlinie: BHIVA revised and updated the Association's guideline development manual in 2011. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations. The scope, purpose and guideline topics were agreed by the Committee and key questions concerning each guideline topic were drafted and a systematic literature review undertaken by an information scientist.

	Two-level grading system of recommendations: **A Grade 1** recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'We recommend'. **A Grade 2** recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'We suggest'. *The quality of evidence is graded from A to D and for the purpose of these guidelines is defined as follows:* **Grade A** evidence means high-quality evidence that comes from consistent results from well- performed randomized controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect. **Grade B** evidence means moderate-quality evidence from randomised trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias. **Grade C** evidence is low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion ofmost potential sources of bias. **Grade D** evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate. Empfehlungen • We recommend where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with triple therapy consisting of pegylated interferon, ribavirin, and either telaprevir or boceprevir (1C). • We recommend 48 weeks of total treatment with a telaprevir- or boceprevir-based regimen for patients who do not have cirrhosis (1C). Good practice points: • We recommend all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them. • We recommend a total of 48 weeks of treatment in patients with cirrhosis and for those who do not achieve an RVR. • We suggest non-cirrhotic patients who were previously null

	responders, partial responders or who experienced breakthrough should, wherever possible, wait for the availability of interferon-sparing regimens or interferon-based regimens including at least two new agents. • We recommend that all patients with advanced or decompensated cirrhosis being treated with triple therapy are managed in a tertiary centre. • We suggest for patients with genotype 1 infection and non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with hepatic elastography or alternative non-invasive testing at least annually. Where there is confirmed progression of fibrosis, treatment initiation should be reconsidered.
Brook 2010: European Guideline for the management of Hepatitis B and C virus infections.	British HIV Association guideline
	Methodik Grundlage der Leitlinie: The Writing Group used an evidence-based medicine approach to produce these guidelines. Level of Evidence: I = randomized controlled trial (RCT) or meta-analysis of several RCTs II = other good quality trial evidence III = observational studies/case reports IV= expert opinion
	Empfehlungen • Chronic HCV infection: Peginterferon alfa with ribavirin will cure chronic infection in approximately 50% of patients (Ia, A) • All other HCV genotypes (including 1 and 4) should be treated for 12-18 months. Treatment should be discontinued if there has not been a reduction in HCV viral load >2 log at week 12 of therapy or undetectable levels at week 24. Patients achieving undetectable viral load at week 4 (rapid virological responders) have the greatest chances of cure and may benefit from shorter courses of therapy. Patients are more likely to respond if they have less advanced liver fibrosis low serum HCV-RNA levels (<500,000 IU/ml), if they are infected with certain HCV genotypes (types 2 and 3) (Ib, A) • Patient selection for therapy depends mainly on HCV genotype and viral load. A liver biopsy is not necessary for making treatment decisions (1b, A)
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection.	EASL Clinical Practice Guideline
	Methodik Grundlage der Leitlinie: The CPGs were established using data collected from PubMed and Cochrane database searches before December 2010. The CPGs have been based as far as possible on evidence from existing publications, and, if evidence was unavailable, the experts personal experience and opinion. Level of Evidence: The quality of the evidence in the CPG has been classified in one of three levels: high (A); moderate (B); low (C)

	The GRADE system offers two grades of recommendation: strong (1) or weak (2)
	Empfehlungen • The combination of pegylated IFN-a and ribavirin is the approved SoC for chronic hepatitis C (LoE: A; GoR: 1). • Two pegylated IFN-a molecules, pegylated IFN-a2a (180 lg once per week) and pegylated IFN-a2b (1.5 lg/ kg once per week), can be used in combination with ribavirin. • Ribavirin should be given at a weight-based dose of 15 mg/ kg per day for genotypes 1 and 4–6 (LoE: A, GoR: 2)
	ANMERKUNGEN FBMED
	• LL nach dem GRADE-approach [High (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2)]

NICE 2012:
Boceprevir for the treatment of genotype 1 chronic hepatitis C.
	Empfehlungen
	
	• Standard treatment for genotype 1 chronic hepatitis C in the UK is peginterferon alfa plus ribavirin for both treatment-naive and previously treated patients.
	• Boceprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease:
	  • who are previously untreated or
	  • in whom previous treatment has failed.
	• Boceprevir plus peginterferon alfa and ribavirin is clinically more effective that peginterferon alfa and ribavirin alone in inducing a sustained virological response in treatment-naive patients and previously treated patients, irrespective of baseline fibrosis level.

	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2012: Telaprevir for the treatment of genotype 1 chronic hepatitis C.	Empfehlungen Telaprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of **genotype 1 chronic hepatitis C** in adults with compensated liver disease: • who are previously untreated **or** • in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did not respond. • Telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously untreated and previously treated patients.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2010: Peginterferon alfa	Empfehlungen

and ribavirin for the treatment of chronic hepatitis C.	Combination therapy with peginterferon alfa (2a or 2b) and ribavirin is recommended as a treatment option for adults with chronic hepatitis C: • who have been treated previously with peginterferon alfa (2a or 2b) and ribavirin in combination, or with peginterferon alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed **or** • who are co-infected with HIV Shortened courses of combination therapy with peginterferon alfa (2a or 2b) and ribavirin are recommended for the treatment of adults with chronic hepatitis C who: • have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test **and** • are considered suitable for a shortened course of treatment. When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (peginterferon alfa-2a or peginterferon alfa-2b), the genotype of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load). ***Peginterferon alfa-2a:*** • When peginterferon alfa-2a is given in combination with ribavirin, people with HCV genotype 1 infections who have detectable HCV RNA at week 4 (that is, there is not a rapid virological response) should receive 48 weeks of treatment. • An extension to the licence for peginterferon alfa-2a now means that some people with hepatitis C are eligible for shortened courses of treatment. People with HCV genotype 1 and a low viral load at the start of treatment, a rapid virological response at week 4 and undetectable HCV RNA at week 24 may complete treatment at week 24 rather than receiving the standard 48 weeks of therapy. • People with HCV genotype 1 whose condition has not responded to prior treatment with peginterferon alfa and ribavirin combination therapy and who are considered for re-treatment should receive 72 weeks of combination therapy. ***Peginterferon alfa-2b*** • People with HCV genotype 1 who have undetectable HCV RNA at week 12 (that is, who have an early virological response) should receive 48 weeks of treatment with peginterferon alfa-2b. • People with a genotype 1 infection without an early virological response are considered unlikely to have a sustained virological response, and consideration should be given to withdrawing treatment. • Re-treatment with peginterferon alfa-2b in combination with ribavirin is recommended in the marketing authorisation for people whose hepatitis C has not shown an adequate response to treatment (non-response) or has responded but subsequently relapsed. • All people re-treated with peginterferon alfa-2b, irrespective of HCV genotype, who have undetectable serum HCV RNA at week 12 should receive 48 weeks of treatment. • People re-treated with peginterferon alfa-2b in whom HCV RNA is still detectable at week 12 are unlikely to have a sustained

<table>
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ANMERKUNGEN FBMED
• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal</td></tr>
<tr><td>Ghany 2009: Diagnosis, Management, and Treatment of Hepatitis C: An Update.</td><td>AASLD PRACTICE GUIDELINE (American Association for the Study of Liver Diseases)
Methodik
Grundlage der Leitlinie: (1) a formal review and analysis of the recently published world literature on the topic (Medline search up to September 2008); (2) the American College of Physicians' Manual for Assessing Health Practices and Designing Practice Guidelines; 1 (3) guideline policies, including the American Association for the Study of Liver Diseases' (AASLD) Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association's Policy Statement on the Use ofMedical Practice Guidelines;2 and (4) the experience of the authors in regard to hepatitis C.

Grading System for Recommendations
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Empfehlungen

Genotypes 1 HCV Infection:
• Treatment with peginterferon plus ribavirin should be planned for 48 weeks; the dose for peginterferon alfa-2a is 180 µg subcutaneously per week together with ribavirin using doses of 1,000 mg for those <75 kg in weight and 1,200 mg for those >75</td></tr>
</table>

	kg; the dose for peginterferon alfa-2b is 1.5 µg/kg subcutaneously per week together with ribavirin using doses of 800 mg for those weighing <65 kg; 1,000 mg for those weighing >65 kg to 85 kg, 1,200 mg for >85 kg to 105 kg, and 1,400 mg for >105 kg (Class I, Level A). • Treatment may be discontinued in patients who do not achieve an early virological response (EVR; >2 log reduction in HCV RNA at week 12 of treatment) (Class I, Level A). • Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued (Class I, Level A). • For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks (Class IIa, Level B). • Patients with genotype 1 infection whose treatment continues through 48 to 72 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative at the end of treatment should be retested for HCV RNA 24 weeks later to evaluate for a sustained virological response (SVR; HCV RNA negative 24 weeks after cessation of treatment) (Class I, Level A).
Ghany 2011: An Update on Treatment of Genotype 1 Chronic Heaptitis C Infection: 2011 Practice	AASLD PRACTICE GUIDELINE (American Association for the Study of Liver Diseases)
	Methodik Grundlage der Leitlinie: Siehe Ghany 2009 **Grading System for Recommendations**

Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44.	**Classification** / **Description** Class I — Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective. Class II — Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment. Class IIa — Weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb — Usefulness/efficacy is less well established by evidence/opinion. Class III — Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful. **Level of Evidence** / **Description** Level A — Data derived from multiple randomized clinical trials or meta-analyses. Level B — Data derived from a single randomized trial, or nonrandomized studies. Level C — Only consensus opinion of experts, case studies, or standard-of-care.
	Empfehlungen • The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir incombination with peginterferon alfa and ribavirin (Class 1, Level A). • Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin (Class 1, Level A).
	ANMERKUNGEN FBMED
	Evidenzbasierte LL
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department	Department of Veterans Affairs Hepatitis C Resource Center
	Methodik Grundlage der Leitlinie: Grading system for recommendations adapted from the AASLD Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C. **Grading System for Recommendations**

of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89.	

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AASLD, American Association for the Study of Liver Diseases; RCT, randomized, controlled trials.

Empfehlungen

Recommendations for PegIFN alfa with or without RBV treatment in genotype 1 patients:

- PegIFN alfa monotherapy may be used to treat patients with contraindications to RBV (Class I, Level A).
- For patients who achieve RVR and have a low baseline viral load (HCV RNA < 400,000 IU / ml), 24-weeks of treatment with PegIFN – RBV may be sufficient (Class I, Level B).

Recommendations in patients with genotype 4 infection:

- Appropriate candidates with HCV genotype 4 infection should be treated with PegIFN alfa-2a 180 mcg per week or PegIFN alfa-2b 1.5 mcg / kg per week, plus RBV up to 1,400 mg per day for 48 weeks (Class I, Level A).

Recommendations in patients with cirrhosis:

- HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class < 7), adequate neutrophils (> 1.5 k/ mm 3), and adequate platelet counts (> 75 k/ mm 3) should be considered for treatment with BOC (for 44 weeks) or TVR (for 12 weeks) combined with PegIFN – RBV at standard doses for 48 weeks (Class I, Level B).
- Patients with cirrhosis remain at risk for HCC and should undergo

	routine screening regardless of viral clearance status, in accordance with current guidelines (Class I, Level B). **Recommendations in patients with decompensated cirrhosis:** • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis (Class I, Level B). • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis (Class II, Level B). • IFN-based therapy in combination with RBV may be considered in patients awaiting liver transplantation with a Child-Pugh score < 7 and a MELD score ≤ 18 (Class I, Level A). • If antiviral therapy is undertaken, reduced IFN doses should be used and growth factors can be given to counteract treatmentassociated cytopenias (Class II, Level B).
	ANMERKUNGEN FBMED
	Evidenzbasierte LL

Leitlinien – Therapienaive Patienten

EASL 2014: EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.	Leitlinie der European Association for the Study of the Liver (EASL)
	Methodik Grundlage der Leitlinie: The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system): **Evidence quality** / **Notes** / **Grading** High — Further research is very unlikely to change our confidence in the estimate of effect — A Moderate — Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate — B Low — Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain — C **Recommendation** / **Notes** / **Grading** Strong — Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost — 1 Weak — Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption — 2
	Empfehlungen *Treatment-naïve patients with genotypes 2, 3, 4, 5, or 6:* • The combination of pegylated IFN-α and ribavirin is the approved standard of care for chronic hepatitis C genotype 2, 3, 4 ,5, and 6 (recommendation A1) • Ribavirin should be given at a weight-based dose of 15 mg/kg for genotypes 4, 5, and 6 and at a flat dose of 800 mg/day for genotypes 2 and 3 (recommendation A2) • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15 mg/kg (recommendation C2)

Ghany 2013: An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases.	AASLD Practice Guideline (American Association for the Study of Liver Diseases)
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	Empfehlungen For Treatment-Naive Patients: • The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone (Class 1, Level A). • Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (Class 2a, Level B). • Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24 (Class 2a, Level B). • The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin (Class 1, Level A). • Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24

	weeks (Class 2a, Level A). • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (Class 2b, Level B). • Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24 (Class 2a, Level B).
Ghany 2011: An Update on Treatment of Genotype 1 Chronic Heaptitis C Infection: 2011 Practice Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44.	AASLD Practice Guideline (American Association for the Study of Liver Diseases)
	Methodik Siehe Seite 45
	Empfehlungen **Recommendations for Treatment-Naive Patients:** • The recommended dose of boceprevir is 800 mg administered with food three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 24-44 weeks preceded by 4 weeks of lead-in treatment with peginterferon alfa and ribavirin alone (Class 1, Level A). • Patients without cirrhosis treated with boceprevir, peginterferon, and ribavirin, preceded by 4 weeks of lead-in peginterferon and ribavirin, whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (Class 2a, Level B). • Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24 (Class 2a, Level B). • The recommended dose of telaprevir is 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12-36 weeks of peginterferon alfa and ribavirin (Class 1, Level A). • Patients without cirrhosis treated with telaprevir, peginterferon, and ribavirin, whose HCV RNA level at weeks 4 and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks (Class 2a, Level A). • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon and ribavirin should receive therapy for a duration of 48 weeks (Class 2b, Level B). • Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24 (Class 2a, Level B).
	ANMERKUNGEN FBMED
	Evidenzbasierte LL
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	Empfehlungen • SVR is achieved in 40–54% of patients infected with HCV genotype 1 treated with pegylated IFN-a plus ribavirin at approved doses for 48 weeks (LoE: A; GoR: 1). • Strongest baseline predictors of SVR are: o HCV genotype (LoE: A; GoR: 1) o Genetic polymorphisms located in chromosome 19 (IL28B), particularly in genotype 1 patients (LoE: A; GoR: 1). o Stage of liver fibrosis (LoE: A; GoR: 1).
	ANMERKUNGEN FBMED
	LL nach dem GRADE-approach [High (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2)]
Leroy 2012: Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French Association for the Study of the Liver.	Guideline by the French Association for the Study of the Liver
	Methodik Grundlage der Leitlinie: The report of the meeting presented the position of FASL and included a rating of agreement on each item (level of agreement expressed as% of voters present in the room). The proposals were also classified according to the principles of the Grading of Recommendations, Assessment, Development and Evaluation working group system, which specifies three levels of evidence. Levels of evidence: A (high), B (moderate), C (low) and two grades of recommendation: 1 (strong), 2 (weak).
	Empfehlungen • Treatment-naive genotype 1 patients with predictive factors of poor response (non-CC genotypes of IL28B or fibrosis F3-F4) should receive triple therapy (PI plus PegIFN-RBV) as the first-line treatment (LoE: A; GoR: 1, level of agreement 84%).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department	Department of Veterans Affairs Hepatitis C Resource Center
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Level C	Only consensus opinion of experts, case studies, or standard-of-care

AASLD, American Association for the Study of Liver Diseases; RCT, randomized, controlled trials.

Empfehlungen

Recommendations for therapy among treatment-naïve patients with genotype 1 infection:

- PegIFN alfa and RBV, in combination with BOC (800 mg orally every 7 – 9 h with food) or TVR (750 mg orally every 7 – 9 h with 20 g of fat) is the standard of care for most treatment-naïve genotype 1-infected patients (**Class I, Level A**).
- If a TVR-containing regimen is used in treatment-naïve noncirrhotic patients who achieve eRVR, TVR should be discontinued at week 12 and PegIFN – RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1,000 IU/ ml at treatment week 4, and remains < 1,000 IU/ml or becomes undetectable by week 12, TVR should be discontinued at week 12, and PegIFN and RBV can be continued for another 36 weeks (**Class I, Level A**).
- If a TVR-containing regimen is used in treatment-naïve cirrhotics
- who achieve an HCV RNA that is undetectable or < 1,000 IU / ml at treatment weeks 4 and 12, TVR should be discontinued at week 12, and PegIFN – RBV can be continued for another 36 weeks (**Class I, Level A**).
- If a BOC-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥ 1 log 10 during the 4-week lead-in, and HCV RNA is undetectable at weeks 8 – 24,

<table>
<tr><td></td><td>treatment with BOC – PegIFN – RBV for 24 weeks is sufficient. If HCV RNA is detectable at week 8, but < 100 IU / ml at week 12, and negative at week 24, BOC – PegIFN – RBV should be continued until week 36, followed by PegIFN – RBV alone for 12 more weeks. If HCV RNA declines by < 1 log 10 during the lead-in, BOC– PegIFN– RBV can be continued for 44 weeks (Class I, Level A).
• If a BOC-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of BOC – PegIFN – RBV is required after the 4-week lead-in (Class I, Level A).
Recommendations for treatment-na ï ve and -experienced patients with genotype 2 or 3 infection:
• Treatment-naïve patients should be treated with PegIFN – RBV for 24 weeks (Class I, Level A).
• For patients with low viral load (HCV RNA < 600,000 IU / ml) and mild fibrosis who achieve a RVR, 12 – 18 weeks of treatment may be sufficient (Class I, Level A).
• For patients with genotype 3 infection and a high HCV RNA (> 600,000 IU / ml), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response (Class I, Level B).
• Retreatment duration is 48 weeks (Class I, Level A).</td></tr>
<tr><td></td><td>ANMERKUNGEN FBMED</td></tr>
<tr><td></td><td>Evidenzbasierte LL</td></tr>
<tr><td>Sarrazzin 2010: Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus (HCV)-Infektion.</td><td>Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten</td></tr>
<tr><td></td><td>Methodik
Klassifizierung der "Evidenz": "Evidenz"level (1-5) und Empfehlungsgrade (A-D) nach Oxford Centre of Evidence Based Medicine
<table>
<tr><th>Empfehlungsgrad</th><th>"Evidenz"grad</th><th>Beschreibung</th></tr>
<tr><td>A</td><td>Ia</td><td>"Evidenz" durch systematisches Review randomisierter kontrollierter Studien (RCT</td></tr>
<tr><td></td><td>Ib</td><td>"Evidenz" durch eine geeignet geplante RCT</td></tr>
<tr><td></td><td>Ic</td><td>Alle-oder-Keiner-Prinzip</td></tr>
<tr><td>B</td><td>IIa</td><td>"Evidenz" durch systematisches Review gut geplanter Kohortenstudien</td></tr>
<tr><td></td><td>IIb</td><td>"Evidenz" durch eine gut geplante Kohortenstudie / RCT mäßiger Qualität (z.B. < 80% Follow-up)</td></tr>
<tr><td></td><td>IIc</td><td>"Evidenz" durch Outcome-Research-Studien</td></tr>
<tr><td></td><td>IIIa</td><td>"Evidenz" durch systematisches Review gut geplanter Fall-Kontrollstudien</td></tr>
<tr><td></td><td>IIIb</td><td>"Evidenz" durch eine Fall-Kontrollstudie</td></tr>
<tr><td>C</td><td>IV</td><td>"Evidenz" durch Fallserien / Kohorten- und Fall-Kontrollstudien mäßiger Qualität</td></tr>
<tr><td>D</td><td>V</td><td>Expertenmeinung ohne explizite kritische Bewertung oder basierend auf physiologischen Modellen, Laborforschungsresultaten oder "first principles"</td></tr>
</table>
</td></tr>
<tr><td></td><td>Empfehlungen

Nicht vorbehandelte Patienten</td></tr>
</table>

	• Die Standardtherapie erfolgt mit einem pegylierten Interferon alfa in Kombination mit Ribavirin [A]. • Bei Kontraindikationen für Ribavirin wird eine Monotherapie mit einem pegylierten Interferon alfa durchgeführt [A]. • Ribavirin sollte körpergewichtsadaptiert dosiert werden [A]. • Die Therapiedauer richtet sich im Wesentlichen nach dem HCV-Genotyp, der HCV-RNA-Konzentration vor Therapie und dem virologischen Verlauf unter der Behandlung [A]. • Die Therapie sollte bei fehlendem virologischem Ansprechen (Non-Response) vorzeitig beendet werden [A].
	ANMERKUNGEN FBMED
	Evidenzbasierte S3-LL Die Leitlinien-Erstellung wurde am 12.11.2007 begonnen und am 07.09.2009 formal abgeschlossen. **Gültigkeit abgelaufen-LL wird z.Zt. überprüft**

Leitlinien – Vorbehandelte Patienten und Nonresponder

EASL 2014: EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.	Leitlinie der European Association for the Study of the Liver (EASL)
	Methodik Grundlage der Leitlinie: The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system): **Evidence quality** / **Notes** / **Grading** High — Further research is very unlikely to change our confidence in the estimate of effect — A Moderate — Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate — B Low — Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain — C **Recommendation** / **Notes** / **Grading** Strong — Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost — 1 Weak — Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption — 2
	Empfehlungen *Triple therapy for genotype 1 patients who experienced virological failure during previous dual PegIFN/RBV therapy – results of phase III studies with BOC and TVR:* • Patients infected with HCV genotype 1 who failed to eradicate HCV on prior therapy with PegIFN/ RBV should be considered for re-treatment with the triple combination of PegIFN/RBV and a PI (recommendation A1) • The previous response to IFN-based therapy is an important predictor of success of triple therapy, with relapsers having higher cure rates than partial responders, who in turn have higher cure rates than null responders. If the pattern of prior response to dual

<table>
<tr><td></td><td>therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy (recommendation A2)
• Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either PI (recommendation B2)
• Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated IFN-α, with or without ribavirin, can be re-treated with pegylated IFN-α and ribavirin (recommendation B2)</td></tr>
<tr><td rowspan="3">Ghany 2013: An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases.</td><td>AASLD Practice Guideline (American Association for the Study of Liver Diseases)</td></tr>
<tr><td>Methodik
Grading System for Recommendations:
<table><tr><th>Classification</th><th>Description</th></tr><tr><td>Class 1</td><td>Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective</td></tr><tr><td>Class 2</td><td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment</td></tr><tr><td>Class 2a</td><td>Weight of evidence/opinion is in favor of usefulness/efficacy</td></tr><tr><td>Class 2b</td><td>Usefulness/efficacy is less well established by evidence/opinion</td></tr><tr><td>Class 3</td><td>Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful</td></tr><tr><td>Level of Evidence</td><td>Description</td></tr><tr><td>Level A</td><td>Data derived from multiple randomized clinical trials or meta-analyses</td></tr><tr><td>Level B</td><td>Data derived from a single randomized trial, or non-randomized studies</td></tr><tr><td>Level C</td><td>Only consensus opinion of experts, case studies, or standard-of-care</td></tr></table></td></tr>
<tr><td>Empfehlungen

For treatment-experienced patients:
• Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (Class 1, Level A).
• Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin (Class 2b, Level B.)
• Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C</td></tr>
</table>

	for telaprevir), may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but cannot be recommended for null responders (Class 3, Level C). • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B). • Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).
Ghany 2009: Diagnosis, Management, and Treatment of Hepatitis C: An Update.	AASLD Practice Guideline (American Association for the Study of Liver Diseases)
	Methodik Siehe Seite 45
	Empfehlungen **Retreatment of Persons Who Failed to Respond to Previous Treatment:** • Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered (for relapsers, Class III, Level C; for non-responders, Class III, Level B). • Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis (Class IIa, Level B). • Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin (Class III, Level B).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Ghany 2011: An Update on Treatment of Genotype 1 Chronic Heaptitis C Infection: 2011 Practice Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44.	AASLD Practice Guideline (American Association for the Study of Liver Diseases)
	Methodik Siehe Seite 45
	Empfehlungen **Recommendations for treatment-experienced patients:** • Re-treatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin (Class 1,Level A). • Re-treatment with telaprevir, together with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin (Class 2b, Level B.) • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir- based regimen can be

	considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir), may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but cannot be recommended for null responders (Class 3, Level C). • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Leroy 2012: Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French Association for the Study of the Liver.	Guideline by the French Association for the Study of the Liver
	Methodik Grundlage der Leitlinie: The report of the meeting presented the position of FASL and included a rating of agreement on each item (level of agreement expressed as% of voters present in the room). The proposals were also classified according to the principles of the Grading of Recommendations, Assessment, Development and Evaluation working group system, which specifies three levels of evidence. Levels of evidence: A (high), B (moderate), C (low) and two grades of recommendation: 1 (strong), 2 (weak).
	Empfehlungen • Patients with PegIFN-RBV treatment failure should receive triple therapy with TVR or BOC and this should be the standard of care (LoE: C; GoR: 2, level of agreement 89%). • In patients who relapsed after PegIFN-RBV therapy, triple therapy should be quickly started in patients with severe fibrosis (F3–F4), is indicated for those with moderate fibrosis (F2) and should be discussed on a case-by-case basis in patients with minimal lesions (F0–F1) (LoE: B; GoR: 2, level of agreement 91%). • Patients who showed a partial response to PegIFN-RBV therapy but have severe fibrosis (F3–F4) should start triple therapy as soon as possible. For those with minimal to moderate fibrosis (_F2), treatment should be discussed on a case-by-case basis (LoE: B; GoR: 2, level of agreement 89%). • In null responders to PegIFN-RBV therapy with severe fibrosis, an SVR with triple therapy can be expected only in about 15% of F4 patients and 40% of F3 patients. • This treatment is indicated in the absence of any alternative (clinical trials). For F0–F2 patients, the chance of success is about 30% and the benefit–risk ratio should be evaluated on a case-by-case basis (LoE: B; GoR: 2, level of agreement 86%).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department	Department of Veterans Affairs Hepatitis C Resource Center
	Methodik Grundlage der Leitlinie: Grading system for recommendations adapted from the AASLD Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C. **Grading System for Recommendations**

of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89. 53.	

	Description
Classification	
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/ efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/ opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation procedure/ treatment is not useful/effective, and in some cases, may be harmful
Level of evidence	
Level A	Data derived from multiple RCT or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinion of experts, case studies, or standard-of-care

AASLD, American Association for the Study of Liver Diseases; RCT, randomized, controlled trials.

Empfehlungen

Recommendations for retreatment of nonresponders and relapsers with genotype 1 infection:

- For patients who previously failed PegIFN – RBV, retreatment with BOC or TVR, and PegIFN – RBV may be considered, particularly in patients who were relapsers (**Class I, Level A**).
- If a BOC-containing regimen is used for re-treatment of noncirrhotic prior partial responders or relapsers, the recommended treatment duration is 36 weeks if HCV RNA is undetectable from weeks 8 to 24. If HCV RNA is detectable at week 12, but < 100 IU / ml, and is undetectable from weeks 24 to 36, BOC can be discontinued at week 36 and PegIFN – RBV can be continued for an additional 12 weeks (**Class I, Level B**).
- If a BOC-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU/ ml, and becomes undetectable from weeks 24 to 36 (**Class I, Level B**).
- If a BOC-containing regimen is used for re-treatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU / ml, and become undetectable from weeks 24 to 36 (**Class II, Level C**).
- If a TVR-containing regimen is used for re-treatment of prior

relapsers and HCV RNA is undetectable from weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN – RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1,000 IU / ml at week 4 and / or 12, TVR can be discontinued at week 12 and PegIFN – RBV can be continued for an additional 36 weeks (**Class I, Level B**).

- If a TVR-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is < 1,000 IU / ml at weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN alfa plus RBV should be continued for an additional 36 weeks (**Class I, Level B**).

ANMERKUNGEN FBMED

- Evidenzbasierte LL

Sarrazin 2010: Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus (HCV)-Infektion.

Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten

Methodik
Klassifizierung der "Evidenz": "Evidenz"level (1-5) und Empfehlungsgrade (A-D) nach Oxford Centre of Evidence Based Medicine

Empfehlungsgrad	"Evidenz"grad	Beschreibung
A	Ia	"Evidenz" durch systematisches Review randomisierter kontrollierter Studien (RCT
	Ib	"Evidenz" durch eine geeignet geplante RCT
	Ic	Alle-oder-Keiner-Prinzip
B	IIa	"Evidenz" durch systematisches Review gut geplanter Kohortenstudien
	IIb	"Evidenz" durch eine gut geplante Kohortenstudie / RCT mäßiger Qualität (z.B. < 80% Follow-up)
	IIc	"Evidenz" durch Outcome-Research-Studien
	IIIa	"Evidenz" durch systematisches Review gut geplanter Fall-Kontrollstudien
	IIIb	"Evidenz" durch eine Fall-Kontrollstudie
C	IV	"Evidenz" durch Fallserien / Kohorten- und Fall-Kontrollstudien mäßiger Qualität
D	V	Expertenmeinung ohne explizite kritische Bewertung oder basierend auf physiologischen Modellen, Laborforschungsresultaten oder "first principles"

Empfehlungen

Patienten mit einem Rückfall auf eine Vortherapie (Relapse)
Empfehlung:

- Patienten mit einem Rückfall auf eine PEG-Interferon alfa-Monotherapie sollten mit PEG-Interferon alfa und Ribavirin behandelt werden [A].
- Bei Patienten mit einem Rückfall auf eine PEG-Interferon alfa/ Ribavirin-Kombinationstherapie sollte die Vortherapie überprüft werden (Dosierung PEG-Interferon alfa und Ribavirin, Dosisreduktionen, Therapiepausen, Therapiedauer, HCV RNA Kinetik, Management von Nebenwirkungen, Compliance, u.a.) [C].
- Diese Faktoren sollten bei einer Re-Therapie optimiert werden [C].

	• Patienten mit einem Rückfall auf eine PEG-Interferon alfa / Ribavirin-Kombinationstherapie sollten unabhängig vom Genotyp 48 [A] bzw. bei langsamem virologischen Ansprechen 72 Wochen [C] behandelt werden. • Fehlender HCV-RNA-Negativierung (HCV RNA nachweisbar mit einem hochsensitiven Assay) zu Woche 12 [A] bzw. 24 [C] bei langsamem Ansprechen in der Ersttherapie sollte die Therapie abgebrochen werden. **Konsens: 95%** **Patienten mit einem fehlenden Ansprechen auf eine Vortherapie (Non-Response)** Empfehlung • Therapieversager unter einer PEG-Interferon alfa-Monotherapie sollten wie unvorbehandelte Patienten mit PEG-Interferon alfa und Ribavirin behandelt werden [B]. • Bei Therapieversagern auf eine PEG-Interferon alfa/ Ribavirin-Kombinationstherapie sollte die Vortherapie überprüft werden (Dosierung PEG-Interferon alfa und Ribavirin, Dosisreduktionen, Therapiepausen, Therapiedauer, HCV RNA Kinetik, Management von Nebenwirkungen, Compliance, u.a.) [C]. • Eine erneute Therapie mit PEG-Interferon alfa und Ribavirin kann bei einer suboptimalen Vortherapie und Verbesserungsmöglichkeiten in der Re-Therapie versucht werden [B] • Eine erneute Therapie mit PEG-Interferon alfa und Ribavirin kann bei einer suboptimalen Vortherapie und Verbesserungsmöglichkeiten in der Re-Therapie versucht werden [B] • Bei fehlender HCV-RNA-Negativierung (HCV RNA nachweisbar mit einem hochsensitiven Assay) zu Woche 12 [A] bzw. 24 [C] bei langsamem Virusabfall in der Ersttherapie sollte die Therapie abgebrochen werden. • Bei einem virologischen Ansprechen sollte die Therapie möglichst über insgesamt 72 Wochen fortgeführt werden [A]. • Eine niedrig-dosierte Langzeitmonotherapie mit PEG-Interferon alfa zur Verhinderung der Fibroseprogression bzw. klinischen Komplikationen der Lebererkrankung kann gegenwärtig nicht generell empfohlen werden [A]. **Konsens: 98%**
	ANMERKUNGEN FBMED
	Evidenzbasierte S3-LL Die Leitlinien-Erstellung wurde am 12.11.2007 begonnen und am 07.09.2009 formal abgeschlossen. **Gültigkeit abgelaufen-LL wird z.Zt. überprüft**

Übersicht aus Leitlinie von Yee 2012

Table 6. HCV PI (BOC or TVR): RGT criteria and futility rules (34,35)

	BOC–PegIFN/RBV	TVR–PegIFN/RBV
Candidates for RGT	Noncirrhotics: Treatment-naïve: 28 weeks Prior relapser/partial responder: 36 weeks	Noncirrhotics: Treatment-naïve: 24 weeks Prior relapser: 24 weeks
Criteria for RGT	HCV RNA undetectable (<10–15 IU/ml) weeks 8–24	HCV RNA undetectable (<10–15 IU/ml) weeks 4 and 12
Futility rules (stop all treatment if any of the following occur)	Week 12: HCV RNA ≥100 IU/ml Or Week 24: HCV RNA detectable Or HCV RNA rebounds at any timepoint (≥1 $\log_{10}$ increase from the nadir HCV RNA)	Week 4 or 12: HCV RNA >1,000 IU/ml Or Week 24: HCV RNA detectable Or HCV RNA rebounds at any timepoint (≥1 $\log_{10}$ increase from the nadir HCV RNA)

HCV, hepatitis C virus; PegIFN, peginterferon; PI, protease inhibitor; RBV, ribavirin; RGT, response-guided therapy; TVR, telaprevir.

Leitlinien – HIV Koinfektion

EASL 2014: EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.	Leitlinie der European Association for the Study of the Liver (EASL)

Methodik

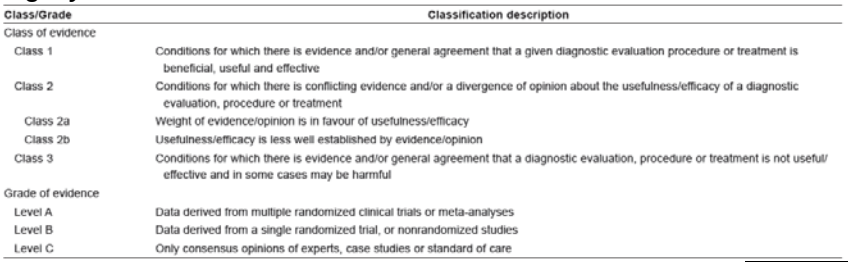
Grundlage der Leitlinie: The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2).

Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system):

Evidence quality	Notes	Grading
High	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	**Notes**	**Grading**
Strong	Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

Empfehlungen

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (recommendation B2)
- The same pegylated IFN-α regimen can be used in HIVco-infected patients as in patients without HIV infection, though prolongation of treatment can be considered for patients with genotypes 2 and 3 who exhibit slow early viral kinetics (recommendation B2)
- HIV patients who are co-infected with HCV genotype 1 should be considered for TVR-containing or BOCcontaining triple therapy, but special care should be taken to minimise or avoid potential drug-drug interactions (recommendation B1)
- HIV patients with a diagnosis of acute HCV infection should be treated with PegIFN/RBV, with duration dependent on viral kinetics independent of HCV genotype (recommendation B2)

Hull 2013: CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of HIV/hepatitis C coinfection in adults.	Canadian Guideline for management and treatment of HIV/hepatitis C coinfection in adults
	Grading System for recommendation:  **Class/Grade** — **Classification description** Class of evidence Class 1: Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful and effective Class 2: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment Class 2a: Weight of evidence/opinion is in favour of usefulness/efficacy Class 2b: Usefulness/efficacy is less well established by evidence/opinion Class 3: Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure or treatment is not useful/ effective and in some cases may be harmful Grade of evidence Level A: Data derived from multiple randomized clinical trials or meta-analyses Level B: Data derived from a single randomized trial, or nonrandomized studies Level C: Only consensus opinions of experts, case studies or standard of care
	RECOMMENDATIONS 25. Genotype 1-infected HIV-HCV coinfected patients should be treated with either boceprevir or telaprevir in combination with pegylated interferon and ribavirin (Class 1, Level A). 26. Telaprevir should be used for the first 12 weeks, while boceprevir should begin after a four-week lead-in of pegylated interferon and ribavirin and continue for the remainder of therapy (Class 1, Level A). 27. At this time, a full 48-week course of pegylated interferon and ribavirin is recommended because there is no current evidence regarding response-guided therapy in coinfected patients (Class 1, Level C). 28. Standard stopping rules at weeks 4, 12 and 24 (telaprevir), or weeks 8, 12 and 24 (boceprevir) developed for monoinfection should be applied to the HIV-HCV coinfection context (Class 1, Level C).
Brook 2010: European Guideline for the management of Hepatitis B and C virus infections.	British HIV Association guideline
	Methodik Grundlage der Leitlinie: The Writing Group used an evidence-based medicine approach to produce these guidelines. Level of Evidence: I = randomized controlled trial (RCT) or meta-analysis of several RCTs II = other good quality trial evidence III = observational studies/case reports IV= expert opinion
	Empfehlungen • HIV-positive patients respond to treatment, although not as well as HIVnegative patients **(Ib, A)**. • Sustained virological response in those completing therapy is 11-29% for genotypes 1 or 4 and 43-73% for genotypes 2 or 3 **(1b, A)**
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Brook 2010: British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010.	British HIV Association guideline
	Methodik Grundlage der Leitlinie: The Writing Group used an evidence-based medicine approach to produce these guidelines. Level of Evidence: I = randomized controlled trial (RCT) or meta-analysis of several RCTs

	II = other good quality trial evidence III = observational studies/case reports IV= expert opinion
	Empfehlungen <u>Patients with HCV infection who are co-infected with HIV:</u> • Anti-HCV treatment should be started before the CD4 count falls below 350 cells/mL and before ART is started, if possible (LoE: I). • The aim of treatment is an SVR (undetectable viral load 24 weeks post treatment) (LoE: I). • An RVR (viral load undetectable) at 4 weeks of treatment predicts response. Lack of EVR (nondetectable viral load or 42 log10 fall at 12 weeks) or detectable viral load at 24 weeks of treatment predicts nonresponse and therapy should be stopped (LoE: I). • Any ART should be stabilized before anti-HCV therapy is commenced (LoE: I). • Careful assessment of liver fibrosis is recommended, especially for patients with HCV genotypes 1 and 4 or those with suspected cirrhosis (LoE: I). • For genotypes 1 a pretreatment liver biopsy is recommended, or a hepatic elastography if the biopsy is refused (LoE: I). • Consider treatment for all patients with genotypes 1/4, especially if there is significant liver fibrosis (Ishak grade F3 or more) (LoE: I). • Treatment in all genotypes should be with pegylated interferon weekly plus ribavirin at 1000–1200mg daily, supported by erythropoietin/growth factors if necessary (LoE: I). • Treat patients with genotypes 1 for 48 weeks if there is an RVR, or 72 weeks if there was a 2 log10 drop but detectable HCV RNA at week 12 and they become PCR negative at 24 weeks (LoE: I).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Ghany 2009: Diagnosis, Management, and Treatment of Hepatitis C: An Update.	AASLD PRACTICE GUIDELINE (American Association for the Study of Liver Diseases)
	Methodik Siehe Seite 45
	<u>Patients with HCV infection who are co-infected with HIV:</u> • Anti-HCV testing should be performed in all HIV-infected persons (Class I, Level B). • HCV RNA testing should be performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV, as well as in those who are negative and have evidence of unexplained liver disease (Class I, Level B). • Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy (Class I, Level A). • Initial treatment of hepatitis C in most HIVinfected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients (see recommendation 13) (Class I, Level A). • When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral

	agent before beginning therapy with ribavirin (Class I, Level C). • HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation (Class IIa, Level C).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection.	EASL Clinical Practice Guideline
	Methodik Grundlage der Leitlinie: The CPGs were established using data collected from PubMed and Cochrane database searches before December 2010. The CPGs have been based as far as possible on evidence from existing publications, and, if evidence was unavailable, the experts personal experience and opinion. Level of Evidence: The quality of the evidence in the CPG has been classified in one of three levels: high (A); moderate (B); low (C) The GRADE system offers two grades of recommendation: strong (1) or weak (2)
	Empfehlungen <u>Patients with HCV infection who are co-infected with HIV:</u> • Indications for HCV treatment are identical to those in patients with HCV monoinfection (LoE: B; GoR: 2). • The same pegylated IFN-a regimen should be used in HIVco-infected patients as in patients without HIV infection, but ribavirin should always be weight-based dosed (LoE: B; GoR: 2). • Longer treatment duration (72 weeks for genotype 1) may be needed (LoE: B; GoR: 2)
	ANMERKUNGEN FBMED
	• LL nach dem GRADE-approach [High (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2)]
NICE 2012: Boceprevir for the treatment of genotype 1 chronic hepatitis C.	<u>Patients with HCV infection who are co-infected with HIV:</u> • The Committee considered the use of boceprevir plus peginterferon alfa and ribavirin in patients with HCV infection who are co-infected with HIV*. * Although these patients were not represented in the pivotal clinical trials, based on the current evidence available, the Committee concluded that there was no reason to make any different provision for these patients.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2012: Telaprevir for the treatment of genotype 1 chronic hepatitis C.	<u>Patients with HCV infection who are co-infected with HIV:</u> The Committee considered what impact excluding from trials patients co-infected with HIV and intravenous drug users had on the generalisability of the results to the UK population. It concluded that although these patients were not represented in the pivotal clinical trials, based on the current evidence available, there was no reason to make any different provision for these patients.

	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2010: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.	Empfehlungen ***Peginterferon alfa-2a*** • People co-infected with HIV should also be treated for 48 weeks, regardless of genotype. ***Peginterferon alfa-2b*** • People co-infected with HIV should be treated for 48 weeks regardless of HCV genotype.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
New York State Department of Health (NYSDH) 2010: Hepatitis C virus.	Empfehlungen RECOMMENDATIONS: • Pegylated interferon with ribavirin for 48 weeks is the standard recommended therapy for HIV/HCV co-infected patients with chronic HCV. (LoE: A; GoR:I) • Weight-based ribavirin dosing is recommended in HIV/HCV co-infected patients with genotypes 1, 4, 5, and 6. (LoE:A; GoR:I)
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department	Department of Veterans Affairs Hepatitis C Resource Center
	Methodik Grundlage der Leitlinie: Grading system for recommendations adapted from the AASLD Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C. **Grading System for Recommendations**

of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89**.**	

	Description
Classification	
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/ efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/ opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation procedure/ treatment is not useful/effective, and in some cases, may be harmful
Level of evidence	
Level A	Data derived from multiple RCT or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinion of experts, case studies, or standard-of-care

AASLD, American Association for the Study of Liver Diseases; RCT, randomized, controlled trials.

	Empfehlungen *Patienten mit HIV / HCV-Ko-Infektionen:* • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy (Class I, Level B). • Patients should be treated with PegIFN – RBV at doses similar to those with HCV monoinfection (Class I, Level B). • Patients should be treated with PegIFN – RBV for 48 weeks, regardless of genotype (Class I, Level A).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Sarrazin 2010: Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der	Empfehlungen *Patienten mit HIV / HCV-Ko-Infektionen:* • Bei HIV-positiven Patienten mit gleichzeitiger Hepatitis C kommt es zu einer beschleunigten Progression der Lebererkrankung. Diese Progression ist bei fortgeschrittenem Immundefekt besonders rasch. Daher sollte eine Behandlungsindikation großzügig gestellt werden. (B) • HIV-positive Patienten mit gleichzeitiger Hepatitis C tragen ein erhöhtes Risiko, unter einer antiretroviralen Therapie (HAART) Lebertoxizität zu entwickeln. Bei der Auswahl der antiretroviralen

Hepatitis-C-Virus (HCV)-Infektion.	Medikamente sind daher Substanzen mit geringem lebertoxischem Potential zu bevorzugen. (B) • Eine gleichzeitige Hepatitis C ist keine Kontraindikation für eine antiretrovirale Therapie. (A) **Konsens: 100%**
	ANMERKUNGEN FBMED
	• Evidenzbasierte S3-LL • Die Leitlinien-Erstellung wurde am 12.11.2007 begonnen und am 07.09.2009 formal abgeschlossen. **Gültigkeit abgelaufen-LL wird z.Zt. überprüft**

Leitlinien – Virusresistenz, Dosismodifikationen und Monitoring

Ghany 2011: An Update on Treatment of Genotype 1 Chronic Heaptitis C Infection: 2011 Practice Guideline by the American Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44.	AASLD PRACTICE GUIDELINE (American Association for the Study of Liver Diseases)
	Methodik Siehe Seite 45
	Empfehlungen • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose (Class 2a, Level A). • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed (Class 1, Level A). • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor (Class 2a, Level C).
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations	Department of Veterans Affairs Hepatitis C Resource Center
	Methodik Grundlage der Leitlinie: Grading system for recommendations adapted from the AASLD Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C. **Grading System for Recommendations**

from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. The American Journal of Gastroenterology 2012; 107 (5): 669-89.

	Description
Classification	
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/ efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/ opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation procedure/ treatment is not useful/effective, and in some cases, may be harmful
Level of evidence	
Level A	Data derived from multiple RCT or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinion of experts, case studies, or standard-of-care

AASLD, American Association for the Study of Liver Diseases; RCT, randomized, controlled trials.

Empfehlungen

Recommendations for dose modification:

- PegIFN alfa and RBV doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin, or platelets, as outlined in Table 5 (Class I, Level A).
- If RBV is stopped for 7 days or more in patients who are concomitantly receiving BOC or TVR, then the PI also should be permanently discontinued (Class I, Level A).
- HCV PIs should be either continued at full dose or discontinued (Class I, Level A).
- Initial management of HCV treatment-related anemia should consist of RBV dose reduction in a symptomatic patient with a hemoglobin < 10g/ dl, or as clinically indicated. Erythropoietin may be administered in patients with symptomatic anemia related to PegIFN – RBV therapy with or without BOC / TVR to limit anemia-related RBV dose reductions or dose discontinuations (Class II, Level C).
- Initial management of HCV treatment-related neutropenia should consist of PegIFN dose reduction for an ANC < 750, or as clinically indicated. Granulocyte colony-stimulating factor should not be given as primary therapy to prevent PegIFN alfa dose reductions (Class I, Level C).

	Recommendations for treatment monitoring: • Patients should be monitored for treatment-related adverse effects at intervals of at least 2 weeks early in the course of therapy, and at intervals of 1 – 2 months during treatment as clinically indicated (Class I, Level C). • Patient adherence to therapy should be assessed at every visit (Class I, Level C). • Patients should be evaluated for depression, suicidal ideation, alcohol, and illicit drug use at each visit (Class I, Level C). • Patients should be counseled about avoiding pregnancy by using two forms of contraception during treatment and for 6 months post-treatment, and pregnancy tests should be performed as indicated in. • If a patient is receiving a BOC- or TVR-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least 6 months after treatment (Class I, Level B). • Serum markers of biochemical and virologic response should be measured, and treatment-related adverse eff ects monitored at intervals as outlined (Class I, Level C). • In patients receiving TVR – PegIFN – RBV, all treatment should be stopped if any of the following occur: (i) HCV RNA level > 1,000 IU / ml at week 4 or 12; or (ii) detectable HCV RNA levels at week 24 or at any timepoint thereaft er; or (iii) HCV RNA rebounds at any timepoint (≥ 1 log10 increase from the nadir HCV RNA) (Class I, Level C). • In patients receiving BOC– PegIFN– RBV, all treatment should be stopped if any of the following occur: (i) HCV RNA level ≥ 100 IU / ml at week 12 with a BOC-containing regimen; or (ii) detectable HCV RNA levels at week 24 or at any timepoint thereafter; or (iii) HCV RNA rebounds at any timepoint (≥ 1 log 10 increase from the nadir HCV RNA; Class I, Level C). • If virologic failure occurs with a BOC- or TVR-containing regimen, the other PI must not be substituted (Class I, Level C).

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NIHR Horizon Scanning Centre *2012:* Sofosbuvir for chronic hepatitis C infection with compensated liver disease.	1. Trial NEUTRINO, NCT01641640; sofosbuvir with peg-IFN and RBV; phase III. Ziel: The primary efficacy objective of NEUTRINO was to determine the efficacy of treatment with SOF+PEG+RBV, as measured by the proportion of subjects with SVR12.
	2. Methodik Population: n=300 (planned); aged >18 years of age; HCV genotype 1, 4, 5 or 6 treatment naive. Schedule: Sofosbuvir 400mg once daily in combination with RBV and peg-IFN. Endpunkte: primary: SVR at week 12; secondary: Efficacy 4 and

<table>
<tr><td></td><td>24 weeks post dosing, HCV RNA during and post-treatment, viral resistance.</td></tr>
<tr><td></td><td>3. Ergebnisse (entnommen aus dem EPAR: Sovaldi)

<table>
<tr><td colspan="2">Number of Subjects with SVR12 n, %
Treatment-naive</td></tr>
<tr><td></td><td>SOF+PEG+RBV 12 Weeks
(N = 327)</td></tr>
<tr><td>Overall SVR12</td><td>296/327 (90.5%)</td></tr>
<tr><td>No Cirrhosis</td><td>253/273 (92.7%)</td></tr>
<tr><td>Cirrhosis</td><td>43/54 (79.6%)</td></tr>
<tr><td>Genotype 1 (1a, 1b, 1a/1b)</td><td>262/292 (89.7%)</td></tr>
<tr><td>Genotype 1a</td><td>206/225 (91.6%)</td></tr>
<tr><td>Genotype 1b</td><td>55/66 (83.3%)</td></tr>
<tr><td>Genotypes 4, 5, or 6</td><td>34/35 (97.1%)</td></tr>
<tr><td colspan="2">Primary Analysis</td></tr>
<tr><td>Treatment group</td><td>SOF + RBV + PEG for 12 weeks</td></tr>
<tr><td>% of subjects with SVR12 (95% CI)</td><td>90.5 (86.8-93.5)</td></tr>
<tr><td>Relapse rate (%)</td><td>8.6</td></tr>
<tr><td>Virologic failure rate (%)</td><td>8.6</td></tr>
</table></td></tr>
<tr><td>NIHR Horizon Scanning Centre 2012:
Sofosbuvir for chronic hepatitis C infection with compensated liver disease.</td><td>1. Trial
QUANTUM, NCT014435044; Sofosbuvir and PSI-352938, PSI-352938 monotherapy, sofosbuvir, PSI-352938 and RBV or sofosbuvir and RBV; phase II</td></tr>
<tr><td></td><td>2. Methodik (Randomised, placebo-controlled)

Population: n=239 (planned) aged >18 years of age; chronic HCV infection; treatment naive.

Arm 1: sofosbuvir 400mg with PSI-352938 300mg once daily for 12 weeks.
Arm 2: PSI-352938 300mg once daily for 12 weeks.
Arm 3: sofosbuvir with RBV 400mg once daily for 12 weeks.
Arm 4: sofosbuvir 400mg with PSI-352938 300mg and RBV once</td></tr>
</table>

	daily for 12 weeks. Arm 5: PSI-352938 300mg once daily for 24 weeks. Arm 6: Sofosbuvir 400mg once daily with PSI-352938 300mg once daily for 24 weeks. Arm 7: sofosbuvir 400mg once daily with RBV for 24 weeks. Arm 8: sofosbuvir 400mg with PSI-352938 300mg and RBV once daily for 24 weeks. Arm 9: Placebo for 24 weeks followed by randomization through arms 1-8. Endpunkte: primary: Decreased HCV RNA at 24 weeks; secondary: AEs, HCV RNA, ALT normalisation, SVR at week 48, drug resistance
	3. Ergebnisse 25 participants randomised to 12 week treatment arms. At 4 weeks post-treatment results available for 17 genotype 1 participants: 59% (n=10) remained HCV RNA undetectable and 41% (n=7) experienced viral relapse. 7 participants who have reached 8 weeks post treatment period have remained HCV RNA undetectable. Adverse effects: Sofosbuvir was well tolerated, with no participants experiencing viral rebound and no discontinuation due to AEs.
NIHR Horizon Scanning Centre *2012:* Sofosbuvir for chronic hepatitis C infection with compensated liver disease.	1. Trial NCT01054729; sofosbuvir 100 mg, 200 mg or 400 mg vs placebo both in combination with peg-IFN and RBV; phase II
	2. Methodik Population: n=64 (planned); 18-65 years of age; HCV genotype 1 Schedule: Arm 1: sofosbuvir 100mg or placebo once daily for 28 days, both with peg-IFN and RBV for 48 weeks. Arm 2: sofosbuvir 200mg or placebo once daily for 28 days with peg-IFN and RBV for 48 weeks. Arm 3:sofosbuvir 400mg or placebo once daily for 28 days with peg-IFN and RBV for 48 weeks. Endpunkte: primary: Safety and tolerability; secondary: HCV RNA
	3. Ergebnisse Sofosbuvir 100mg, 200mg, and 400mg were generally safe and well tolerated with no dose-dependent changes in the adverse event profile. Clinical efficacy was higher in the 200mg and 400mg dosing groups. Adverse effects: Sofosbuvir 100mg, 200mg, and 400mg were generally safe and well tolerated with no dose-dependent changes in the adverse event profile.
Horizon Scanning	1. Trial

Centre *2013:* Sofosbuvir with ledipasvir for hepatitis C, genotype 1.	LONESTAR, NCT01726517, GS-US-337-0118; sofosbuvir/ledipasvir with and without ribavirin; phase II
	2. Methodik Population: n=100 (planned); aged 18 years and older; HCV infection; genotype 1; chronic; treatment naïve or experienced. Schedule: Treatment naïve participants sofosbuvir/ledipasvir, oral, 400mg/90mg once daily for 8 or 12 wks; or sofosbuvir/ledipasvir, oral, 400mg/90mg once daily, with ribavirin, 500mg or 600mg twice daily for 8 wks; Treatment experienced participants sofosbuvir/ledipasvir, oral, 400mg/90mg once daily for 12 wks; or sofosbuvir/ledipasvir, oral, 400mg/90mg once daily, with ribavirin, 500mg or 600mg twice daily for 12 wks Endpunkte: primary: SVR; safety and tolerability; secondary: Viral resistance to study drug; viral dynamics; pharmacokinetics.
	3. Ergebnisse For treatment naïve participants: sofosbuvir/ledipasvir 8wks, 12wks and sofosbuvir/ledipasvir with ribavirin respectively, 95% achieved SVR8a, 100% achieved SVR4b, 100% achieved SVR8; for treatment experienced participants: for sofosbuvir/ledipasvir and sofosbuvir/ledispavir with ribavirin respectively, 95% achieved SVR4, 95% achieved SVR4. Adverse effects: Not reported

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 18.12.2013

#	Suchfrage
#1	MeSH descriptor Hepatitis C, Chronic explode all trees
#2	MeSH descriptor: [Hepatitis C, Chronic] explode all trees and with qualifiers: [Drug therapy - DT]
#3	MeSH descriptor Drug Therapy explode all trees
#4	#1 and #3
#5	#2 or #4
#6	(HCV):ti,ab,kw
#7	(chronic):ti,ab,kw and (hepatitis):ti,ab,kw and (c):ti,ab,kw
#8	#1 or #6 or #7
#9	#8 and #3
#10	#9 or #2
#11	#10 from 2008 to 2013

SR, HTAs Pubmed am 18.12.2013

#	Suchfrage
1	("Hepatitis C, Chronic/drug therapy"[Mesh])
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]
3	HCV[Title/Abstract]
4	(#2) OR #3
5	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
6	(#4) AND #5
7	(#1) OR #6
8	"Hepatitis C, Chronic"[Mesh]
9	"drug therapy"[MeSH Terms]
10	(#8) AND #9
11	(#7) OR #10
12	(#11) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
13	(#11) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
14	(#12) OR #13
15	(#14) AND ("2008/12/01"[PDAT] : "2013/12/18"[PDAT])

Leitlinien in PubMed am 18.12.2013

#	Suchfrage
#1	("Hepatitis C, Chronic/drug therapy"[Mesh])
#2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND c[Title/Abstract]
#3	HCV[Title/Abstract]
#4	(#2) OR #3
#5	(drug[Title/Abstract]) AND therap*[Title/Abstract]
#6	(#4) AND #5
#7	(#1) OR #6
#8	"Hepatitis C, Chronic"[Mesh]
#9	"drug therapy"[MeSH Terms]
#10	(#8) AND #9
#11	(#7) OR #10
#12	(#11) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title])
#13	(#12) AND ("2008/12/01"[PDAT] : "2013/12/18"[PDAT])

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