Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2013-B-118 ABT-450/r/ABT-267 mit ABT-333 in Kombination mit Ribavirin

Stand: Februar 2015

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

Dasabuvir **[Behandlung der chronischen Hepatitis C (CHC) Genotyp 1a/1b Infektion bei Erwachsenen]** **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 - Simeprevir (Genotypen 1 und 4) - Daclatasvir (Genotypen 1,3 und 4) - Ledipasvir/Sofosbuvir (Genotypen 1,3 und 4)
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
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 (Beschluss nach § 35a SGB V vom 17.07.2014) - Simeprevir (Beschluss nach § 35a SGB V vom 20.11.2014) - Daclatasvir (Verfahren nach § 35a SGB V vom 01.09.2014) - Ledipasvir/Sofosbuvir (Verfahren nach § 35a SGB V vom 01.12.2014)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **Handelsname** **ATC-Code**	**Anwendungsgebiet** (Text aus Fachinformation)

Zu bewertendes Arzneimittel:

Dasabuvir

Exviera

Exviera 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.

Empfohlene(s) Kombinationsarzneimittel und Behandlungsdauer für Exviera nach Patientenpopulation (siehe Abschnitt 4.2 (Tabelle 1)).

Patientenpopulation	**Therapie (1)**	**Dauer**
Genotyp 1b-Patienten ohne Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir	12 Wochen
Genotyp 1b-Patienten mit kompensierter Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir	12 Wochen
Genotyp 1a-Patienten ohne Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir + Ribavirin (1)	12 Wochen
Genotyp 1a-Patienten mit kompensierter Zirrhose	Exviera + Ombitasvir/Paritaprevir/Ritonavir + Ribavirin (1)	24 Wochen (siehe Abschnitt 5.1)

(1) Hinweis: Bei Patienten mit unbekanntem Genotyp-1-Subtyp oder einer gemischten Genotyp-1-Infektion sind die Dosierungsempfehlungen für Genotyp 1a zu befolgen.

<u>Besondere Patientengruppen</u>

	HIV-1-Koinfektion Es gelten die Dosierungsempfehlungen in Tabelle 1. Zu Dosierungsempfehlungen zusammen mit antiviralen Arzneimitteln gegen HIV siehe Abschnitt 4.4 (Behandlung von Patienten mit einer HIV-Koinfektion) und Abschnitt 4.5. Für weitere Informationen siehe Abschnitt 5.1. ***Lebertransplantierte Patienten*** Für lebertransplantierte Patienten wird eine Behandlung mit Exviera und Ombitasvir/Paritaprevir/Ritonavir in Kombination mit Ribavirin über 24 Wochen hinweg empfohlen. Initial kann eine niedrigere Ribavirindosis angezeigt sein. In der Studie an Patienten nach einer Lebertransplantation wurde Ribavirin individuell dosiert; die meisten Studienteilnehmer erhielten 600 bis 800 mg pro Tag (siehe Abschnitt 5.1). Zu Dosierungsempfehlungen bei gleichzeitiger Anwendung von Calcineurininhibitoren siehe Abschnitt 4.5.
Ribavirin Copegus® (J05AB04)	Copegus wird in Kombination mit anderen Arzneimitteln zur Behandlung von chronischer Hepatitis C (CHC) angewendet.
Peginterferon alfa 2a Pegasys® (L03AB11)	***Erwachsene Patienten*** Pegasys ist in Kombination mit anderen Arzneimitteln für die Behandlung der chronischen Hepatitis C (CHC) bei Patienten mit kompensierter Lebererkrankung indiziert (siehe Abschnitte 4.2, 4.4 und 5.1). Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis C Virus (HCV), siehe Abschnitte 4.2 und 5.1.
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.
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. **<u>Nicht vorbehandelte (naive) Patienten</u>** ***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. **<u>Vorbehandelte Patienten</u>** ***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.

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(HCV-RNA)- 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.
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.**
Ribavirin (gen.) z.B. Ribavirin-ratiopharm®	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. […]

(J05AB04)	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® wird angewendet: - 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) allein oder in Kombination mit Ribavirin nicht angesprochen haben (siehe Abschnitt 5.1). - in Kombination mit Interferon alfa-2b indiziert 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.
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.
Telaprevir Incivo® (J05AE11)	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).
Sofosbuvir Sovaldi® (J05AX15)	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.

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<tr>
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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>

* 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“
</td>
</tr>
<tr>
<td>Simeprevir
Olysio®
(J05AE14)</td>
<td>
OLYSIO ist bei erwachsenen Patienten in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) indiziert (siehe Abschnitte 4.2, 4.4 und 5.1).

Für die Hepatitis-C-Virus (HCV)-genotypspezifische Aktivität, siehe Abschnitte 4.4 und 5.1.
</td>
</tr>
</table>

Abschnitt 4.2 der Fachinformation:

Tabelle 1: Empfohlene Arzneimittel und Therapiedauer im Rahmen der Kombinationstherapie mit OLYSIO

Patientengruppe Behandlung Dauer	**Behandlung**	**Dauer**
Therapienaive Patienten und Patienten mit Rückfall auf eine Vortherapie (Relapse) mit HCVGenotyp 1 oder 4[1]	OLYSIO + Peginterferon alfa + Ribavirin[2]	24 Wochen[3] Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa und Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 12-wochigen Behandlung mit Peginterferon alfa und Ribavirin.
Vorherige Non-Responder (einschließlich partieller und Null-Responder) mit HCV-Genotyp 1 oder 4[1]	OLYSIO + Peginterferon alfa + Ribavirin[2]	48 Wochen Die Behandlung mit OLYSIO muss in Kombination mit Peginterferon alfa und Ribavirin begonnen und über einen Zeitraum von 12 Wochen fortgeführt werden, gefolgt von einer weiteren 36-wochigen Behandlung mit Peginterferon alfa und Ribavirin.
Patienten mit HCV-Genotyp 1 oder 4, unabhängig von vorherigen Behandlungen[4]	OLYSIO + Sofosbuvir (+/– Ribavirin)[5]	12 Wochen (siehe Abschnitte 4.4, 4.8 und 5.1)

[1] Einschließlich Patienten mit oder ohne Zirrhose und mit dem humanen Immundefizienzvirus (HIV) koinfizierte Patienten. Relapse oder Non-Response nach Vortherapie mit Interferon (pegyliert oder nicht pegyliert), mit oder ohne Ribavirin (siehe Abschnitt 5.1).

[2] Wird eine Therapie mit OLYSIO, Peginterferon alfa und Ribavirin bei Patienten mit HCV-Genotyp 1a erwogen, soll vor Behandlungsbeginn eine Untersuchung auf einen NS3-Q80KPolymorphismus durchgeführt werden (siehe Abschnitt 4.4).

[3] Therapienaive Patienten und vorherige Relapser mit Zirrhose und HIV-Koinfektion sollten 48 Wochen behandelt werden. Die Therapie mit OLYSIO muss in Kombination mit Peginterferon alfa und Ribavirin uber einen Zeitraum von 12 Wochen eingeleitet werden, gefolgt von einer weiteren 36-wochigen Behandlung mit Peginterferon alfa und Ribavirin. Siehe „Besondere Patientengruppen – HCV/HIV-1(humanes Immundefizienzvirus Typ 1)-Koinfektion“.

[4] Einschließlich therapienaiven Patienten oder Patienten mit vorherigem Therapieversagen unter Peginterferon alfa und Ribavirin, mit oder ohne Zirrhose.

[5] OLYSIO in Kombination mit Sofosbuvir sollte nur bei Patienten angewendet werden, bei denen Interferon nicht geeignet ist oder die es nicht vertragen und bei denen eine Behandlung dringend ist. Basierend auf einer klinischen Bewertung jedes einzelnen Patienten kann Ribavirin hinzugefügt werden (siehe Abschnitte 4.4, 4.8 und 5.1). Die empfohlene Behandlungsdauer beträgt 12 Wochen. Eine längere Behandlungsdauer mit OLYSIO zusammen mit Sofosbuvir (mit oder ohne Ribavirin) (bis zu 24 Wochen) kann im Einzelfall in Betracht gezogen werden (siehe Abschnitte 4.4, 4.8 und 5.1).

Daclatasvir
Daklinza®
(J05AX14)

Daklinza wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Infektion mit dem Hepatitis-C-Virus (HCV) bei Erwachsenen angewendet (siehe Abschnitte 4.2, 4.4 und 5.1).

Zur spezifischen Aktivität gegen die verschiedenen HCV-Genotypen, siehe Abschnitte 4.4 und 5.1

Abschnitt 4.2 der Fachinformation:

Tabelle 1: Empfehlungen zu Behandlungsregimen und Behandlungsdauer für die Kombinationstherapie mit Daklinza®

HCV Genotyp und Patientenpopulation*	**Behandlung**	**Behandlungsdauer**
Genotyp 1 oder 4 ohne Zirrhose	Daklinza + Sofosbuvir	12 Wochen Bei vorbehandelten Patienten, deren Therapie auch einen NS3/4A-Proteaseinhibitor beinhaltete, ist zu erwägen, die Behandlung auf 24 Wochen zu verlängern (siehe Abschnitte 4.4 und 5.1).
Genotyp 1 oder 4 mit kompensierter Zirrhose	Daklinza + Sofosbuvir	24 Wochen Bei vorher unbehandelten Patienten mit Zirrhose und positiven Prognosefaktoren, wie IL28B-CC-Genotyp und/oder niedrige Ausgangsvirenlast, kann erwogen werden, die Behandlung auf 12 Wochen zu verkürzen. Bei Patienten mit weit fortgeschrittener Lebererkrankung oder anderen negativen Prognosefaktoren, wie Vorbehandlung, kann die zusätzliche Anwendung von Ribavirin erwogen werden.
Genotyp 3 mit kompensierter Zirrhose und/oder behandlungserfahren	Daklinza + Sofosbuvir + Ribavirin	24 Wochen

<table>
<tr><td></td><td>
<table>
<tr><td>Genotyp 4</td><td>Daklinza
+ Peginterferon alfa
+ Ribavirin</td><td>24 Wochen Daklinza in Kombination mit 24 – 48 Wochen Peginterferon alfa und Ribavirin

Wenn der Patient nicht-nachweisbare HCV-RNA-Titer sowohl in Woche 4 als auch in Woche 12 erreicht, sollten alle 3 Komponenten des Regimes insgesamt 24 Wochen angewendet werden. Wenn der Patient nicht-nachweisbare HCV-RNA-Titer erreicht, jedoch nicht in Woche 4 sowie in Woche 12, sollte Daklinza nach 24 Wochen abgesetzt werden, aber die Behandlung mit Peginterferon alfa und Ribavirin für eine Gesamtdauer von 48 Wochen weitergeführt werden.</td></tr>
</table>
*Für das 12-wochige Behandlungsregime Daklinza + Sofosbuvir liegen nur Daten für therapienaive Patienten mit Genotyp-1-Infektion vor. Für Daklinza + Sofosbuvir mit oder ohne Ribavirin liegen Daten für Patienten mit fortgeschrittener Lebererkrankung (≥ F3) ohne Zirrhose vor (siehe Abschnitte 4.4 und 5.1). Die empfohlene Anwendung von Daklinza + Sofosbuvir bei Genotyp-4-Infektion beruht auf einer Extrapolation der Genotyp-1-Daten. Für das Regime von Daklinza + Peginterferon alfa + Ribavirin liegen Daten für behandlungsnaive Patienten vor (siehe Abschnitt 5.1).
</td></tr>
<tr><td>Ledipasvir/Sofosbuvir
Harvoni®
(J05AX65)</td><td>
Harvoni wird bei Erwachsenen zur Behandlung der chronischen Hepatitis C (CHC) 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:

Empfohlene Dauer der Behandlung mit Harvoni und empfohlene kombinierte Anwendung mit Ribavirin für bestimmte Subgruppen (Tabelle 1 der FI).
<table>
<tr><th>Patientengruppe*</th><th>Behandlung</th><th>Behandlungsdauer</th></tr>
<tr><td colspan="3">Patienten mit CHC vom Genotyp 1 oder Genotyp 4</td></tr>
<tr><td>Patienten ohne Zirrhose</td><td>Harvoni</td><td>12 Wochen

8 Wochen können bei therapienaiven Patienten mit einer Infektion vom Genotyp 1 in Betracht gezogen werden
(siehe Abschnitt 5.1, ION-3-Studie).

24 Wochen sind bei vorbehandelten Patienten mit ungewissen nachfolgenden Optionen für eine Wiederbehandlung in Betracht zu ziehen (siehe Abschnitt 4.4).).</td></tr>
</table>
</td></tr>
</table>

Patienten mit kompensierter Zirrhose	Harvoni	24 Wochen 12 Wochen können bei Patienten mit einem geringen Risiko einer klinischen Krankheitsprogression, die nachfolgend Optionen für eine Wiederbehandlung haben, in Betracht gezogen werden (siehe Abschnitt 4.4).
Patienten mit dekompensierter Zirrhose bzw. vor oder nach Lebertransplantation	Harvoni + Ribavirin	24 Wochen (siehe Abschnitte 4.4 und 5.1).
Patienten mit CHC vom Genotyp 3		
Patienten mit Zirrhose und/oder Versagen einer vorherigen Behandlung	Harvoni + Ribavirin	24 Wochen (siehe Abschnitte 4.4 und 5.1).

*Einschließlich Patienten mit Koinfektion mit dem humanen Immundefizienzvirus (HIV).

Quellen: AMIS-Datenbank, Fachinformationen

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

Indikation für die Recherche für ABT-450/r/ABT-267 mit ABT-333 in Kombination mit Ribavirin

ABT-450/r/ABT-267 mit ABT-333 in Kombination mit Ribavirin zur Behandlung der chronischen Hepatitis C vom Genotyp 1.

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

Die Proteaseinhibitoren Telaprevir und Boceprevir sind für Patienten mit einer HIV – Koinfektion nicht zugelassen.

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 159 eingeschlossene Quellen, die anschließend im Volltext überprüft wurden. Daraus konnten 58 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
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 Fachberatung Medizin des G-BA:** 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 Fachberatung Medizin des G-BA:** 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:** Primäre Endpunkte: 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. Fazit der Autoren:

	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 Fachberatung Medizin des G-BA:** 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 chronic hepatitis C genotype 1 infected slowresponder adult patients.	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. **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:** <u>Primäre Endpunkte:</u> Overall mortality; HCV-related mortality; Liver-related morbidity <u>Sekundäre Endpunkte:</u> 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 / HTA

Alavian 2011: Optimal Duration of Treatment for HCV Genotype 1 Infection in Slow Responders: A Meta-Analysis.	*Systematischer Review mit einer Metaanalyse zum Vergleich einer 72-Wochen vs. 48-Wochen anti-HCV Therapie mit Peg-Interferon und Ribavirin.* Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** Zusammenfassen der Ergebnisse von Studien, welche die optimale Behandlungsdauer für HCV-Patienten vom **Genotyp 1-Infektion** bei „slow responders“ beinhalten. **Suchzeitraum:** k.A. **Endpunkte:** SVR-Rate **Anzahl der Patienten:** 1206 Patienten **Anzahl der Studien:** 7 Studien **Ergebnisse** (basierend auf 7 Studien (alles RCTs): • Slow virological responders, welche die 72-wöchige Therapie erhielten, hatten eine signifikant höhere Wahrscheinlichkeit für das

<table>
<tr><td></td><td>Erreichen SVR als Patienten, die die 48-wöchige Therapie erhielten [RR = 1.44 (95% CI, 1.20–1.73)]

<u>Fazit der Autoren:</u> Die Meta-Analyse zeigte, dass die 72-wöchige Therapie mit Peginterferon und Ribavirin deutlich besser ist, als die Standard-48-wöchige Therapie in „slow responders“ mit HCV vom Genotyp 1-Infektion.</td></tr>
<tr><td>Canadian Agency for Drugs and Technologies in Health 2012: Boceprevir and Telaprevir for Chronic Hepatitis C Infection.</td><td>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]
<table><tr><th>Trial</th><th>SVR for Patients Treated with Boceprevir plus PR</th><th>SVR for Patients Treated with Placebo plus PR</th></tr><tr><td>SPRINT-2: Treatment-naive patients</td><td>63% to 66%</td><td>38%</td></tr><tr><td>RESPOND-2: Patients with a history of non-response or relapse on PR</td><td>59% to 66%</td><td>21%</td></tr><tr><td>Study 5685: Patients with a history of non-response or relapse on PR</td><td>64%</td><td>21%</td></tr></table>PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.

For telaprevir:[2]
<table><tr><th>Trial</th><th>SVR for Patients Treated with Telaprevir plus PR</th><th>SVR for Patients Treated with Placebo plus PR</th></tr><tr><td>ADVANCE: Treatment-naive patients</td><td>75%</td><td>44%</td></tr><tr><td>REALIZE: Treatment-experienced patients</td><td>64% to 66%</td><td>16%</td></tr></table>PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.</td></tr>
<tr><td>Chou 2013: Comparative Effectiveness of Antiviral Treatment for Hepatitis C Virus Infection in</td><td>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%

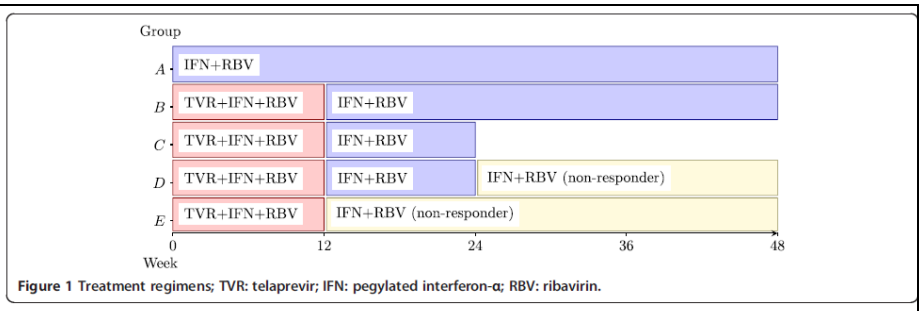
Fragestellung: To compare benefits and harms of antiviral regimens for chronic HCV infection in treatment-naive adults.</td></tr>
</table>

Adults: A Systematic Review.	**Suchzeitraum:** 1947 bis August 2012 **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:** von Beginn der jeweiligen DB bis Oktober 2011 **Endpunkte:** <u>Primäre Endpunkte:</u> dauerhaftes virologisches Ansprechen, Rezidive und Therapieabbruch; <u>Sekundäre Endpunkte:</u> 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) <u>Fazit der Autoren:</u> 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 hepatitis C patients: an indirect comparison using Bayesian network meta-analysis.	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. **Suchzeitraum:** Januar 2000 bis Juli 2011 **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 September 2010 **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 5 Studien **Endpunkte:** Primäre Endpunkte: SVR-Rate, end of treatment response (ETR); Sekundäre Endpunkte: 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.
Flori 2013: Pegylated interferon-α2a and ribavirin versus pegylated interferon-α2b and ribavirin in chronic hepatitis C : a meta-analysis.	1. Fragestellung Our objective was to determine which PEG-IFN (α2a or α2b), in association with ribavirin, is the most effective for the treatment of chronic hepatitis C by performing an updated meta-analysis.
	2. Methodik Population: Adult patients with chronic hepatitis C (Studies including HIV-positive patients or liver transplant recipients were excluded) Vergleich: (PEG-IFN)-α2a vs. PEG-IFN-α2b Endpunkte: sustained virologic response (SVR) Suchzeitraum (Aktualität der Recherche): 1950-2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 26 studies (n=18,260)
	3. Ergebnisdarstellung

	a. 11 der eingeschlossenen Studien waren RCTs (15 Studien keine RCTs) / von den eingeschlossenen Patienten wurden 8,125 mit PEG-IFN-α2a und 10,135 mit PEG-IFN-α2b behandelt b. Meta-analysis that included randomized trials only: • SVR was significantly higher for patients treated with PEG-IFN-α2a than for those treated with PEG-IFN-α2b for genotypes 1 and 4 [odds ratio (OR) 1.45; 95 % CI 1.09-2.06; p = 0.013] and for all genotypes (OR 1.34; 95 % CI 1.05-1.72; p = 0.02) In the meta-analysis including both randomized and non-randomized studies: • SVR was significantly higher for PEG-IFN-α2a than for PEG-IFN-α2b for all genotypes (OR 1.24; 95 % CI 1.10-1.40; p < 0.001) and for genotypes 1 and 4 (OR 1.25; 95 % CI 1.14-1.36; p < 0.001); for genotypes 2 and 3, the SVR was greater for treatment with PEG-IFN-α2a than with PEG-IFN-α2b, with the difference tending towards significance (OR 1.15; 95 % CI 0.98-1.35; p = 0.08).
	4. Anmerkungen/Fazit der Autoren Current evidence suggests that PEG-IFN-α2a and ribavirin is associated with a higher SVR than PEG-IFN-α2b and ribavirin in patients mono-infected with hepatitis C, particularly for genotypes 1 and 4.
Goralcyk 2013: 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.	1. Fragestellung 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.
Hartwell 2011: Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation.	Systematischer Review ohne Meta-Analyse zu Telaprevir**.** Patienten vom Genotyp 1, 2 und 3. Patienten mit einer HIV/HCV-Koinfektion. **Fragestellung**: To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C virus (HCV) in three specific patient subgroups affected by recent licence changes: those eligible for shortened treatment courses [i.e. those with low viral load (LVL) and who attained a rapid virological response (RVR) at 4 weeks of treatment], those eligible for re-treatment following previous nonresponse or relapse, and those co-infected with human immunodeficiency virus (HIV). **Suchzeitraum:** Bis Oktober 2009 **Endpunkte:** sustained virological response (SVR), relapse rate and adverse events **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 4 Studien **Ergebnisse** (basierend auf 4 RCTs): • All six included RCTs were in patients who were eligible for shortened treatment duration. • No RCTs comparing peginterferon alfa with or without ribavirin with BSC were identified for the HCV/HIV co-infection or re-treatment

	patient groups. • In the subgroup of patients who achieved an RVR and had LVL at baseline, SVR rates were comparable (i.e. no statistically significant differences) between groups who received the standard duration of treatment and those who received shortened courses, for both genotype 1 and genotypes 2 and 3. This implies that this patient group can receive shortened courses of peginterferon combination therapy without compromising SVR rates. • For both genotype 1 and genotype 2 and 3 patients, there were no statistically significant differences in rates of RVR between treatment groups who received the standard duration of treatment and those who received shortened courses. Rates of RVR in genotype 2/3 patients were observed to be generally higher than in genotype 1 patients. • Relapse rates in the subgroup of patients with LVL and RVR (one trial) were low and not significantly different between those treated for 24 versus 48 weeks. • Treatment for 24 weeks resulted in a significantly lower biochemical response rate (reduction of ALT to normal levels) and histological response rate than 48 weeks of treatment in one trial of genotype 1 patients. Shortening the treatment duration had no effect on biochemical response in one trial of genotype 2/3 patients. Rates of biochemical and histological response should be treated with caution, as the results relate only to those patients with available data and rates were not reported in the subgroup of patients with LVL and RVR. • Adverse events were presented for treatment groups as a whole and the reporting of statistical tests varied. However, the most frequently occurring adverse events were similar across all the trials and included flu-like symptoms, insomnia, anorexia, dermatological symptoms and alopecia. • There was a trend for a lower incidence of adverse events in patients who were treated for a shorter duration (three trials), although statistically they were comparable between treatment arms. The incidence of dose discontinuations was significantly lower in those receiving a shortened treatment regimen in one trial. <u>Fazit der Autoren:</u> The clinical trial evidence indicates that patients may be successfully treated with a shorter course of peginterferon combination therapy without compromising the likelihood of achieving an SVR.
Parikh 2011: Extended treatment duration for treatment naive chronic hepatitis C genotype 1 late viral responders: a meta-analysis comparing 48 weeks vs 72 weeks of	Systematischer Review mit Meta-Analyse zum Vergleich einer 48-Wochen vs. 72-Wochen Therapie mit Peg-Interferon+Ribavirin. 5 RCTs in die Analyse eingeschlossen. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen. **Fragestellung**: In this study, we undertook a systematic review of the literature and performed a metaanalysis to compare 72 weeks of treatment to the standard duration of 48 weeks in HCV genotype I patients with LVR. **Suchzeitraum:** 2004 bis 2010 **Anzahl der Patienten:** k.A.**Anzahl der Studien:** 5 Studien

pegylated interferon and ribavirin. J Viral Hepat **2011**; 18 (4): e99-103.	**Endpunkte:** End of Treatment Response, sustained virological response (SVR), Rückfallraten **Anzahl der Patienten:** k.A**.** **Anzahl der Studien:** 5 Studien **Ergebnisse** (basierend auf 5 Studien)**:** • End of Treatment Response [Response bei Behandlungsende]: kein stat. sign. Unterschied • SVR: 25% für 48 Wochen vs. 32% für 72 Wochen mit einem OR 1,67 (1,16–2,40) und p=0,006, I^2=0%. • Rückfallraten: 55% für 48 Wochen vs. 35% für 72 Wochen mit einem OR 0,39 (0,25-0,61) und p<0,0001, I^2=0%. <u>Fazit der Autoren:</u> „Extending the treatment duration from 48 to 72 weeks in genotype 1 infected patients with late virological response improves SVR. Thus, therapy extension in genotype 1 late viral responders (LVR) may be a consideration to improve treatment response; however, the proportion of patients with LVR that might benefit from 72-week therapy appears to be small."
Park 2013: Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype 1: a meta-analysis.	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 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 c. 10 der eingeschlossenen Studien speziell für Fragestellung bzw. Patientenpopulation) 4421 der eingeschlossenen Patienten speziell für Fragestellung d. 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.
Romero Gómez 2013: Meta-analysis: pegylated interferon a-2a achieves higher early virological responses than a-2b in chronic hepatitis C.	1. Fragestellung To compare RVR and EVR rates of peginterferon a-2a vs. peginterferon a-2b through a meta-analysis of previously published randomised control trials (RCT).
	2. Methodik Population: chronic hepatitis C patients >18 years (RCT including patients with human immunodeficiency virus or hepatitis B virus co-infection, haemophilia, decompensated liver cirrhosis, hepatocellular carcinoma and liver or renal transplantation were excluded) Intervention: peginterferon α-2a Komparator: peginterferon α-2b Endpunkte: Rapid virological response (RVR), complete early virological response (cEVR) Suchzeitraum (Aktualität der Recherche): bis 09/2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 RCTs (n=4566 patients)
	3. Ergebnisse *cEVR included seven trials (n = 4359)* Estimated effect in favour of peginterferon a-2a: - Crude Efficacy (CEf) was 53.3% vs. 43.8%, RE = 1.118 (CI 95% = 1.039–1.203; P = 0.0028) - Heterogeneity Q = 8.959; I2 = 33.0% (P = 0.1759) - A sub-analysis of three studies with 3409 genotype-1 patients yielded CEf: 49.4% vs. 40.2%, RE = 1.151 (CI 95% = 0.968–1.369; P = 0.1124), Q = 9.802; I2 = 79.6% (P = 0.0074) *RVR included five trials (n = 3833)* Estimated effect in favour of peginterferon a-2a: - CEf = 25.0% vs. 16.8%, RE = 1.151 (CI 95%:1.042–1.272; P = 0.0056), Q = 1.461; I2 = 0.0% (P = 0.8335) - Analysis of four studies reporting RVR including 3499 patients with genotypes 1 and 4 resulted in CEf: 18.3% vs. 12.7% RE = 1.206 (CI 95% = 1.059–1.374; P = 0.0048), Q = 1.116; I2 = 0.0% (P = 0.7733).
	4. Anmerkungen/Fazit der Autoren Peginterferon α-2a may be associated with a higher cEVR and RVR than peginterferon α-2b. These findings could help to achieve higher SVR rates and support clinical decision-making in the present scenario of triple combination therapy.

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 Oktober 2012 **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. <u>Fazit der Autoren:</u> 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 Januar 2011 **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%. <u>Fazit der Autoren:</u> "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; 26 (4): 205-10.	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. **Suchzeitraum:** bis September 2011 **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.

Leitlinien

Allgemeine Empfehlungen

<table>
<tr><td rowspan="3">EASL 2014: EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.</td><td>Leitlinie der European Association for the Study of the Liver (EASL)</td></tr>
<tr><td>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):

<table>
<tr><th>Evidence quality</th><th>Notes</th><th>Grading</th></tr>
<tr><td>High</td><td>Further research is very unlikely to change our confidence in the estimate of effect</td><td>A</td></tr>
<tr><td>Moderate</td><td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td><td>B</td></tr>
<tr><td>Low</td><td>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</td><td>C</td></tr>
<tr><th>Recommendation</th><th>Notes</th><th>Grading</th></tr>
<tr><td>Strong</td><td>Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost</td><td>1</td></tr>
<tr><td>Weak</td><td>Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption</td><td>2</td></tr>
</table>
</td></tr>
<tr><td>Empfehlungen:
• 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) 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</td><td>AASLD Practice Guidelines</td></tr>
<tr><td>Methodik
Grading System for Recommendations:</td></tr>
</table>

<table>
<tr><td rowspan="2">Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases.</td><td>
<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:
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 <u>www.sign.ac.uk/guidelines/fulltext/50/index.html</u>.</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

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].

Children and Hepatitis C

- Children infected with all genotypes of hepatitis C with evidence of moderate or severe liver disease should be considered for treatment with pegylated IFN and ribavirin[A].
- Children infected with HCV genotypes 2 and 3 should be considered for treatment with pegylated IFN and ribavirin irrespective of disease stage[B].
- In children with mild disease and infection with other genotypes, benefits of treatment need to be balanced against risks of side effects[C].

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.
Christensen 2012: Treatment for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection - Danish national guidelines 2011.	**Monitoring during treatment** **Patients with genotype 1** • For patients with genotype 1 treated with pegylated interferon-alpha/ribavirin/telaprevir HCV-RNA should be measured after 4, 8, and 12 weeks of treatment. Telaprevir is administered for 12 weeks. For patients without cirrhosis, who have undetectable HCV-RNA at both 4 and 12 weeks of treatment, pegylated interferon-alpha and ribavirin can be stopped after 24 weeks. • For patients with HCV-RNA >1000 IU/mL at either 4 or 12 weeks of treatment, and/or detectable HCV-RNA after 24 weeks, treatment must be stopped as it is unlikely to lead to SVR. • For patients with genotype 1 treated with pegylated interferon-alpha/ribavirin/boceprevir after a lead-in phase of pegylated interferon-alpha/ribavirin HCV-RNA should be measured after 4, 8, 12, and 24 weeks of treatment. If HCV-RNA is negative at these measurements, treatment can be stopped after 28 weeks (4 weeks of lead in with pegylated interferonalpha/ ribavirin and 24 weeks of pegylated interferon-alpha /ribavirin/boceprevir). Patients who are HCV-RNA positive at week 8 and negative week 24 should continue tipple therapy until week 36 and receive an additional 12 weeks of pegylated interferon-alpha/ribavirin (total treatment duration 48 weeks). • If HCV-RNA is > 100 IU/mL after 12 weeks of treatment or positive after 24 weeks, treatment must be stopped, as it is unlikely to lead to SVR. • If lead-in is used and the patient has a RVR, then treatment with

	pegylated interferon-alpha/ribavirin, without DAAs, is continued for a total of 24 weeks. HCV-RNA should be measured after 4, 12, and 24 weeks. • If HCV-RNA has not decreased by 2 log after 12 weeks or is detectable after 24 weeks of treatment, treatment must be stopped as the likelihood to obtain SVR is <2%. • All patients negative of HCV-RNA 24 weeks after end of treatment are cured for hepatitis C.
	Anmerkungen Fachberatung Medizin des G-BA:
	• Systematische Literaturrecherche. k.A. • LoE und GoR: k.A.
Brok 2010: European Guideline for the management of Hepatitis B and C virus infections.	• 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 Fachberatung Medizin des G-BA:
	• Evidenzbasierte LL
de Bruijne 2008: Treatment of chronic hepatitis C virus infection – Dutch national guidelines.	**Recommendations:** • Antiviral therapy consists of the administration of peginterferon and ribavirin for 24 or 48 weeks. Patients with HCV genotype 1 or 4 are treated for 48 weeks (Level 1). • In patients with an undetectable HCV RNA after 4 weeks of treatment and baseline HCV RNA <600,000 IU/ml, a shorter treatment is equally effective (24 weeks for HCV genotype 1 with baseline HCV RNA ≤600,000 IU/ml) (Level 1).
	Anmerkungen Fachberatung Medizin des G-BA:
	Grade Definition: • Level 1, Study of level A1 or at least two independent studies of level A2
Makara 2012: [Hungarian consensus guideline for the diagnosis and treatment of B, C, and D viral hepatitis.] Ajanlas a B-, a C- es a D-virus hepatitisek diagnosztikajara es antiviralis kezelesere. Orv Hetil 2012; 153 (10): 375-	Leitlinie in Ungarisch! Angaben lediglich dem Abstract entnommen!!! • „Naive Patienten mit chronischer Hepatitis C sollten zunächst eine Kombinationstherapie aus Interferon (pegylated) und Ribavirin erhalten." • Wenn die Response bei Genotyp 1 Patienten nach 4 oder 12 Wochen unzureichend ausfällt, wird die Gabe von Boceprevir oder Telaprevir empfohlen. Die Behandlungsdauer beträgt i.d.R. 48 Wochen, bei früher viraler Response wird eine kürzere Behandlung empfohlen. • Treatment-failure Patienten mit Genotyp 1 Infektion sollten für die Dauer von 48 Wochen eine Dreifachtherapie mit einem Protease-

94.	Inhibitor bekommen. Allerdings ist bei einem Rückfall (relapse) ohne Zirrhose und mit schneller viraler Response eine kürzere Behandlungen mit Telaprevir ausreichend. **Anmerkungen Fachberatung Medizin des G-BA:** • Systematische Literaturrecherche. nicht im Abstract angegeben • LoE und GoR: k.A.
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection.	• 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 Fachberatung Medizin des G-BA:** • 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 2013: Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people.	NICE technology appraisal guidance Peginterferon alfa-2a plus ribavirin and peginterferon alfa-2b plus ribavirin are recommended as treatment options, within their licensed indications, for children and young people with chronic hepatitis C. Empfehlungen: • The Committee agreed that peginterferon alfa (2a and 2b) plus ribavirin were more effective and less costly than best supportive care across all genotypes, and it was certain that addressing the shortcomings identified in the economic evaluations presented would not alter its conclusion. The Committee was not convinced that there was sufficient evidence to recommend 1 treatment over the other.

NICE 2012: Boceprevir for the treatment of genotype 1 chronic hepatitis C.	• 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 Fachberatung Medizin des G-BA:
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal

NICE 2012: Telaprevir for the treatment	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:

of genotype 1 chronic hepatitis C.	• 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 Fachberatung Medizin des G-BA:
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2010: Peginterferon alfa 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 virological response after 48 weeks of therapy.
	Anmerkungen Fachberatung Medizin des G-BA:
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
Ghany 2009: Diagnosis, Management, and Treatment of Hepatitis C: An Update.	*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 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 Guideline by the American	• 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**).

Association for the study of Liver diseases. Hepatology **2011**; 54(4):1433-44.	**Anmerkungen Fachberatung Medizin des G-BA:** • Evidenzbasierte LL
Haute Autorité de Santé (HAS) **2012 :** Hepatite chronique C. Guide ALD no 6, Actes et prestations sur l'hepatite chronique C. Stand: Juni 2012.	• Behandlungsstandard: Genotype 1, in Abhängigkeit vom Polymorphismus IL28-B: - IFN PEGα-2a oder IFN PEGα-2b + ribavirine: • Dreifachthérapie (mit boceprevir bzw. telaprevir), möglich für folgende Patienten : génotype 1 - therapienaiv oder Versager unter vorheriger Therapie bei nicht-dekompensierter Lebererkrankung: - IFN PEGα-2a ou IFN PEGα-2b + ribavirine + boceprevir oder telaprevir
	Anmerkungen Fachberatung Medizin des G-BA: Methodik der Leitlinienerstellung ungenügend beschrieben, so dass Beurteilung der methodischen Qualität nicht möglich; aufgrund Aktualität dennoch aufgenommen
Ramachandran 2012: UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients. Aliment Pharmacol Ther 2012; 35 (6): 647-62	CONSENSUS STATEMENTS 1. Which patients to treat? • Due to the improvements in cure rates and potential for shortened therapy, protease inhibitor-based regimens should be considered for all genotype 1 chronic HCV-infected patients. This is applicable for treatmentnaïve patients and patients who have had virological failure following prior exposure to SoC [Standard of care] therapy 2. Which treatment regimens to use? **(a) Which peginterferon-ribavirin to use?** The treatment regimens used differ between the two PIs and the different trials. One critical difference between the studies is the use of different peginterferonribavirin preparations and doses. In general, in the boceprevir studies, pegylated IFN-a2b (PegIntron; Merck, Whitehouse Station, NJ, USA) at a dose of 1.5 lg/kg once weekly and ribavirin (Rebetol; Merck) at weightbased dose of 600–1400 mg daily in two divided doses were used. In the telaprevir studies, pegylated IFN-a2a (Pegasys; Roche, Welwyn Garden City, UK) at a dose of 180 lg/week and ribavirin (Copegus; Roche) at a weight dependent dose of 1000 mg (<75 kg) or 1200 mg (_75 kg) per day were used. Direct comparison studies between Peg IFN-a2a and Peg IFN-a2b in SoC treatment have not shown any significant difference in overall response rates.10 Furthermore, in small studies, telaprevir has been used with Peg IFN-a2b45 and boceprevir with IFN-a2a46 with no detrimental effect. **(i) Peg IFN-a2a or Peg IFN-a2b can be used interchangeably with either telaprevir or boceprevir according to local preferences.** **(ii) Ribavirin brands can be used interchangeably in treatment regimens.** **(b) Which protease inhibitor to use?** The documented evidence clearly shows a benefit for the use of either

	boceprevir or telaprevir as part of a triple therapy regimen in both treatment-naïve patients and patients with previous virological failure. Largely, the magnitude of beneficial effect is similar for either drug. No direct comparison studies between boceprevir and telaprevir have been conducted, and thus, neither drug can be recommended over the other. However, specific characteristics of each drug may lead to their use in certain circumstances. Boceprevir-based regimens use a 4-week lead-in with peginterferon-ribavirin, which may offer extra information on treatment tolerability and the likelihood of achieving an SVR. In addition, differences in side-effect profiles and the duration of treatment may lead to the choice of either PI for specific patients. Furthermore, the pill burden for patients differs, with boceprevir currently four tablets t.d.s., whereas telaprevir is two tablets t.d.s. It is therefore important that both drugs are available to treating units to enable selection of the most appropriate regimen for individual patients. **(i) Both boceprevir and telaprevir are effective and should be available for use by treating units.** <u>ADVERSE EFFECTS</u> • Whilst the appropriate use of PIs with peginterferon+ribavirin provides significant increases in cure rates of genotype 1 chronic HCV infection, there is also an increased rate of adverse effects with the use of triple therapy. • … the principal side-effects associated with **boceprevir** treatment are dysgeusia (altered sense of taste), anaemia and neutropenia. The dysgeusia does not usually need any alteration in treatment. Dose reduction of boceprevir should not be used in the management of adverse effects, as suboptimal dose will promote the emergence of resistant species in failing regimens. • With **telaprevir** treatment regimens, the adverse effect profile is slightly different from boceprevir. Studies have shown an increase in skin rash and anorectal symptoms (discomfort and pruritus) with telaprevir treatment. The anorectal symptoms are usually tolerable for the duration of telaprevir treatment, and rarely (0.5%) led to discontinuation. One of the principal adverse events in telaprevir treatment is rash. This leads to discontinuation of telaprevir in 5–7% of cases,19, 21, 41 at which point the rash invariably resolves (although this may take several weeks). The rash is predominantly eczematous and pruritic. Fifty percent of patients developing rash do so within the first 4 weeks of treatment, although it can occur at any time. <u>The provision of care</u> (a) Due to the importance of RGT and stopping rules in PI-based regimens and the increased risk of adverse effects, the use of PI treatment should be limited to centres providing the following standards of care: (i) Adherence to national standards for HCV. (ii) Continuous audit of SVR rates to therapy. (iii) Continuous audit of treatment discontinuation rates. (iv) A high level of expertise in the use of antiviral drugs.

	(v) Access to viral load estimation results within five working days of sampling. (vi) Access to HCV PCR with a lower limit of detection of at most 15 IU/mL.43 (vii) Access to non-invasive investigations and/or liver biopsy to assess the degree of hepatic fibrosis. (viii) Sufficient specialised medical and nursing staff to provide year round support to patients on therapy. (ix) A series of protocols to minimise the risk of developing and to manage adverse reactions to therapy. (x) A comprehensive and skilled consultation service for patients emphasising the risks and benefits of therapy along with the requirement for adherence. (b) Where possible, all patients should be invited to participate in ongoing research initiatives (e.g. enrolment to the HCV research UK3 database). (c) Ongoing recruitment to clinical trials should continue where feasible.
	Anmerkungen Fachberatung Medizin des G-BA:
	Methodik der Leitlinienerstellung ungenügend beschrieben, so dass Beurteilung der methodischen Qualität nicht möglich; aufgrund Aktualität dennoch aufgenommen
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: 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.	**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 Fachberatung Medizin des G-BA:
	Evidenzbasierte LL

Leitlinien – Therapienaive Patienten

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 Guidelines
	Methodik Grading System for Recommendations: **Classification** — **Description** 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 favor 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/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 non-randomized studies Level C — Only consensus opinion of experts, case studies, or standard-of-care
	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.	**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 <u>without cirrhosis</u> 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 <u>without cirrhosis</u> 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 Fachberatung Medizin des G-BA:** • Evidenzbasierte LL
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection.	• 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 Fachberatung Medizin des G-BA:
	• 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.	*Recommendations:* • 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 Fachberatung Medizin des G-BA:
	• Evidenzbasierte LL
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: 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.	*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, 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).
	Anmerkungen Fachberatung Medizin des G-BA:
	• Evidenzbasierte LL
Sarazzin 2010: Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der **Hepatitis-C-Virus (HCV)-Infektion.**	**Nicht vorbehandelte Patienten** Empfehlung: • 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 Fachberatung Medizin des G-BA:
	• 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

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 Guidelines
	Methodik Grading System for Recommendations:

Classification	Description
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 favor 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/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 non-randomized studies
Level C	Only consensus opinion of experts, case studies, or standard-of-care

	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 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.	**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 Fachberatung Medizin des G-BA:
	• 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	**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**.)

diseases. Hepatology **2011**; 54(4):1433-44.	• 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 Fachberatung Medizin des G-BA:
	• Evidenzbasierte LL
Leroy 2012: Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French Association for the Study of the Liver.	Recommendations: • 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 Fachberatung Medizin des G-BA:
	• Evidenzbasierte LL
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: 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. 53	**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 Fachberatung Medizin des G-BA: • Evidenzbasierte LL
Sarazin 2010: Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der **Hepatitis-C-Virus (HCV)-Infektion.**	**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 Fachberatung Medizin des G-BA:
	• 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

Hull 2013: CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of	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

HIV/hepatitis C coinfection in adults.	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.	• 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 Fachberatung Medizin des G-BA:** • Evidenzbasierte LL
Brook 2010: British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010.	<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 Fachberatung Medizin des G-BA:** • Evidenzbasierte LL
Ghany 2009: Diagnosis, Management, and	<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).

Treatment of Hepatitis C: An Update.	• 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 Fachberatung Medizin des G-BA:
	• Evidenzbasierte LL
EASL Clinical Practice Guidelines 2011: Management of hepatitis C virus infection.	<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 Fachberatung Medizin des G-BA:
	• 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 Fachberatung Medizin des G-BA:
	• 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 Fachberatung Medizin des G-BA:
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2010: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.	***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 Fachberatung Medizin des G-BA:
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
New York State Department of Health (NYSDH) 2010: Hepatitis C virus.	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 Fachberatung Medizin des G-BA:
	• 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 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.	*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 Fachberatung Medizin des G-BA:
	• Evidenzbasierte LL
Sarazin 2010: Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: Leitlinie Prophylaxe, Diagnostik und Therapie der **Hepatitis-C-Virus (HCV)-Infektion.**	*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 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 Fachberatung Medizin des G-BA:
	• 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.	**Recommendations:** • 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 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.	**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**).

Zusätzliche Referenzen

Sarazin 2012: Expertenempfehlungen zur Triple-Therapie der HCVInfektion mit Boceprevir und Telaprevir.	**Genotyp 1:** *Ersttherapie:* • Unvorbehandelte Patienten mit HCV-Genotyp-1-Infektion profitieren signifikant von der Triple-Therapie und sollten primär mit einer proteaseinhibitorbasierten Therapie behandelt werden. • Bei unvorbehandelten Patienten mit günstigen Voraussetzungen für ein rasches virologisches Ansprechen (RVR) auf eine PEG-Interferon/Ribavirin Therapie (d. h. keine fortgeschrittene Fibrose, HCVRNA < 600 000 – 800 000 IU/ml, günstiger IL28B-Genotyp) kann auch primär eine alleinige Therapie mit PEG-Interferon plus Ribavirin erwogen werden. • Dies sollte individuell mit dem Patienten besprochen werden. *Re-Therapie:* • Bei Patienten mit fehlendem dauerhaften Ansprechen auf eine antivirale Vortherapie leitet sich die prinzipielle Indikation zur Re-Therapie aus der bereits erfolgten Vorbehandlung ab. • Therapieerfahrene Patienten mit HCV-Genotyp-1-Infektion ohne dauerhaftes virologisches Ansprechen (SVR) sollten eine Re-Therapie mit einem Proteaseinhibitor basierten Regime erhalten. • Das individuelle Ausmaß des Ansprechens (virale Suppression) auf die Vorbehandlung mit PEG-Interferon alpha und Ribavirin stellt den entscheidenden Faktor für die Effektivität und den Erfolg der Triple-Re-Therapie dar **Koinfektionen HIV/HCV-Koinfektion:** • Für Patienten mit einer HCV-Genotyp 1 Infektion bestand die Standardtherapie bisher aus einer Behandlung mit PEG-Interferon alpha und Ribavirin (1000 – 1200 mg/d) über 48 Wochen bei

	RVR und Fibrosegrad < F2 und ansonsten über 72 Wochen. • Mit der Zulassung der beiden HCV-Proteaseinhibitoren Boceprevir und Telaprevir haben sich nun die therapeutischen Optionen für Patienten mit einer HCV-Genotyp 1 Infektion erweitert.
Vogel 2010: HIV- und Hepatitis-C-Koinfektion.	**Therapie der akuten Hepatitis-C-Infektion** • Therapie der Wahl ist eine Kombinationstherapie mit pegyliertem Interferon und Ribavirin. • HIV-positive Patienten sollten unabhängig vom HCV-Genotyp eine gewichtsadaptierte Dosierung des Ribavirins erhalten. • Bisherige Studien zeigen, dass eine frühe Behandlung der akuten HCV-Infektion hohe Ausheilungsraten erreicht. **Non-Responder** • Bei Nicht-Ansprechen auf eine Therapie ist das weitere Vorgehen abhängig von der Ursache. • War das verwendete Interferon nicht pegyliert oder aber das Ribavirin niedrig dosiert kann eine „Re-Therapie“ sinnvoll sein. • Wurde hingegen aktuelle Empfehlungen für eine moderne Therapie berücksichtigt, sind eine erneute Therapie oder Interferon-Erhaltungstherapie nicht sinnvoll. • Neue Substanzen zur Behandlung der Hepatitis C stellen hier auch für HIV-positive Patienten eine Hoffnung auf bessere Behandlungsmöglichkeiten dar.

Hinweise zu den Leitlinien

Evidenzgraduierung bei Ghany 2011 und Yee 2012:
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 favor 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/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

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])

Literatur:

Alavian SM, Tabatabaei SV, Behnava B, Mahboobi N. Optimal duration of treatment for HCV genotype 1 infection in slow responders: a meta-analysis. Hepat Mon 2011; 11 (8): 612-9.

Bota S, Sporea I, Popescu A, Sirli R, Neghina AM, Danila M, Strain M. Response to standard of care antiviral treatment in patients with HCV liver cirrhosis: a systematic review (Provisional abstract). Journal of Gastrointestinal and Liver Diseases 2011; 20 (3): 293-8.

Brok J, Gluud LL, Gluud C. Ribavirin plus interferon versus interferon for chronic hepatitis C. Cochrane Database Syst Rev 2010; (1): CD005445.

Brok J, Ribavirin monotherapy for chronic hepatitis C, Gluud C. Ribavirin monotherapy for chronic hepatitis C. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd Chichester, UK 2009; (4): CD005527.

Brook G, Main J, Nelson M, Bhagani S, Wilkins E, Leen C, Fisher M, Gilleece Y, Gilson R, Freedman A, Kulasegaram R, Agarwal K, Sabin C, Deacon-Adams C. British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. HIV Med 2010; 11 (1): 1-30.

Brook GM, Soriano V, Bergin C. European Guideline for the management of Hepatitis B and Cvirus infections. Stand: 2010. http://www.iusti.org/regions/europe/Euro_Guideline_Hep%20B_and_C_Europe_04.10.pdf, Zugriff am 14.03.2011.

Canadian Agency for Drugs and Technologies in Health (CADTH). Boceprevir and Telaprevir for Chronic Hepatitis C Infection. Stand: Mai 2012. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2012 - 52.www.cadth.ca/media/pdf/Drug_Plan_Mgmnt_Issues_en.pdf, Zugriff am 16.07.2012.

Chan AH, Partovi N, Ensom MH. The utility of therapeutic drug monitoring for ribavirin in patients with chronic hepatitis C--a critical review. Ann Pharmacother 2009; 43 (12): 2044-63.

Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. Ann Intern Med 2013; 158 (2): 114-23.

Christensen PB, Clausen MR, Krarup H, Laursen AL, Schlichting P, Weis N. Treatment for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection - Danish national guidelines 2011. Dan Med J 2012; 59 (6): C4465.http://www.danmedj.dk/portal/page/portal/danmedj.dk/dmj_forside/PAST_ISSUE/2012/DMJ_2012_06/C4465, Zugriff am 10.06.2013.

Cooper CL, Druyts E, Thorlund K, Nachega JB, El Khoury AC, O'Regan C, Mills EJ. Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1 infection: an indirect comparison meta-analysis. Ther Clin Risk Manag 2012; 8 105-30.

Cure S, Diels J, Gavart S, Bianic F, Jones E. Efficacy of telaprevir and boceprevir in treatment-naive and treatment-experienced genotype 1 chronic hepatitis C patients: an indirect comparison using Bayesian network meta-analysis. Curr Med Res Opin 2012; 28 (11): 1841-56.

Dang SS, Wang WJ, Wang XF, Li YP, Li M, Jia XL, Wang Y, Liu E, Zhao S. Telaprevir for chronic hepatitis C with genotype 1: a meta-analysis. Hepatogastroenterology 2012; 59 (114): 461-8.

European Association for the Study of the Liver (EASL). Clinical Practice Guidelines: management of hepatitis C virus infection, Stand: Juni 2011. J Hepatol 2011; 55 (2): 245-64.

European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2014; 60 392-420.

Flori N, Funakoshi N, Duny Y, Valats JC, Bismuth M, Christophorou D, Daures JP, Blanc P. Pegylated interferon-?2a and ribavirin versus pegylated interferon-?2b and ribavirin in chronic hepatitis C : a meta-analysis. Drugs 2013; 73 (3): 263-77.

Foote BS, Spooner LM, Belliveau PP. Boceprevir: a protease inhibitor for the treatment of chronic hepatitis C. Ann Pharmacother 2011; 45 (9): 1085-93.

Gemeinsamer Bundesausschuss (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) Boceprevir. Berlin (Ger): G-BA 2013; (BAnz. Nr. 52 (S. 1269) vom 30.03.2012): http://www.g-ba.de/downloads/39-261-1454/2012-03-01_AM-RL-XII_Boceprevir_BAnz.pdf, Zugriff am 05.06.2013.

Gemeinsamer Bundesausschuss (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; (BAnz AT 10.05.2012 B3): http://www.g-ba.de/downloads/39-261-1469/2012-03-29_AM-RL-XII_Telaprevir_BAnz.pdf, Zugriff am 05.06.2013.

Gevers TJ, Slavenburg S, van Oijen MG, Drenth JP. Treatment extension benefits HCV genotype 1 patients without rapid virological response: a systematic review. Neth J Med 2011; 69 (5): 216-21.

Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. 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. Hepatology 2011; 54 (4): 1433-44.www.aasld.org/practiceguidelines/Documents/2011UpdateGenotype1HCVbyAASLD24641.pdf, Zugriff am 16.07.2012.

Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. 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, Stand: Januar 2013. Alexandria (VA): American Association for the Study of Liver Diseases (AASLD), 2013 2013; http://www.aasld.org/practiceguidelines/Documents/AASLDUpdateTreatmentGenotype1HCV11113.pdf, Zugriff am 19.12.2013.

Ghany MG, Strader DB, Thoms DL, Seeff LB. Diagnosis,Management,and Treatment of Hepatitis C: An Update. Hepatology 2009; 49 (4): 1335-74.

Gluud LL, Marchesini E, Iorio A. Peginterferon plus ribavirin for chronic hepatitis C in patients with human immunodeficiency virus. Am J Gastroenterol 2009; 104 (9): 2335-41.

Goralczyk AD, Cameron S, Amanzada A. Treatment of chronic HCV genotype 1 infection with telaprevir: a Bayesian mixed treatment comparison of fixed-length and response-guided treatment regimens in treatment-naive and -experienced patients. BMC Gastroenterol 2013; 13 148.

Gu L, Chen Q, Xie J, Yan Y, Wu G, Tan J, Liang B, Chen W, Wu P, Su L, Tang N. Telaprevir for genotype 1 chronic hepatitis C: a systematic review and meta-analysis. Pharmazie 2012; 67 (12): 963-72.

Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess 2011; 15 (17): i-210.

Haute Autorité de Santé (HAS). Hepatite chronique C. Guide ALD no 6, Actes et prestations sur l'hepatite chronique C. Stand: Juni 2012. Saint-Denis La Plaine: Haute Autorité de Santé, 2012 http://www.has-sante.fr/portail/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=c_554271, Zugriff am 13.07.2012.

Hull M, Klein M, Shafran S, Tseng A, Giguere P, Cote P, Poliquin M, Cooper C. CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of HIV/hepatitis C coinfection in adults. Can J Infect Dis Med Microbiol 2013; in press

Iorio A, Marchesini E, Awad T, Gluud LL. Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd Chichester, 2010; (1): CD004888.

Katz LH, Goldvaser H, Gafter GA, Tur KR. Extended peginterferon plus ribavirin treatment for 72 weeks versus standard peginterferon plus ribavirin treatment for 48 weeks in chronic hepatitis C genotype 1 infected slow-responder adult patients. Cochrane Database of Systematic Reviews 2012; (9):

Koretz RL, Pleguezuelo M, Arvaniti V, Barrera BP, Ciria R, Gurusamy KS, Davidson BR, Burroughs AK. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. Cochrane Database of Systematic Reviews 2013; (1): CD003617.pub2.

Leroy V, Serfaty L, Bourliere M, Bronowicki JP, Delasalle P, Pariente A, Pol S, Zoulim F, Pageaux GP. Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French Association for the Study of the Liver. Liver Int 2012; 32 (10): 1477-92.

Makara M, Horvath G, Gervain J, Par A, Szalay F, Telegdy L, Tornai I, Ujhelyi E, Hunyady B. [Hungarian consensus guideline for the diagnosis and treatment of B, C, and D viral hepatitis.]
Ajanlas a B-, a C- es a D-virus hepatitisek diagnosztikajara es antiviralis kezelesere. Orv Hetil 2012; 153 (10): 375-94.

Marcellin P, Roberts SK, Reddy KR, Harrison SA, Jensen DM, Hadziyannis S, Diago M, Weltman M, Messinger D, Tatsch F, Rizzetto M. 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. Expert Opin Drug Saf 2012; 11 (6): 901-9.

National Institute for Health and Care Excellence (NICE). Boceprevir for the treatment of genotype 1 chronic hepatitis C (TA 253), Stand: April 2012. Manchester: National Institute for Health and Care Excellence, 2012 http://guidance.nice.org.uk/TA253, Zugriff am 16.07.2012.

National Institute for Health and Care Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. Manchester (UK): National Institute for Health and Care Excellence 2010; (TA200): http://publications.nice.org.uk/peginterferon-alfa-and-ribavirin-for-the-treatment-of-chronic-hepatitis-c-ta200/contents, Zugriff am04.06.2013.

National Institute for Health and Care Excellence (NICE). Peginterferon alfa and ribavirin for treating chronic hepatitis C in children and young people (TA 300), Stand: November 2013. Manchester: National Institute for Health and Care Excellence, 2013 http://www.nice.org.uk/nicemedia/live/14311/65882/65882.pdf, Zugriff am 19.12.2013.

National Institute for Health and Care Excellence (NICE). Telaprevir for the treatment of genotype 1 chronic hepatitis C. Manchester (UK): National Institute for Health and Care Excellence 2012; (TA252): http://www.nice.org.uk/nicemedia/live/13717/58912/58912.pdf, Zugriff am 04.06.2013.

New York State Department of Health (NYSDH). Hepatitis C virus. Stand: Mai 2010. New York: New York State Department of Health, 2010 http://www.hivguidelines.org/wp-content/uploads/hepatitis-c-virus-posted-09-23-2010.pdf, Zugriff am 17.07.2012.

NIHR Horizon Scanning Centre (NIHR HSC). Boceprevir for hepatitis C. Stand: May 2010. Birmingham (UK): NIHR Horizon Scanning Centre (NHSC) 2010; (Horizon Scanning Technology Briefing): http://www.haps.bham.ac.uk/publichealth/horizon/outputs/documents/2010/may-aug/Boceprevir.pdf, Zugriff am 17.07.2012.

NIHR Horizon Scanning Centre (NIHR HSC). Faldaprevir with BI 207127 for chronic hepatitis C infection, genotype 1. NIHR Horizon Scanning Centre (NIHR HSC) 2012; (2): http://www.hsc.nihr.ac.uk/files/downloads/1974/2329.4859affe.Faldaprevir_Nov12.pdf, Zugriff am 10.06.2013.

NIHR Horizon Scanning Centre (NIHR HSC). Telaprevir (VX-950) for hepatitis C. Stand: April 2010. Birmingham: National Horizon Scanning Centre (NHSC) 2010; (Technology Briefing):

Parikh M, Singh A, Sood G. Extended treatment duration for treatment naive chronic hepatitis C genotype 1 late viral responders: a meta-analysis comparing 48 weeks vs 72 weeks of pegylated interferon and ribavirin. J Viral Hepat 2011; 18 (4): e99-103.

Park C, Jiang S, Lawson KA. Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype 1: a meta-analysis. J Clin Pharm Ther 2013;

Ramachandran P, Fraser A, Agarwal K, Austin A, Brown A, Foster GR, Fox R, Hayes PC, Leen C, Mills PR, Mutimer DJ, Ryder SD, Dillon JF. UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients. Aliment Pharmacol Ther 2012; 35 (6): 647-62.

Romero-Gomez M, Planas R, Ampuero J, Sola R, Garcia-Samaniego J, Diago M, Crespo J, Calleja JL, Turnes J. Meta-analysis: pegylated interferon alpha-2a achieves higher early virological responses than alpha-2b in chronic hepatitis C. Aliment Pharmacol Ther 2013; 37 (11): 1065-73.

Sarrazin C, Berg T, Ross RS, Schirmacher P, Wedemeyer H, Neumann U, Schmidt HH, Spengler U, Wirth S, Kessler HH, Peck-Radosavljevic M, Ferenci P, Vogel W, Moradpour D, Heim M, Cornberg M, Protzer U, Manns MP, Fleig WE, Dollinger MM, Zeuzem S. Update der S 3-Leitlinie Prophylaxe, Diagnostik und Therapie der Hepatitis-C-Virus(HCV)-Infektion, AWMF-Register-Nr.: 021/012, Stand: September 2009. Z Gastroenterol 2010; 48 (2): 289-351.

Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C, Stand: Juli 2013. Edinburgh: SIGN, 2013 http://www.sign.ac.uk/pdf/sign133.pdf, Zugriff am 19.12.2013.

Singal AG, Waljee AK, Shiffman M, Bacon BR, Schoenfeld PS. Meta-analysis: re-treatment of genotype I hepatitis C nonresponders and relapsers after failing interferon and ribavirin combination therapy. Aliment Pharmacol Ther 2010; 32 (8): 969-83.

Singal AK, Jampana SC, Anand BS. Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naive patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. Dig Dis Sci 2011; 56 (8): 2221-6.

Sitole M, Silva M, Spooner L, Comee MK, Malloy M. Telaprevir versus boceprevir in chronic hepatitis C: a meta-analysis of data from phase II and III trials. Clin Ther 2013; 35 (2): 190-7.

Smith LS, Nelson M, Naik S, Woten J. Telaprevir: an NS3/4A protease inhibitor for the treatment of chronic hepatitis C. Ann Pharmacother 2011; 45 (5): 639-48.

Vogel M, Boesecke C, Wasmuth JC, Rockstroh JK. [HIV and hepatitis C co-infection] HIV- und Hepatitis-C-Koinfektion. Dtsch Med Wochenschr 2010; 135 (23): 1186-91.

Wilby KJ, Partovi N, Ford JA, Greanya E, Yoshida EM. Review of boceprevir and telaprevir for the treatment of chronic hepatitis C. Can J Gastroenterol 2012; 26 (4): 205-10.

Wilkins E, Nelson M, Agarwal K, Awoyemi D, Barnes E, Bhagani S, Brook G, Brown A, Castelino S, Cooke G, Fisher M, Geretti AM, James R, Kulasegaram R. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. HIV Med 2013; 14 (Suppl. 4): 1-71.

Yee HS, Chang MF, Pocha C, Lim J, Ross D, Morgan TR, Monto A. Update on the management and treatment of hepatitis C virus infection: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office. Am J Gastroenterol 2012; 107 (5): 669-89.

Zhu Q, Li N, Han Q, Zhang P, Yang C, Zeng X, Chen Y, Lv Y, Liu X, Liu Z. Statin therapy improves response to interferon alfa and ribavirin in chronic hepatitis C: a systematic review and meta-analysis. Antiviral Res 2013; 98 (3): 373-9.