Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2014-B-054 Ledipasvir (in Kombination mit Sofosbuvir)

Stand: August 2014

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

Ledipasvir (in Kombination mit Sofosbuvir)
[Behandlung der chronischen Hepatitis C (CHC) Genotyp 1 und Genotyp 3 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 (Genotyp 1 und 4) - Daclatasvir (Genotyp 1,3 und 4) (Erteilung der Zulassung August 2014)
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 (Verfahren nach § 35a SGB V vom 17.07.2014)
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 **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ledipasvir (in Kombination mit Sofosbuvir) **ATC-Code und Handelsname liegen nicht vor**	Behandlung der chronischen Hepatitis C (CHC) Genotyp 1 und Genotyp 3 Infektion bei Erwachsenen *[Hinweis: Ledipasvir in Kombination mit dem zugelassenen Wirkstoff Sofosbuvir als Single Tablet Regimen (STR)]*
Ribavirin Copegus® (J05AB04)	Copegus ist indiziert zur Behandlung der chronischen Hepatitis C und darf **nur als Teil einer Kombinationstherapie mit Peginterferon alfa-2a oder mit Interferon alfa-2a** angewendet werden. Copegus darf nicht als Monotherapie angewendet werden. Die Kombination von Copegus mit Peginterferon alfa-2a oder Interferon alfa-2a ist indiziert bei ***erwachsenen Patienten,*** die Serum-HCV-positiv sind, einschließlich Patienten mit kompensierter Zirrhose. Die Kombination mit Peginterferon alfa-2a ist auch indiziert bei Patienten mit einer klinisch stabilen HIV-Begleitinfektion, einschließlich Patienten mit kompensierter Zirrhose. Die Kombination von Copegus und Peginterferon alfa-2a ist indiziert **bei unvorbehandelten Patienten und bei Patienten, bei denen eine vorhergehende Therapie** mit Interferon alfa (pegyliert oder nicht pegyliert) alleine oder in der Kombinationstherapie mit Ribavirin versagt hat. Bitte beachten Sie die Fachinformation von Peginterferon alfa-2a oder Interferon alfa-2a für Informationen zur Anwendung des jeweiligen Arzneimittels. (Stand 07/2012)
Peginterferon alfa 2a Pegasys® (L03AB11)	Pegasys ist indiziert zur Behandlung ***erwachsener Patienten*** mit chronischer Hepatitis C, deren Serum HCV-RNA-positiv ist, einschließlich Patienten mit kompensierter Zirrhose und/oder mit einer klinisch stabilen HIV-Begleitinfektion. Pegasys wird bei Patienten mit chronischer Hepatitis C am besten **in Kombination mit Ribavirin** angewendet. Die Kombination von Pegasys und Ribavirin ist indiziert bei **unvorbehandelten Patienten** und bei **Patienten, bei denen eine vorhergehende Therapie mit Interferon alfa (pegyliert oder nicht pegyliert) alleine oder in der Kombinationstherapie mit Ribavirin versagt hat**. Die Monotherapie ist hauptsachlich bei einer Intoleranz oder Kontraindikationen gegen Ribavirin indiziert. (Stand 10/2013)
Interferon alfa 2a Roferon® (L03AB04)	– Histologisch nachgewiesene chronische Hepatitis C bei *erwachsenen Patienten*, bei denen HCV-Antikörper oder HCVRNA und erhöhte Serumspiegel der Alaninaminotransferase (ALT) ohne Leberdekompensation vorliegen. – Die Wirksamkeit von Interferon alfa-2a bei der Behandlung der Hepatitis C wird durch die Kombination mit Ribavirin erhöht. Roferon-A sollte als Monotherapie nur bei Intoleranz oder Kontraindikationen gegen Ribavirin angewendet werden. (Stand 07/2013)

Ribavirin Rebetol® (J05AB04)	**3-fach-Kombinationstherapie:** Rebetol ist, in Kombination mit **Boceprevir und Peginterferon alfa-2b,** bestimmt zur Behandlung der chronischen Hepatitis- C(CHC)-Infektion vom Genotyp 1 bei erwachsenen Patienten (18 Jahre und älter) mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Bitte beachten Sie die Fachinformationen zu Peginterferon alfa-2b und Boceprevir, wenn Rebetol in Kombination mit diesen Arzneimitteln angewendet wird. **Therapie mit zwei Arzneimitteln (Duale Therapie):** Rebetol ist bestimmt zur Behandlung der chronischen Hepatitis-C-Virusinfektion bei Erwachsenen, Kindern ab dem Alter von 3 Jahren und Jugendlichen und darf **nur als Teil eines Kombinations-Dosierungsschemas mit Peginterferon alfa-2b oder Interferon alfa-2b** angewendet werden. Eine Rebetol Monotherapie darf nicht angewendet werden. Bitte beachten Sie die Fachinformationen zu Interferon alfa-2b und Peginterferon alfa-2b, wenn Rebetol in Kombination mit diesen Arzneimitteln angewendet wird. Es liegen keine Informationen zur Sicherheit oder Wirksamkeit für die Anwendung von Rebetol mit anderen Formen von Interferon (d. h. kein alfa-2b) vor. **<u>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. (Stand 11/2013)
Peginterferon alfa 2b Pegintron® (L03AB10)	***Erwachsene (3-fach-Kombinationstherapie):*** PegIntron ist, in Kombination mit **Ribavirin und Boceprevir** (3-fach-Kombinationstherapie), indiziert zur Behandlung der chronischen Hepatitis-C(CHC)-Infektion vom Genotyp 1 bei erwachsenen Patienten (18 Jahre und älter) mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Bitte beachten Sie die Fachinformationen zu Ribavirin und Boceprevir, wenn Sie PegIntron in Kombination mit diesen Arzneimitteln anwenden. ***Erwachsene (Duale Therapie und Monotherapie):*** PegIntron ist indiziert zur Behandlung erwachsener Patienten (18 Jahre und älter) mit CHC, die Hepatitis-C-Virus-RNA(HCVRNA)-positiv sind, einschließlich Patienten mit kompensierter Zirrhose und/oder Patienten, die klinisch stabil mit HIV co-infiziert sind. PegIntron in **Kombination mit Ribavirin** (Duale Therapie) ist indiziert zur Behandlung der CHC-Infektion bei nicht vorbehandelten erwachsenen Patienten, einschließlich Patienten, die klinisch stabil mit HIV co-infiziert sind, und bei erwachsenen Patienten, die nicht auf eine vorangegangene Kombinationstherapie mit Interferon alfa (pegyliert oder nicht-pegyliert) und Ribavirin oder auf eine Interferon alfa-Monotherapie angesprochen bzw. einen Rückfall erlitten haben. Die Interferon-Monotherapie, einschließlich PegIntron, ist hauptsächlich indiziert im Fall einer Intoleranz oder einer Gegenanzeige gegenüber Ribavirin. Bitte beachten Sie die Fachinformation zu Ribavirin, wenn PegIntron in Kombination mit Ribavirin angewendet wird. (Stand 05/2013)
Interferon alfa 2b IntronA® (L03AB05)	Vor Behandlungsbeginn mit IntronA sollten die Ergebnisse von klinischen Studien zum Vergleich von IntronA mit pegyliertem Interferon berücksichtigt werden. ***Erwachsene*** IntronA ist indiziert zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die erhöhte Transaminasenwerte ohne Leberdekompensation haben und die Hepatitis C-Virus-RNA (HCV-RNA)-positiv sind. Die beste Art, IntronA bei dieser Indikation anzuwenden, ist die **Kombination mit Ribavirin.** (Stand 03/2013)
Ribavirin Ribavirin-ratiopharm® (J05AB04)	Ribavirin-ratiopharm ® ist indiziert zur Behandlung der chronischen Hepatitis-C-Virusinfektion (HCV-Infektion) bei Erwachsenen und darf nur als Teil eines Kombinations- Dosierungsschemas mit Peginterferon alfa-2b oder Interferon alfa-2b angewendet werden. Eine Ribavirin-ratiopharm ®-Monotherapie darf nicht angewendet werden. Es liegen keine Informationen zur Unbedenklichkeit oder Wirksamkeit für die Anwendung von Ribavirin-ratiopharm ® mit anderen Formen von Interferon (d.h. kein alfa-2b) vor. <u>Vorbehandelte Patienten</u> <u>Erwachsene</u> Ribavirin-ratiopharm ® ist in Kombination mit Interferon alfa-2b indiziert zur Behandlung von erwachsenen Patienten mit chronischer

<table>
<tr><td></td><td>Hepatitis C, die zunächst auf eine Interferon-alfa-Monotherapie angesprochen haben (mit Normalisierung der ALT-Werte am Ende der Behandlung), jedoch später einen Rückfall erlitten haben. Ribavirin-ratiopharm® ist indiziert in Kombination mit Peginterferon alfa-2b zur Behandlung von erwachsenen Patienten mit chronischer Hepatitis C, die auf eine vorangegangene Therapie mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin nicht angesprochen, bzw. einen Rückfall erlitten haben. (Stand 05/2012)</td></tr>
<tr><td>Boceprevir
Victrelis®
(J05AE12)</td><td>Victrelis ist indiziert zur Behandlung der chronischen Hepatitis C(CHC)-Infektion vom Genotyp 1 in Kombination mit Peginterferon alfa und Ribavirin bei erwachsenen Patienten mit kompensierter Lebererkrankung, die nicht vorbehandelt sind oder die nicht auf eine vorangegangene Therapie angesprochen bzw. einen Rückfall erlitten haben. Siehe Abschnitte 4.4 und 5.1. (Stand 03/2014)</td></tr>
<tr><td>Telaprevir
Incivo®
(J05AE11)</td><td>INCIVO ist in Kombination mit Peginterferon alfa und Ribavirin zur Behandlung der chronischen Hepatitis C vom Genotyp 1 bei erwachsenen Patienten mit kompensierter Lebererkrankung (einschließlich Zirrhose) indiziert:
- die nicht vorbehandelt sind;
- die entweder mit Interferon alfa (pegyliert oder nicht-pegyliert) allein oder in Kombination mit Ribavirin vorbehandelt wurden, einschließlich Patienten, die einen Rückfall (Relaps) erlitten haben, Patienten mit partiellem Ansprechen oder Patienten mit fehlendem Ansprechen (Null-Responder) (siehe Abschnitte 4.4 und 5.1). (Stand 12/2013)</td></tr>
<tr><td>Sofosbuvir
Sovaldi®
(J05AX15)</td><td>Sovaldi wird in Kombination mit anderen Arzneimitteln zur Behandlung der chronischen Hepatitis C (CHC) bei Erwachsenen angewendet (siehe Abschnitte 4.2, 4.4 und 5.1).

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

Abschnitt 4.2 der Fachinformation:
Tabelle 1: Empfohlene(s) gleichzeitig angewendete(s) Arzneimittel und Behandlungsdauer für die Kombinationstherapie mit Sovaldi
<table>
<tr><th>Patientengruppe* Behandlung Dauer</th><th>Behandlung</th><th>Dauer</th></tr>
<tr><td rowspan="2">Patienten mit CHC vom Genotyp 1, 4, 5 oder 6</td><td>Sovaldi + Riba virin + Peginterferon alfa</td><td>12 Wochen [a, b]</td></tr>
<tr><td>Sovaldi + Ribavirin
Nur zur Anwendung bei Patienten, die für eine Therapie mit Peginterferon alfa ungeeignet sind oder eine Unverträglichkeit gegenüber Peginterferon alfa haben (siehe Abschnitt 4.4)</td><td>24 Wochen</td></tr>
<tr><td rowspan="2">Patienten mit CHC vom Genotyp 2</td><td>Sovaldi + Ribavirin</td><td>12 Wochen[b]</td></tr>
<tr><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</td></tr>
</table>

Abschnitt 4.4).
[b] Es ist zu erwägen, die Dauer der Therapie möglicherweise über 12 Wochen hinaus auf bis zu 24 Wochen verlängern; dies gilt insbesondere für Subgruppen mit einem oder mehreren der negativen prädiktiven Faktoren, die in der Vergangenheit mit niedrigeren Ansprechraten auf Interferon-haltige Therapien (z. B. fortgeschrittene Fibrose/Zirrhose, hohe Ausgangsviruslast, schwarze Hautfarbe, IL28B-Non-CC-Genotyp, früheres Nichtansprechen auf Peginterferon alfa und Ribavirin) assoziiert waren.
[c] Siehe unten: „Besondere Patientengruppen – Patienten, die auf eine Lebertransplantation warten“.

(Stand 04/2014)

Simeprevir
Olysio®
(J05AE14)

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.

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).

(Stand 06/2014)

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 Aktivitat 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
Genotyp 4	Daklinza + Peginterferon alfa + Ribavirin	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.

*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). (Stand 8/2014)

Quellen: AMIS-Datenbank, Fachinformationen

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

Indikation für die Recherche von Ledipasvir und Sofosbuvir:
Behandlung der chronischen Hepatitis C (CHC) Genotyp 1 und Genotyp 3 Infektion bei Erwachsenen.

Berücksichtigte Wirkstoffe/Therapien:
Für das Anwendungsgebiet zugelassenen Arzneimittel, siehe Tabelle II. „Zugelassene Arzneimittel im Anwendungsgebiet".

Systematische Recherche:
Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„**chronische Hepatitis C" durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***17.07.2014*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Die Leitlinien der DGVS und AASLD wurden nach dem Recherchezeitraum publiziert, jedoch aufgrund ihrer Aktualität in die Synopse aufgenommen. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.
Die Recherche ergab **525** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **162** Quellen eingeschlossen, und **2** Leitlinen per Handsuche aufgenommen. Insgesamt ergab dies **44** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

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

IQWiG 2014:
Sofosbuvir
Nutzenbewertung gemäß § 35a SGB V

Fragestellung
Das Ziel des vorliegenden Berichts ist die Bewertung des Zusatznutzens von Sofosbuvir im Vergleich zur zweckmäßigen Vergleichstherapie bei erwachsenen Patienten mit chronischer Hepatitis C (CHC).

Sofosbuvir - Ausmaß und Wahrscheinlichkeit des Zusatznutzens

Patientengruppe mit CHC	**Zweckmäßige Vergleichstherapie[a]**	**Ausmaß und Wahrscheinlichkeit des Zusatznutzens**
Genotyp 1, therapienaiv ohne Zirrhose sowie therapieerfahren mit und ohne Zirrhose	PEG + RBV oder[b] **BOC + PEG + RBV bzw. TVR + PEG + RBV**	Zusatznutzen nicht belegt
Genotyp 1, therapienaive Patienten mit Zirrhose	PEG + RBV	Zusatznutzen nicht belegt
Genotyp 3	PEG + RBV	Zusatznutzen nicht belegt

a: Dargestellt ist jeweils die vom G-BA festgelegte zweckmäßige Vergleichstherapie. In den Fällen, in denen der pU aufgrund der Festlegung der zweckmäßigen Vergleichstherapie durch den G-BA aus mehreren Alternativen eine Vergleichstherapie auswählen kann, ist die entsprechende Auswahl des pU **fett** markiert. b: Die Angaben der Fachinformationen der Kombinationspartner der zweckmäßigen Vergleichstherapie sind insbesondere bezüglich der jeweils zugelassenen Anwendungsgebiete, der Dosierungen, der Therapiedauer und Prognosefaktoren zu berücksichtigen. Eine Abwägung der Notwendigkeit des Einsatzes einer Triple-Therapie bei Vorliegen günstiger Prognosefaktoren ist vorzunehmen.
BOC: Boceprevir; CHC: chronische Hepatitis C; HIV: humanes Immundefizienz-Virus; PEG: Peginterferon alfa; RBV: Ribavirin; SOF: Sofosbuvir; TVR: Telaprevir

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL):
Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Sofosbuvir

Stand: 17.07.2014

Zugelassenes Anwendungsgebiet:
Sofosbuvir (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 der Fachinformation von Sovaldi®).
Zur spezifischen Aktivität gegen die verschiedenen Genotypen des Hepatitis-C-Virus (HCV) siehe Abschnitte 4.4 und 5.1. der Fachinformation von Sovaldi®).

a) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir) bei therapienaiven Patienten ohne Zirrhose mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1)

Zweckmäßige Vergleichstherapie:
Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **oder** Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir):
Anhaltspunkt für einen geringen Zusatznutzen.

	b) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin bei therapienaiven Patienten mit Zirrhose mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin:** Anhaltspunkt für einen geringen Zusatznutzen. c) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir) therapieerfahrenen Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) oder Triple-Therapie (Kombination aus einem Proteaseinhibitor (Boceprevir oder Telaprevir), Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin + Proteaseinhibitor (Boceprevir oder Telaprevir):** Ein Zusatznutzen ist nicht belegt. f) In Kombination mit Ribavirin gegenüber Peginterferon alfa + Ribavirin bei therapienaiven und therapieerfahrenen Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 3) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin:** Anhaltspunkt für einen geringen Zusatznutzen. g) In Kombination mit Peginterferon alfa + Ribavirin gegenüber Peginterferon alfa + Ribavirin bei therapienaiven und therapieerfahrenen Patienten mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 3) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin:** Ein Zusatznutzen ist nicht belegt. i) In Kombination mit Peginterferon alfa + Ribavirin bzw. Kombination mit Ribavirin gegenüber Peginterferon alfa + Ribavirin bei Patienten mit einer HIV-Koinfektion (therapienaiv, therapieerfahren) mit chronischer Hepatitis-C-Virus (cHCV) Infektion (Genotyp 1-6) **Zweckmäßige Vergleichstherapie:** Duale Therapie (Kombination aus Peginterferon alfa und Ribavirin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Peginterferon alfa + Ribavirin:** Anhaltspunkt für einen geringen Zusatznutzen.

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.

Hauser 2014: Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C (Review).	**Fragestellung:** To systematically evaluate the benefits and harms of peginterferon plus ribavirin versus interferon plus ribavirin for patients with chronic hepatitis C. **Systematische Literaturrecherche im Suchzeitraum:** bis 09/2013 **Vergleich:** peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin vs. interferon plus ribavirin **Population:** Patients with chronic hepatitis C **Anzahl der Patienten:** 5938 Patienten **Anzahl der Studien:** 27 Studien (in 10 trials, all participants were infected with hepatitis C virus genotype one) **Endpunkte:** primary: Liver-related morbidity plus all-cause mortality: number of participants who developed cirrhosis, ascites, variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma, or who died; adverse events leading to treatment discontinuation; Quality of life; secondary: Sustained virological response **Ergebnisse** <u>Liver-related morbidity plus all-cause mortality</u> *peginterferon plus ribavirin versus interferon plus ribavirin:* - No significant difference in liver-related morbidity or all-cause mortality was noted *Peginterferon plus ribavirin:* Four deaths (suicide (suspected drug overdose), ruptured oesophageal varices, traffic-related, and unexplained) *Interferon plus ribavirin:* three deaths (following surgery for colon cancer, hypertensive heart disease, and brain tumour) <u>Adverse events</u> - Data from 17 trials yielded a non-significant difference regarding adverse events leading to treatment discontinuation of peginterferon plus ribavirin when compared with interferon plus ribavirin (332/2692 (12.3%) versus 409/2176 (18.8%); RR 0.86, 95% CI 0.66 to 1.12; 17 trials) <u>Quality of life</u> - Only one trial reported quality of life in the Methods section - This trial is published only as an abstract, no data in the Results section <u>Sustained virological response</u> - Peginterferon plus ribavirin seems to significantly increase the number of participants achieving sustained virological response compared with interferon plus ribavirin (1673/3300 (50.7%) versus 1081/2804 (38.6%); RR 1.39, 95% CI 1. 25 to 1.56; I2 = 64%; 27 trials)

Peginterferon plus ribavirin versus non-pegylated interferon plus ribavirin for chronic hepatitis C

Patient or population: patients with chronic hepatitis C.
Settings: mainly outpatients.
Intervention: peginterferon.
Comparison: non-pegylated.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-pegylated	Peginterferon				
Liver-related morbidity plus all-cause mortality	Five per 1000	Six per 1000 (two to 17)	OR 1.14 (0.38 to 3.42)	1789 (five studies)	⊕⊕◯◯ low[1]	
Adverse events leading to treatment discontinuation	207 per 1000	178 per 1000 (141 to 226)	RR 0.86 (0.68 to 1.09)	4571 (15 studies)	⊕⊕◯◯ low[2,3]	
Sustained virological response	386 per 1000	537 per 1000 (482 to 602)	RR 1.39 (1.25 to 1.56)	6104 (27 studies)	⊕◯◯◯[4,5] very low	All trials had high risks of bias. Only an unvalidated surrogate outcome.

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.
[1]Low due to imprecision and indirectness wide confidence interval. The meta-analysis included only nine events.
[2]Low due to imprecision and indirectness.The proportions of observed adverse events differ substantially across trials, and the direction of effect is heterogeneous. However, because the event rate is still relatively low across trials, all of the included trials may be subject to considerable random error, thus explaining the apparent heterogeneity in the direction of estimates.
[3]The observed treatment effects differ in both direction and magnitude, but most confidence intervals have considerable overlap. Low due to indirectness.
[4]Sustained virological response does not seem to be a valid surrogate marker for assessing hepatitis C virus treatment efficacy of
interferon treatment. Very low due to high risk of bias in all trials and imprecision and indirectness due to surrogate [5]Only randomised clinical trials were included.

<u>Fazit der Autoren:</u>
Peginterferon plus ribavirin versus interferon plus ribavirin seems to significantly increase the proportion of patients with sustained virological response, as well as the risk of certain adverse events. However, we have insufficient evidence to recommend or reject peginterferon plus ribavirin for liver-related morbidity plus all-cause mortality compared with interferon plus ribavirin. The clinical consequences of achieved sustained virological response are unknown, as sustained virological response is still an unvalidated surrogate outcome. We found no evidence of the potential benefits on quality of life in patients with achieved sustained virological response. Further high-quality research is likely to have an important impact on our confidence in the estimate of patient-relevant outcomes and is likely to change our estimates.There is very low quality evidence that peginterferon plus ribavirin increases the proportion of patients with sustained virological response in comparison with interferon plus ribavirin. There is evidence that it also increases the risk of certain adverse events.

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.
Katz 2012: Extended peginterferon plus ribavirin treatment for 72 weeks versus	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.

standard peginterferon plus ribavirin treatment for 48 weeks in chronic hepatitis C genotype 1 infected slowresponder adult patients.	**Fragestellung:** To compare the therapeutic benefits and harms of different antiviral regimens in patients with hepatitis C re-infected grafts after liver transplantation. **Population:** Patients with hepatitis C viral re-infection of the liver graft irrespective of age, cadaveric or living donor transplant, indication for liver transplantation, first or retransplantation, and the immunosuppressive therapy used. **Anzahl der Studien:** 7 Studien **Anzahl der Patienten:** 1369 Patienten **Vergleiche:** Peginterferon (alfa-2a or alfa-2b) and ribavirin for 72 weeks versus peginterferon (alfa-2a or alfa-2b) and ribavirin for 48 weeks **Endpunkte:** Primäre Endpunkte: Overall mortality; HCV-related mortality; Liver-related morbidity Sekundäre Endpunkte: Number of participants with sustained virological response (SVR); Number of participants with end of treatment response (EOR); Number of participants who relapsed; Adherance to treatment; Reduction of treatment dose; Occurrence of adverse events **Ergebnisse (basierend auf 7 eingeschlossenen RCTs):** • None of the included trials mentioned primary outcomes. **Sustained virological response** • extension of the treatment period to 72 weeks increased the sustained virological response according to both definitions (71/217 (32.7%) versus 52/194 (26.8%); risk ratio (RR) 1.43, 95% CI 1.07 to 1.92, P = 0.02, I2 = 8%; and 265/499 (53.1%) versus 207/496 (41.7%); RR 1.27, 95% CI 1.07 to 1.50, P = 0.006, I2 = 38%), with a risk difference of 0.11 and calculated number needed to treat of nine. **End of treatment response and number of participants who experienced virological relapse after treatment** • The end of treatment response was not significantly different between the two treatment groups. • The number of participants who relapsed virologically was found to be lower in the groups that had been treated for 72 weeks using both definitions (27/84 (32.1%) versus 46/91 (50.5%); RR 0.59, 95% CI 0.40 to 0.86, P = 0.007, I2 = 18%, 3 trials; and 85/350 (24.3%) versus 146/353 (41.4%); RR 0.59, 95% CI 0.47, 0.73, P < 0.000001, I2 = 0%, 3 trials). **Adherence to treatment, reduction of treatment dose, and adverse events** • The length of treatment did not significantly affect the adherence (247/279 (88.5%) versus 252/274 (92.0%); RR 0.95, 95% CI 0.84 to 1.07, P = 0.42, I2 = 69%, 3 trials). • In the single trial that reported adverse events, no significant difference was seen between the two treatment groups. Fazit der Autoren: 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.
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:** Primäre Endpunkte: failure of serum (or plasma) sustained virological response (SVR); liver-related morbidity plus all-cause mortality; all adverse events Sekundäre Endpunkte: failure of end-of-treatment virological response; failure of histological response; quality of life. **Ergebnisse:** **Failure of serum sustained virological response** • Combination therapy significantly reduced the number with failure of SVR when all patients were combined (RR 0.75, 95% CI 0.71 to 0.79; 67 trials) • Combination therapy had a significant effect on the response in subgroups of naive (RR 0.72, 95% CI 0.68 to 0.75; 25 trials, I2 = 34%), relapsers (RR 0.62, 95% CI 0.54 to 0.70; 14 trials, I2 = 57%), and non-responders (RR 0.89, 95% CI 0.84 to 0.93; 22 trials, I2 = 63%) • Sensitivity analyses of trials with genotype 1 (RR 0.67, 95% CI 0.56 to 0.80, 7 trials) gave the same overall results showing that adding ribavirin significantly reduced the number with failure of SVR. **Liver-related morbidity plus all-cause mortality** • Few patients developed cirrhosis, hepatocellular carcinoma, or died • On combination therapy the number of outcomes was 16 out of 7482 patients, and on monotherapy the number of outcomes was 29 out of 5225 patients. • Combination therapy significantly reduced morbidity plus mortality (Peto OR 0.43, 95% CI 0.23 to 0.79, I2 = 0%). • The results were not significant for naive alone (Peto OR 0.55, 95% CI 0.20 to 1.55), relapsers alone (Peto OR 0.13, 95% CI 0.00 to 6.78), or non-responders alone (Peto OR 0.56, 95% CI 0.17 to 1.19). **Adverse events and reactions** • The most frequent adverse reaction was anaemia, which occurred in 727 out of 4448 patients (16%) on combination therapy and 43 out of 2944 (1%) on monotherapy (RR 9.45, 95% CI 7.42 to 12.05; 35 trials). • Combination therapy significantly increased the risk of leukopenia (RR 3.42, 95% CI 1.38 to 8.49; 3 trials), but not neutropenia or

	thrombocytopenia. • Combination therapy increased the risk of several dermatological adverse reactions, eg,dermatitis (RR 1.67, 95% CI 1.21 to 2.30; 3 trials), pruritus (RR 1.62, 95% CI 1.29 to 2.02; 18 trials), and rash (RR 1.74, 95%CI 1.17 to 2.61; 12 trials). • Combination therapy also led to a significant increase in gastrointestinal adverse reactions (dyspepsia and anorexia or nausea), insomnia, and miscellaneous adverse events (cough, dyspnoea, and fatigue). **Failure of end-of-treatment virological response** • Combination therapy significantly reduced the number of patients with failure of virological response (RR0.72, 95%CI 0.69 to 0.77; 78 trials). • Combination therapy also had a significant effect on virological response of naive patients, relapsers, and non-responders individually. **Failure of histological response** • All post-treatment biopsies were performed between 3 to 12 months after the end of treatment. Combination therapy significantly reduced the number of patients with failure on both inflammation score (grading) (RR 0.84, 95% CI 0.77 to 0.91; 11 trials) and fibrosis score (staging) (RR 0.95, 95% CI 0.92 to 0.97;9 trials). • Combination therapy also had a significant effect on liver histology of naive patients, relapsers, and non-responders individually. **Quality of life** • Only one trial with 257 relapsers reported data on quality of life. • Combination therapy had a significant beneficial effect on some subscales. These included scales on general health (MD 7.00, 95% CI 0.67 to 13.33), social functioning (MD 6.00, 95% CI 1.22 to 10.78), and mental health (MD 5.00, 95% CI 1.53 to 8.47). <u>Fazit der Autoren:</u> Compared with interferon alone, ribavirin plus interferon is more effective in clearing hepatitis C virus from the blood. Combination therapy may reduce liver-related morbidity and all-cause mortality, but we need more evidence. The number needed to treat to obtain a beneficial effect is considerable considering the increased risk of several severe adverse reactions and costs. **Anmerkungen FBMed:** Subgruppenanalysen für „Failure of serum sustained virological response“ für Patienten mit Genotyp 1 Patienten wurden durchgeführt.
Iorio 2010: Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus.	Systematische Literaturrecherche bis Mai 2009. The mean proportion of patients with hepatitis C genotype 1 ranged from 44% to 78%. Ansonsten vom Genotyp 2,3 und 4. Alles Patienten mit einer HIV/HCV-Koinfektion. **Fragestellung:** To assess the benefits and harms of antiviral treatment for **chronic hepatitis C in patients with HIV.** **Population:** Patients with chronic hepatitis C and stable HIV co-infection. **Anzahl der Studien:** 14 Studien **Anzahl der Patienten:** 2269 Patienten **Vergleiche:** • Randomised comparisons of peginterferon (any type, ie, alpha 2a or 2b) plus ribavirin versus peginterferon or interferon (any type, ie, alpha 2a or 2b) plus ribavirin • randomised comparisons of peginterferon plus ribavirin given for different doses or treatment durations

	Endpunkte: 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. <u>Fazit der Autoren:</u> Peginterferon plus ribavirin may be considered a treatment for patients with chronic hepatitis C and stable HIV who have not received treatment for hepatitis C as the intervention may clear the blood of HCV RNA. Supporting evidence comes mainly from the analysis of this non-validated surrogate outcome assessed in comparisons against other antiviral treatments. There is no evidence on treatment of patients who have relapsed or did not respond to previous therapy. Careful monitoring of adverse events is warranted. **Anmerkungen FBMed:** Subgruppenanalysen für die anhaltende virologische Ansprechrate der Patienten mit Genotyp 1 und 4 Patienten wurden durchgeführt.
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:** <u>Primäre Endpunkte:</u> Failure of serum (or plasma) sustained virological response, Liver-related morbidity plus all-cause mortality All adverse events <u>Sekundäre Endpunkte:</u> Failure of end of treatment virological response, Failure of sustained biochemical response, Failure of end of treatment biochemical response, Failure of histological response, Quality of life

	Ergebnisse (basierend auf 14 eingeschlossenen RCTs): **Compared with placebo or no intervention:** • ribavirin had no significant effect on the sustained virological response (RD 0%, 95% CI -2% to 3%, five trials) or end of treatment virological response (RD 0% 95% CI -3% to 3%, ten trials). • Ribavirin had no significant effect on liver-related morbidity plus mortality (RD0%, 95%CI -2%to 3%, 11 trials). • Ribavirin significantly increased the risk of adverse reactions, including anaemia. • Ribavirin significantly improved end of treatment biochemical and histological response but not the sustained biochemical response. **Ribavirin versus interferon** • Compared with ribavirin, interferon significantly increased the number of patients with an end of treatment virological response (RD 17%; 95% CI 7% to 27%, five trials), but not the number with sustained virological response (RD 13%; 95% CI -4% to 29%, two trials). • Ribavirin was significantly inferior to interferon regarding virological and biochemical responses (five trials) • No liver-related morbidity or mortality was reported in any trial. • Compared with ribavirin, interferon increased the number with end of treatment and sustained biochemical responses. • no significant difference in adverse events or treatment discontinuations between ribavirin and interferon. • None of the trials reported histological response or quality of life. <u>Fazit der Autoren:</u> Ribavirin seems without beneficial effects on serum virological response and liver-related morbidity or mortality, and significantly increased the risk of adverse reactions. Ribavirin monotherapy seems significantly inferior to interferonmonotherapy. The total number of included patients is small, and more trials are perhaps needed. The use of ribavirin monotherapy for chronic hepatitis C cannot be recommended outside randomised trials. **Anmerkungen FBMed:** Der Anteil der Patienten mit Hepatitis-C-Virus vom Genotyp 1 wurde in acht Studien (Median 73%, von 40% auf 97%) berichtet.

Coppola 2014: Peg-Interferon Plus Ribavirin with or without Boceprevir or Telaprevir for HCV Genotype 1: A Meta-Analysis on the Role of Response Predictors.

1. Fragestellung:

To compare the efficacy of pegylated-interferon (Peg-IFN) a-2a or a-2b and ribavirin given as dual therapy versus triple therapy (Peg-IFN and ribavirin plus boceprevir or telaprevir) in patients with HCV-1 chronic hepatitis naive for anti-HCV therapy or relapsers to dual therapy in relation to the presence of constitutional, clinical and virological predictors of treatment response.

2. Methodik

Population: patients with HCV-1 chronic hepatitis
Vergleich: dual therapy versus triple therapy
Endpunkte: SVR
Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (3,652 patients)
Suchzeitraum: 01/2008 bis 06/2013
Qualitätsbewertung: Jadad-Skala

3. Ergebnisse

Meta-analysis data on the achievement of SVR and tolerability with pegylated interferon a plus ribavirin or pegylated interferon a, ribavirin and a direct-acting antiviral in patients with chronic hepatitis C due to HCV genotype 1:

SVR in patients with	N° of studies	N° of patients PR/ PR+DAA	N° and (%) of events PR/PR+DAA	RR (efficacy)	95% CI (efficacy)	*p*
IL28-B CC	5 [29–32,34]	150/337	99(66)/283(84)	0.78	0.69–0.89	<0.0001
IL28-B CT or TT	5 [29–32,34]	347/849	92(26.5)/569(67)	0.4	0.33–0.47	<0.0001
RVR	5 [28–32]	80/965	77(96)/810(84)	1.11	1.04–1.19	0.002
No RVR	5 [28–32]	890/1,356	286(32)/831(61)	0.56	0.5–0.62	<0.0001
No advanced fibrosis	5 [28–32]	788/1,911	322(41)/1,360(71)	0.57	0.52–0.63	<0.0001
Advanced fibrosis	5 [28–32]	145/422	41(28)/271(64)	0.45	0.34–0.59	<0.0001
Genotype 1a	5 [28–32]	500/1,287	183(37)/769(60)	0.55	0.49–0.62	<0.0001
Genotype 1b	5 [28–32]	373/898	152(41)/700(78)	0.51	0.45–0.58	<0.0001
Low HCV RNA	6 [28–32]	217/437	135(62.2)/389(79)	0.78	0.69–0.87	<0.0001
High HCV RNA	6 [28–32]	793/2,005	261(33)/1,355(67.5)	0.54	0.49–0.6	<0.0001
Patients with						
Discontinuation for AE	7 [28–34]	1,170/2,987	122(10)/471(16)	0.67	0.55–0.81	<0.0001
Severe AE	6 [28–32,34]	1,107/2,861	76(0.6)/297(10)	0.65	0.51–0.83	0.001
Anemia	7 [28–34]	1,170/2,987	202(17)/1,124(38)	0.47	0.41–0.54	<0.0001
Severe anemia	7 [28–34]	1,170/2,987	23(0.2)/208(0.7)	0.3	0.2–0.46	<0.0001
Neutropenia	5 [28–30,32,34]	746/2,137	132(18)/621(29)	0.59	0.5–0.7	<0.0001

SVR: sustained virological response; PR: pegylated interferon plus ribavirin; DAA: direct-acting antivirals; IL28-B: interleukin 28B; RVR: rapid virological response; AE: adverse event
doi:10.1371/journal.pone.0094542.t004

- As regards the HCV-1 subgenotype, dual therapy less frequently than triple therapy achieved SVR both in 1,797 patients with HCV-1a subgenotype (RR = 0.55; 95% CI =0.49–0.62, p<0.0001)
- In 1,271patients with HCV-1b (RR = 0.51; 95% CI = 0.45–0.58, p<0.0001).

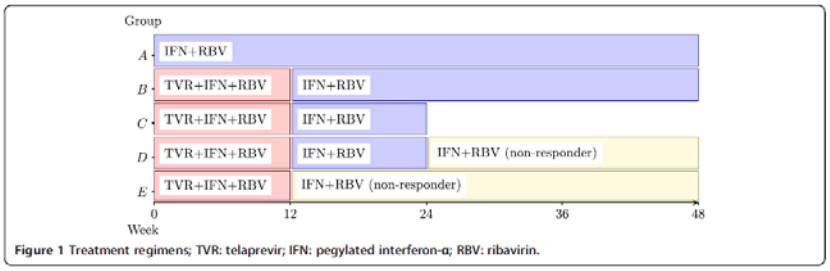
4. Fazit der Autoren:

Triple therapy provides a significantly higher SVR rate than dual therapy, but dual therapy obtains a significantly higher SVR rate in patients with RVR. The data stress the clinical importance of a 4-week lead-in phase in directacting antiviral-based treatment.

Goralcyk 2013: Treatment of chronic HCV genotype 1

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

infection with telaprevir: a Bayesian mixed treatment comparison of fixed-length and response-guided treatment regimens in treatment-naïve and –experienced patients.	weeks, group C) tail of Peg-IFN-α/RBV treatment, and RGT with 12 weeks of TVR, Peg-IFN-α/RBV followed by 12 weeks of Peg-IFN-α/RBV (group D) or no therapy (group E).
	2. Methodik **Population:** Adult patients with chronic HCV genotype 1 **Vergleich:** Standardtherapie vs. TVR **Endpunkte:** sustained virologic response (SVR) **Suchzeitraum (Aktualität der Recherche):** bis 02/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7 studies (n=3505 patients)
	3. Ergebnisdarstellung Behandlungsgruppen:  Figure 1 Treatment regimens; TVR: telaprevir; IFN: pegylated interferon-α; RBV: ribavirin. • Compared to standard-treatment (group A), treatment-naïve patients allocated to groups B, C, and D were significantly more likely to achieve sustained-virological-response (SVR, odds ratios (OR): B vs. A 3.5 (credibility interval [CrI] 2.2-5.4), C vs. A 3.0 (CrI 1.8-4.9), D vs. A 3.4 (CrI 2.5-4.6)) • Treatment-experienced patients achieved increased SVR rates when they were treated in group B (OR: 8.2 (CrI 5.0-13.5)), C (OR 7.0 (CrI 3.9-12.8)), or simulated group D (OR 8.2 (CrI 4.3-15.3)). • Patients treated with short RGT (simulated group E) did also have a significant improvement when they were treatment-experienced (simulated OR 3.6 (CrI 1.6-8.2)), whereas the effect was not significant in treatment-naïve patients (OR E vs. A 1.6 (CrI 0.9-2.7))
	4. Anmerkungen/Fazit der Autoren Long FLT and RGT regimens are useful treatment options for HCV-genotype-1 in both treatment-naïve and -experienced patients. A short 24-weeks FLT regimen does not seem to be inferior and should further be evaluated in clinical trials to reduce side effects and costs of treatment.
Park 2013: Efficacy and safety of telaprevir and boceprevir in patients with hepatitis C genotype 1: 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 a. 10 der eingeschlossenen Studien speziell für Fragestellung bzw. Patientenpopulation) 4421 der eingeschlossenen Patienten speziell für Fragestellung b. Overall, triple therapy was significantly associated with a higher achievement of SVR than dual therapy: (i) telaprevir-based triple therapy in treatment-naïve patients (relative risk [RR] = 1,62; 95% confidence interval [CI], 1,47–1,78) (ii) telaprevir-based triple therapy in treatment-experienced patients (RR = 3,85; 95% CI, 3,03–4,90) (iii) boceprevir-based triple therapy in treatment-naïve patients (PR = 1,70; 95% CI, 1,56–1,86) and (iv) boceprevir-based triple therapy in treatment-experienced patients (RR = 2,98; 95% CI, 2,29–3,87) • Patients on triple therapies had the significantly increased incidences of treatment discontinuation attributable to adverse events and serious adverse events when compared to dual therapy, especially treatment-experienced patients.
	4. Anmerkungen/Fazit der Autoren Regarding achieving SVR, triple therapies including either PI are superior to dual therapy for both treatment-naïve and treatment-experienced patients.
Sitole 2013: Telaprevir Versus Boceprevir in Chronic Hepatitis C: A Meta-Analysis of Data From Phase II and III Trials.	Systematischer Review mit Meta-Analyse zu Teleprevir. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. Patienten von Genotyp 1. **Fragestellung:** This meta-analysis compared 24- and 48- week sustained viral responses (SVR) and drug-related adverse events (AEs) between telaprevir and boceprevir triple-therapy regimens in the treatment of chronic HCV infection. **Suchzeitraum:** 1995 bis 10/2012 **Vergleich:** telaprevir vs. boceprevir **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 8 Studien **Endpunkte:** SVR-Rate, AEs ((anemia, diarrhea, nausea, pruritis, and rash), discontinuations **Ergebnisse** (basierend auf 8 Studien)**:** • With telaprevir, the ORs (95% CI) for SVR at 24 weeks in treatment-naive and treatment-experienced patients were 3.31 (2.27– 4.82; *P* < 0.0001) and 4.21 (1.83–9.72; *P*<0.001), respectively. • Telaprevir triple therapy did not result in more drug related discontinuations but did cause additional rash, pruritis, and anemia. • With boceprevir, the ORs (95% CI) were improved in both treatment-naive and treatment experienced patients (3.55 [2.66-4.56; *P*< 0.0001] and 7.34 [3.92–13.9; *P* <0.0001]), but with more treatment-related anemia and dysgeusia. <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.

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.
Chou 2013: Comparative Effectiveness of Antiviral Treatment for Hepatitis C Virus Infection in Adults: A	Systematischer Review mit Metaanalyse zum Vergleich der 2 Fach-Therapie und 3 Fach-Therapie. **Alle Genotypen.** The proportion of patients with HCV genotype-1 ranged from 44% to 78% **Fragestellung:** To compare benefits and harms of antiviral regimens for chronic HCV infection in treatment-naive adults. **Suchzeitraum:** 1947 bis 08/2012

Systematic Review.	**Vergleich:** • dual therapy with pegylated interferon alfa-2b plus ribavirin versus pegylated interferon alfa-2a plus ribavirin; • triple therapy with pegylated interferon (alfa-2a or -2b), ribavirin, and either telaprevir or boceprevir versus dual therapy; • different doses or durations of dual or triple therapy. **Endpunkte:** SVR-Rate **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 90 Studien **Ergebnisse:** • Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower likelihood of SVR than was pegylated interferon alfa-2a plus ribavirin (absolute difference, 8 percentage points [95% CI, 3 to 14 percentage points]) on the basis of 7 poor- to fair-quality trials. • For genotype 1 infection, fair-quality trials found that triple therapy with pegylated interferon, ribavirin, and either boceprevir (2 trials) or telaprevir (4 trials) was associated with a higher likelihood of SVR than was dual therapy (absolute difference, 22 to 31 percentage points). • Compared with dual therapy, boceprevir triple therapy increased risk for hematologic adverse events and telaprevir triple therapy increased risk for anemia and rash. A large well-designed cohort study and 18 smaller cohort studies found that an SVR after antiviral therapy was associated with lower risk for all-cause mortality than was no SVR. <u>Fazit der Autoren:</u> SVR rates for genotype 1 infection are higher with triple therapy that includes a protease inhibitor than with standard dual therapy. Die SVR-Rate nach einer antiviralen Therapie scheint mit verbesserten klinischen Ergebnissen assoziiert.
Canadian Agency for Drugs and Technologies in Health 2012: Boceprevir and Telaprevir for Chronic Hepatitis C Infection.	Health Canada recently approved boceprevir (Victrelis) and telaprevir (Incivek) for **treatment of chronic hepatitis C, genotype 1 infection**: • for previously treated patients, adding a protease inhibitor (PI) to standard therapy with peginterferon alfa and ribavirin (PR) can triple the likelihood of treatment success • there are no head-to-head trials to provide guidance on where each drug should be positioned with respect to the other Das Expertenkomitee empfiehlt die Ergänzung der Standardtherapie (Ribavirin plus Peginterferon) mit Boceprevir oder Telaprevir, wenn folgende Kriterien gelten: • reduzierter Preis • nachweisbare Viruslast (level of Hep. C Virus detectable) in den letzten 6 Monaten • ein mittels Biopsie nachgewiesenes Fibrosestadium von F2, F3 oder F4 • keine HIV- Ko-Infektion • nur eine Therapieoption (entweder 12 Wochen Telaprevir oder bis zu 44 Wochen Boceprevir) Bisher liegen lediglich umfassende Studien zum Endpunkt dauerhaftes virologisches Ansprechen (SVR) vor (vgl. siehe Abbildung).

	For boceprevir:[1] 	Trial	SVR for Patients Treated with Boceprevir plus PR	SVR for Patients Treated with Placebo plus PR
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SPRINT-2: Treatment-naive patients	63% to 66%	38%
RESPOND-2: Patients with a history of non-response or relapse on PR	59% to 66%	21%
Study 5685: Patients with a history of non-response or relapse on PR	64%	21% | *PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.* For telaprevir:[2] | Trial	SVR for Patients Treated with Telaprevir plus PR	SVR for Patients Treated with Placebo plus PR
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ADVANCE: Treatment-naive patients	75%	44%
REALIZE: Treatment-experienced patients	64% to 66%	16%	 *PR = peginterferon alfa and ribavirin; SVR = sustained virologic response.*
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 **Vergleich:** boceprevir or telaprevir in combination with pegylated interferon and ribavirin compared with pegylated interferon and ribavirin alone **Anzahl der Patienten:** k.A. **Ergebnisse** Der Review enthält eine deskriptive Beschreibung von 4 Phase III Studien (je 2 RCTs für Boceprevir (SPRINT-2, RESPOND-2) und 2 für Telaprevir (ADVANCE, REALIZE), die bereits im Rahmen der frühen Nutzenbewertung bewertet wurden. <u>Fazit der Autoren:</u> Boceprevir and telaprevir will revolutionize the management of hepatitis C genotype 1 patients and will most likely decrease the burden of end-stage disease worldwide. However, current clinical limitations include establishing appropriate and cost-effective treatment durations, and use in special populations such as transplant patients and patients coinfected with HIV. Future research will need to clarify these clinical obstacles to clearly define the role of these agents in hepatitis C management.
Cooper 2012: Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1 infection: an indirect comparison meta-analysis. Therapeutics and Clinical Risk Management 2012; 8:105-130.	Systematischer Review mit Metaanalyse zur Wirksamkeit und Sicherheit von Boceprivir und Telaprevir in Kombination mit pegiliertem Interferon Alpha und Ribavirin. Keine Angaben zu Patienten mit einer HIV/HCV-Koinfektion zu entnehmen. **Fragestellung**: Das Ziel dieser Studie war es, die relative Wirksamkeit und Sicherheit von Boceprevir und Telaprevir in einem indirekten Vergleich / Meta-Analyse zu untersuchen, wenn sie in Kombination mit pegyliertem Interferon alpha und Ribavirin verwendet werden. **Suchzeitraum:** Beginn der jeweiligen DB bis 10/2011 **Vergleich:** telaprevir or boceprevir coadministered with peginterferon alpha plus ribavirin (intervention) and placebo coadministered with peginterferon alpha plus ribavirin (control).

	Endpunkte: Primäre Endpunkte: dauerhaftes virologisches Ansprechen, Rezidive und Therapieabbruch; Sekundäre Endpunkte: unerwünschte Ereignisse wie Anämie, Neutropenie, Ausschlag und Juckreiz
	Anzahl der Patienten: 5072 Patienten
	Anzahl der Studien: 10 Studien
	Ergebnisse (basierend auf 10 ***Phase II- und III- Studien*** *(alles RCTs), davon 4 zu BOC und 6 zu TVR):*
	• Im indirekten Vergleich ergaben sich weder für therapie-naive noch für vorbehandelte Patienten signifikante Unterschiede in Bezug auf die primären Endpunkte
	• Im direkten Vergleich ergaben sich signifikante Unterschiede für die Dreifachtherapie sowohl mit BOC als auch mit TVR versus Placebo+Ribavirin+PegIFN Alpha für therapie-naive als auch für vorbehandelte Patienten
	  • **SVR** naive Patienten: RR 1,91 [95%KI 1,65-2,21]
	  • **SVR** vorbehandelte Patienten: RR 3,09 [95%KI 2,24-4,28]
	  • **Relapse** naive Patienten: RR 0,24 [95%KI 0,06-1,0]
	  • **Relapse** vorbehandelte Patienten: RR 0,36 [95%KI 0,2-0,62]
	  • **Therapieabbruch** naive Patienten: RR 0,65 [95%KI 0,47-0,89]
	  • **Therapieabbruch** vorbehandelte Patienten: RR 0,54 [95%KI 0,45-0,65]
	• TVR war häufiger assoziiert mit Ausschlag und Juckreiz; bei therapie-naiven Patienten traten unter BOC häufiger Neutropenien auf (RR 1,46 (95%KI 1,09-1,95)
	
	Fazit der Autoren:
	Boceprevir und Telaprevir erscheinen vergleichbar in Bezug auf die anhaltende virologische Ansprechrate, Rückfall, oder Behandlungsabbruch für Patienten, welche mit der Standard-Dosis-Therapie und „response-guided“ Behandlungsdauer behandelt wurden.

Cure 2012: Efficacy of telaprevir and boceprevir in treatment-naive and treatment-experienced genotype 1 chronic 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:** 01/2000 bis 07/2011 **Vergleich:** PR (alfa-2a or 2b) to another PR or TVR- or BOC-based therapy **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 11 Studien **Endpunkte:** SVR- Rate (defined as undetectable HCV RNA level 24 weeks after the end of therapy) **Anzahl der Patienten:** 5318 Patienten **Ergebnisse (basierend auf 11 Studien):** *Treatment-naive patients:* • for telaprevir (12 weeks+response guided treatment [RGT] 24/48 weeks PR) and boceprevir (24 weeks+RGT 28/48 weeks PR) versus PR were respectively 3.80 (2.78–5.22) and 2.99 (2.23–4.01). • The OR for telaprevir versus boceprevir was 1.42 (0.89–2.25), with a probability for telaprevir being more effective (P[OR41]) of 0.93. *Treatment-experienced patients:* • OR of telaprevir (12 weeksÞ48 weeks PR) and boceprevir (32

	weeksþRGT 36/48 weeks PR) versus PR were respectively 13.11 (7.30–24.43) and 5.36 (2.90–10.30). • The OR for telaprevir versus boceprevir was 2.45 (1.02–5.80), with telaprevir having a probability of 0.98 of being more effective. Fazit der Autoren: In the absence of direct comparative head-to-head studies between telaprevir and boceprevir for the treatment of chronic HCV genotype 1 patients, an indirect comparison based on Bayesian network meta-analysis suggests better efficacy for telaprevir than boceprevir in both treatment-naive and treatmentexperienced patients.
Dang 2012: Telaprevir for Chronic Hepatitis C with Genotype 1: A Meta-Analysis.	Systematischer Review zu Telaprevir (ohne Meta-Analyse). Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: We assessed its antiviral efficiency in untreated patients and in patients who did not have an SVR to previous therapy in order to identify an optimal regimen for each type of patient. **Suchzeitraum:** Bis 09/2010 **Vergleich:** telaprevir administered at any dose, duration and route administration, given separately or in combination *versus* no intervention, placebo or other intervention. **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 5 Studien **Endpunkte:** 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.
Gu 2012: Telaprevir for genotype 1 chronic hepatitis C: a systematic review and meta-analysis.	Systematischer Review mit Meta-Analyse zu Telaprevir**.** Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung**: To assess the beneficial and harmful effects of telaprevir for patients with genotype 1 chronic hepatitis C. **Suchzeitraum:** 1980 bis 05/2012 **Vergleich:** telaprevir in combination with peginterferon alfa and ribavirin

	versus no intervention or placebo in combination with peginterferon alfa and ribavirin **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 6 Studien **Endpunkte:** Primäre Endpunkte: SVR-Rate, virologic response at the end of treatment; Sekundäre Endpunkte: relapse rate**,** severe adverse events, treatment discontinuations, commonly reported adverse events, including anemia, neutropenia, rash and pruritus. **Ergebnisse (basierend auf 6 Studien):** • Telaprevir in combination with peginterferon alfa and ribavirin seemed to show a significant effect on sustained virologic response, virologic response at the end of treatment and relapse rate in naive patients and previously unsuccessfully treated patients, except T12PR12 which seemed without beneficial effect on: o Sustained virologic response: OR=1.41; 95% CI 0.83 to 2.40) o relapse rate (Odds Ratio OR=1.55; 95% CI 0.71 to 3.36) in naive patients. • It also was associated with a significantly higher incidence of severe: o adverse events OR=2.15, 95% CI1.29 to 3.58) o treatment discontinuation OR=4.79, 95% CI1.72 to 13.37) because of adverse events in previously unsuccessfully treated patients, but not in naive patients. Fazit der Autoren: Telaprevir in combination with peginterferon alfa and ribavirin has been recommended as option for the treatment of genotype 1 chronic hepatitis C. It has been considered as effective to improve viral response and reduce relapse rate in patient who suffer genotype 1 chronic hepatitis C. However, the treatment should be monitored carefully as it may cause some severe adverse events. For further confirmation of its treatment effect and clarify its possible adverse events, more randomized clinical trials need to be carried out.
Smith 2011: Telaprevir: an NS3/4A protease inhibitor for the treatment of chronic hepatitis C.	Review zu Telaprevir. Einzelne deskriptive Darstellung der verfügbaren Studien der Phasen I bis III. Patienten vom Genotyp 1. Patienten mit einer HIV/HCV-Koinfektion wurden ausgeschlossen. **Fragestellung:** To review the use of telaprevir for the treatment of chronic hepatitis C. **Suchzeitraum:** 1966 bis 01/2011 **Vergleich:** telaprevir with concomitant ribavirin treatment compared to 48 weeks of ribavirin treatment **Endpunkte:** SVR rates **Anzahl der Patienten:** k.A. **Ergebnisse:** • Telaprevir has activity against HCV genotype 1 infection in vitro and in vivo, but monotherapy results in rapid viral resistance. • In 3 Phase 2 and 3 Phase 3 randomized placebo-controlled trials, 12 weeks of telaprevir, along with varying durations of ribavirin treatment, induced higher sustained virologic response (SVR) compared with ribavirin alone. • SVR was approximately 70% in treatment-naïve patients, 50-60% for patients in whom • SVR had not occurred with prior ribavirin treatment, and 40-45% of those who received ribavirin alone.

	• There was a high incidence of maculopapular rash (52% in 1 trial) and anemia (27% in 1 trial) in telaprevir-treated patients. • The average dropout rate in Phase 3 trials as a result of adverse effects was 13%. Fazit der Autoren: "Twelve weeks of telaprevir with concomitant ribavirin treatment increases SVR for treatment-naïve and non-naïve patients with genotype 1 chronic HCV compared to 48 weeks of ribavirin treatment. Telaprevir may shorten the length of ribavirin therapy for some patients with extended rapid viral response, but viral mutations, adverse effects, and a high dropout rate may reduce the SVR see in clinical practice."

Systematische Reviews

Hinweis: Behandlung der chronischen Hepatitis C vom Genotyp 2 und 3
(je nach Darstellung Studienergebnisse auch andere Genotypen mit extrahiert)

Hartwell 2009: Pegylated and non-pegylated interferon-alfa and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and meta-analysis.	**Fragestellung:** The aim of this systematic review was to assess the clinical effectiveness of pegylated (PEG) and non-pegylated interferon (IFN) alfa and ribavirin (RBV) for the treatment of adults with histologically mild HCV. **Systematische Literaturrecherche im Suchzeitraum bis 2007** **Vergleich** Therapien: IFN (2a or 2b) + RBV vs PEG (2a or 2b) + RBV oder Monotherpie PEG, wenn RBV nicht möglich ist • Studies were included comparing the different drugs with placebo, each other, or best supportive care. **Population** Patients with mild HCV (1 Studien mit Patienten mit HIV Ko-infektionen; Überwiegend wurden therapienaive Patienten eingeschlossen) **Anzahl der Patienten:** 2,776 **Anzahl der Studien:** 10 Studien **Endpunkte:** SVR **Ergebnisse (10 Studien)** • Treatment with PEG + RBV combination therapy resulted in significantly higher sustained virological response (SVR) rates than treatment with IFN + RBV combination therapy. • Treatment for 48 weeks with PEG + RBV was significantly more effective than the same treatment for 24 weeks. • Significantly higher SVR rates were seen with IFN + RBV compared with either IFN monotherapy or no treatment. • Five IFN trials reported significantly higher SVR rates with IFN + RBV (range, 33–69 percent) compared with either IFN monotherapy (range, 18–23 percent) or no treatment (zero response). • A total of 460 participants were enrolled in the four trials included in the meta-analysis comparing IFN + RBV with IFN monotherapy or IFN + placebo. The relative risk (RR) of not experiencing an SVR was 0.59 (95 percent CI, 0.51 – 0.69) and was statistically significant (p < .00001). Heterogeneity was not statistically significant (p = .29) and the I^2 value was 20.7 percent.

	SVR by Genotype • SVR rates according to genotype were reported by all the included studies with broadly similar results. It should be noted that reporting of genotype groups was not consistent across trials making comparisons difficult, and few trials reported within-group comparisons. • SVRs were higher for patients with the more favorable genotypes (i.e., genotypes 2 and 3, commonly labeled as “non-1”) compared with genotype 1, irrespective of treatment. • In two of the PEG trials, between-group comparisons showed that patients with genotype 1 treated for 48 weeks had significantly higher response rates than patients on the same therapy for 24 weeks. • Treatment duration did not have a significant effect on virologic response for patients with genotype 2 or 3 for either of these PEG trials. **Fazit der Autoren** Patients with histologically mild HCV can be successfully treated with both PEG and IFN combination therapy, and response rates are broadly comparable with those achieved in patients with advanced disease. Treating patients in the early milder stages of HCV is, therefore, a clinically effective option.
Slavenburg 2009: Optimal length of antiviral therapy in patients with hepatitis C virus genotypes 2 and 3: a meta-analysis.	**Fragestellung:** The purpose of this study is to systematically analyse all randomized controlled trials (RCTs) that compare short (12-16 weeks) versus standard (24 weeks) duration in HCV genotypes 2 and 3, in order to assess the relative efficacy of each arm. **Systematische Literaturrecherche im Suchzeitraum:** 2000-2008 **Population:** Pat. mit HepC Typ 2 + 3 **Anzahl der Patienten:** k.A. **Anzahl der Studien:** 8 Studien Vergleich: standard pegylated interferon and ribavirin combination therapy in HCV genotypes 2 and 3 patients and compared short (12-16 weeks) with standard (24 weeks) treatment duration. (Pat. Mit HIV-Koinfektion wurden nicht eingeschlossen.) **Endpunkte: SVR** **Ergebnisse (8 Studien, n=2786):** • Meta-analyses were carried out on SVR data from three studies randomized at baseline and five studies randomized at rapid virological response (RVR) to either 12-16 weeks or a 24-week course. • Pooled SVR data were higher in standard treatment in RCTs that randomized at baseline, with a relative risk (RR) of 0.88 (95% confidence interval [Cl] 76-1.01). • The pooled proportion of SVR rates of RCTs that randomized at RVR were similar in the short treatment group (82%) as in the standard treatment (83%), with the pooled effect given by a RR of 1.00 (95% Cl 0.92-1.09) **Fazit der Autoren** In conclusion, this study shows that for HCV genotype 2 and 3 patients achieving RVR at week 4, the efficacy of a shorter (12-16 weeks) treatment with pegylated interferon and ribavirin is not different from 24 weeks. Patients who do not achieve RVR at week 4 should receive at least 24 weeks of treatment.

Hinweis: Behandlung der chronischen Hepatitis C alle Genotypen
(d.h. keine Differenzierung)

Awad 2010: Peginterferon alpha-2a Is Associated with Higher Sustained Virological Response than Peginterferon alfa-2b in Chronic Hepatitis C: Systematic Review of Randomized Trials.	Systematischer Review zu Peginterferon alpha-2a im Vergleich zu Peginterferon alpha-2b **Fragestellung:** We conducted a Cochrane systematic review to identify, assess, and collectively analyze all RCTs that would add to the body of evidence and strengthen inferences about which form of peginterferon may work best. **Suchzeitraum:** systematische Literaturrecherche bis Juli 2009 **Population:** alle Hepatitis C Genotypen (Eine Studie mit vorbehandelten Patienten, eine Studie mit HIV-Koinfektionen) **Anzahl der Patienten:** 5008 Patienten **Anzahl der Studien:** 12 Studien **Endpunkte*:*** SVR, liver-related morbidity plus all-cause mortality, and adverse events leading to treatment discontinuation. **Ergebnisse** (12 Studien, 5008 Patienten) • Overall, peginterferon alpha-2a significantly increased the number of patients who achieved an SVR (47%) versus peginterferon alfa-2b (41%) (RR 1.11, 95% CI 1.04-1.19; P = 0.004). • The number needed to treat was 25 patients (95% CI 14-100). • Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.58, and the heterogeneity was I^2 = 0% (Fig. 2). • Data from six trials for genotype 1 and 4 yielded an RR in favor of peginterferon alpha-2a (RR 1.21, 95% CI 1.03-1.42). Using relative risk as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.21, and the heterogeneity was I^2 = 30%. • Data from five trials for genotype 2 and 3 yielded an RR in favor of peginterferon alpha-2a (RR 1.11, 95% CI 1.02-1.22). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.89, and the heterogeneity was I^2 = 0%. Fazit der Autoren Current evidence suggests that peginterferon alpha-2a is significantly superior to peginterferon alfa-2b regarding benefits (SVR, which is clearance of the virus from the blood). However, there is insufficient evidence to detect any differences regarding harms (mortality and adverse events). Future trials must further the correlation between achieving SVR and clinically relevant outcomes such as risk of cirrhosis, hepatocellular carcinoma, and mortality.
Alavian 2010: The comparative efficacy and safety of peginterferon alpha-2a vs. 2b for the treatment	**Fragestellung:** The purpose of this meta-analysis is to compare the advantages and disadvantages of dual therapy with PEG-IFN-α2a, with dual therapy with PEG-IFN-α2b, based on the results of head-to- head randomized controlled trials. **Suchzeitraum:** Syst. Literaturrecherche; Suchzeitraum 2006-2010

of chronic HCV infection: a meta-analysis.	**Population:** Pat mit HepC Genotyp 1 + 4 treated for at least 48 weeks Pat mit HepC Genotyp 2 + 3 treated for at least 24 weeks (Pat mit Ko-infekionen HIV wurden ausgeschlossen) **Anzahl der Patienten:** 3518 Patienten **Anzahl der Studien:** 7 Studien **Endpunkte:** SVR (defined as undetectable HCV-RNA for the 6 months after treatment cessation) **Ergebnisse (7 Studien, n=3518 Patienten)** The probability of achieving SVR was higher in patients treated with PEG-IFN-α2a and ribavirin when compared with PEG-IFN-α2a and ribavirin, with an OR of 1.38 (95% CI 1.02-1.88; P=0.03). Heterogeneity was significant among the included studies (P=0.05, I^2=55%). In the subset of naïve patients with genotype 1/4 and 2 infection, OR of achieving SVR was also higher in those patients who received PEG-IFN-α2a plus ribavirin. The likelihood of SVR was also greater in PEG-IFN-α2a *vs*. 2b in the subset of naïve patients with both hard-to-treat HCV types: genotype 1/4 [6% (95% CI 0-12)] and genotype 2 [14% (95% CI 6-22)]. Anmerkung FB Med Der Anteil der Patienten mit Genotyp 1 + 4 lag in 3 Studien bei 100%, in den restlichen Studien bei 52-80 %.

Leitlinien

Allgemeine Empfehlungen

<table>
<tr><td rowspan="2">DGVS 2014:
Aktuelle Empfehlung der DGVS und des bng zur Therapie der chronischen Hepatitis C.</td><td>Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten e.V.</td></tr>
<tr><td>Methodik
Grundlage der Leitlinie: Die folgenden Empfehlungen sind bis zur Zulassung weiterer Therapiemöglichkeiten gültig und werden im Verlauf mit der Verfügbarkeit neuer Substanzen zeitnah aktualisiert.

Literatursuche: k.A.

Klassifikation der Evidenz nach dem Oxford-Schema:

<table>
<tr><th>Klasse</th><th>Therapie</th><th>Diagnostik</th><th>Prognose</th></tr>
<tr><td>Ia</td><td>ematische Übersicht (SR) von rando-misierten klinischen Studien (RCTs)</td><td>SR von diagnostischenKlasse 1-Studien; Clini-cal Decision Rule (CDR)[1]
von Klasse 1b-Studien
aus verschiedenen Zentren</td><td>SR von Inzeptionskohortenstudien; CDR[1], validiert inverschiedenen Populationen</td></tr>
</table>
</td></tr>
</table>

Ib	Einzelne RCTs	Validierungskohorten studie mit guten 2 Refe-renzstandards; oder CDR[1] getestet in einem Zentrum	Inzeptionskohortenst udie mit >80% Follow-up; CDR[1] validiert in einer Population
Ic	Alls-oder-Nichts[2]	Absolute SpPins und SnNouts[2]	Alles-oder-Nichts-Fallserien
IIa	SR von Kohortenstudien	SR[2] von Klasse 2-Studien	SR von retrospektiven Kohortenstudien oder Placebogruppen in RCTs
IIb	einzelne Fallkontrollst	explorative Kohortenstudien mit guten Referenzstandards; CDR[1] nach Ableitung, oder validiert nur anTeilgruppen[2] oder Datenbanken	Retrospektive Kohortenstudie oder Follow-up der Placebogruppe in einem RCT; CDR[1] nach Ableitung, oder validiert nur anTeil-gruppen[2]
IIc	Outcomes -Research-Studien, ökologische Studien	/	„Outcomes“ – Research-Studien
IIIa	SR2 von Fallkontrollstudien	SR2 von Klasse 3-Studien	/
IIIb	Einzelne Fallkontrollstudie	Nicht konsekutive Studie, oder ohne konsistenz angewandte Referenzstandards	/
IV	Fallserien (oder Kohorten-/Fall-Kontrollstudien mäßiger Qualität[2])	Fall.Kontroll-Studien, schlechter oder nicht unabhängiger Referenzstandard	Fallserien oder prognostische Kohortenstudien mäßiger Qualität2
V	Expertenmeinung ohne explizite Bewertung der Evidenz, oder basierend auf physiologischen Modellen, Laborforschung oder Definitionen	Expertenmeinung ohne explizite Bewertung der Evidenz, oder basierend auf physiologischen Modellen, Laborforschung oder Definitionen	Expertenmeinung ohne explizite Bewertung der Evidenz, oder basierend auf physiologischen Modellen, Laborforschung oder Definitionen

An den Evidenzgrad kann ein Minuszeichen (−) angehängt werden, um zu zeigen, dass keine schlüssige Antwort gegeben werden kann wegen: entweder einer einzelnen Arbeit mit weitem Konfidenzintervall oder eines SR mit beunruhigender Heterogenität2.

Derartige Evidenz ist als „unschlüssig“zu werten und kann somit nur zu einem Evidenzgrad D führen.

SpPins: high Specificity, a Positive result rules in the diagnosis; SnNouts: high Sensitivity, a Negative result rules out the diagnosis

[1]Algorithmen oder Punktesysteme, die helfen, eine Prognose oder diagnostische Kategorie abzuschätzen.

[2]Weitere Erläuterungen unter www.cebm.net/index.asp?o=1024

<table>
<tr><td></td><td>Empfehlungen

<u>Genotyp 1:</u>
Für Patienten mit einer HCV Genotyp 1 Infektion werden unter Berücksichtigung des Vortherapiestatus, viraler Resistenzen, der Dringlichkeit der Behandlung und der individuellen Interferonverträglichkeit folgende Therapieoptionen empfohlen:
• Sofosbuvir, PEG-Interferon und Ribavirin für 12 Wochen (Evidenzgrad Ib bzw. IIb, s.u.)
• Simeprevir plus Sofosbuvir +/- Ribavirin für 12 Wochen bei Interferon-Unverträglichkeit bzw. -Kontraindikationen (Evidenzgrad IIb)

<u>Genotyp 3:</u>
Für Patienten mit einer HCV Genotyp 3 Infektion werden unter Berücksichtigung des Vortherapiestatus, des Leberfibrosestadiums und der Interferonverträglichkeit folgende Therapieoptionen empfohlen:
• Sofosbuvir, PEG-Interferon und Ribavirin für 12 Wochen (Evidenzgrad IIb)
• Sofosbuvir plus Ribavirin für 24 Wochen (Evidenzgrad Ib)

Besondere Patientengruppen:

<u>Therapie vor und nach Lebertransplantation sowie bei dekompensierter Leberzirrhose</u>
Für Patienten vor und nach Lebertransplantation werden unter Berücksichtigung der Interferonverträglichkeit folgende Therapieoptionen empfohlen:
• Sofosbuvir plus Ribavirin (Evidenzgrad IIb)
• Sofosbuvir, PEG-Interferon und Ribavirin für 12 Wochen (Evidenzgrad IIb)
• Sofosbuvir plus Simeprevir +/- Ribavirin für 12 Wochen (Evidenzgrad IIb)</td></tr>
<tr><td>AASLD 2014:
Recommendations for Testing, Managing, and Treating Hepatitis C.</td><td>Leitlinie der American Association For The Study Of Liver Diseases

Methodik
Grundlage der Leitlinie: The Guidance was developed using an evidence-based review of information that is largely available to health care practitioners. Data from the following sources are considered by Panel members when making recommendations: research published in the peer-reviewed literature or presented at major national or international scientific conferences, safety warnings from FDA or other regulatory agencies or from manufacturers, drug interaction data, prescribing information from FDA-approved products, and registration data for new products under FDA review. Unpublished or presented reports, data on file and personal communications are generally not considered.

Literatursuche: 2010 bis 11/2013

Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation
<table>
<tr><td>Classification</td><td>Description</td></tr>
<tr><td>Class I</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 II</td><td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment</td></tr>
</table>
</td></tr>
</table>

Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it 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	Consensus opinion of experts, case studies, or standard of care

Empfehlungen

Genotype 1

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility

Rating: Class IIa, Level B

Alternative regimen for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN:

Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 to 24 weeks is an alternative for retreatment of IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

Alternative regimen for PEG/RBV (without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN:

Daily simeprevir (150 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) and weekly PEG for 48 weeks is an alternative for IFN-eligible persons with HCV genotype 1 infection. (All patients with cirrhosis who are receiving simeprevir should have well compensated liver disease.)

Rating: Class IIa, Level A

The following regimens are NOT recommended for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1:

- PEG/RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

- Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

For nonresponder patients with genotype 1 and a history of decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), treatment is not indicated because of the risks of PEG and boceprevir and telaprevir in this population.

	Genotype 3 *Recommended regimen for HCV genotype 3 PEG/RBV nonresponders:* Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for retreatment of HCV genotype 3 infection. Rating: Class IIa, Level A *Alternate regimen for HCV genotype 3 PEG/RBV nonresponder patients who are eligible to receive IFN:* Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 3 infection. Rating: Class IIa Level B
	The following regimens are NOT recommended for nonresponder patients with HCV genotype 3 infection: • PEG/RBV with or without telaprevir, boceprevir or simeprevir Rating: Class IIb, Level A • Monotherapy with PEG, RBV, or a DAA Rating: Class III, Level A
	Patients with Cirrhosis *Compensated Cirrhosis:* Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis. Rating: Class I, Level A *Decompensated Cirrhosis:* *Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).* Rating: Class I, Level C *If the decision to treat has been made, the recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. This regimen should be used only by highly experienced HCV providers:* Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks Rating: Class IIb, Level B
	The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe *hepatic impairment; CTP class B or C):* • Any IFN-based therapy Rating: Class III, Level A • Monotherapy with PEG, RBV, or a DAA Rating: Class III, Level A • Telaprevir-, boceprevir-, or simeprevir-based regimens Rating: Class III, Level A
World Health Organization 2014: Guidelines for the	Leitlinie der WHO
	Methodik Grundlage der Leitlinie: Systematic reviews and meta-analyses of the primary literature were commissioned to address the research questions

screening, care and treatment of persons with hepatitis C infection.	and patient-important outcomes. The final recommendations were agreed upon by consensus during a meeting of the Guidelines DevelopmentGroup in June 2013. These are the first WHO guidelines on the screening, care and treatment of persons with HCV infection. They are intended to complement existing guidance on the primary prevention of HCV and other bloodborne viruses by improving blood and injection safety, and health care for people who inject drugs (PWID) and other vulnerable groups, including those living with HIV. This guidelines document will be revised in 2016. Because a number of new medicines are expected to become available in the meantime, WHO will issue interim guidance twelve months after publication of these guidelines to provide recommendations regarding newly approved medicines. Suchzeitraum: k.A. ***GRADE categories of quality of evidence:*** *High:* We are very confident that the true effect lies close to that of the estimate of the effect *Moderate:* We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different *Low:* Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect *Very low:* We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect
	Empfehlungen *Assessing for HCV treatment:* All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviraltreatment. (Strong recommendation, moderate quality of evidence) *Treatment with pegylated interferon and ribavirin:* Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin. (Strong recommendation, moderate quality of evidence) *Treatment with telaprevir or boceprevir:* Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with pegylated interferon and ribavirin, is suggested for genotype 1 chronic HCV infection rather than pegylated interferon and ribavirin alone. (Conditional recommendation, moderate quality of evidence) *Treatment with sofosbuvir:* Sofosbuvir, given in combination with ribavirin with or without pegylated interferon (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than pegylated interferon and ribavirin alone (or no treatment for persons who cannot tolerate interferon). (Strong recommendation, high quality of evidence) *Treatment with simeprevir:* Simeprevir, given in combination with pegylated interferon and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than pegylated interferon and ribavirin alone. (Strong recommendation, high quality of evidence)

	Note: Recommendations 8 and 9 were made without taking resource use into consideration, as pricing information was not available for any country other than the United States at the time this recommendation was formulated.
EASL 2014: EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.	Leitlinie der European Association for the Study of the Liver (EASL)
	Methodik Grundlage der Leitlinie: The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system): **Evidence quality** / **Notes** / **Grading** High: Further research is very unlikely to change our confidence in the estimate of effect — A Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate — B Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain — C **Recommendation** / **Notes** / **Grading** Strong: Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost — 1 Weak: Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption — 2
	Empfehlungen *Indications for treatment: Who should be treated?* • All treatment-naive patients with compensated disease due to HCV should be considered for therapy (recommendation A1) • Treatment should be scheduled, not deferred, for patients with significant fibrosis (METAVIR score F3 to F4) (recommendation A1) • In patients with less severe disease, the indication for and timing of therapy can be individualized (recommendation B1) *Drug dosing in HCV genotype 1 therapy:* • The combination of PegIFN/RBV and TVR or BOC is the approved standard of care for chronic hepatitis C genotype 1 (recommendation A1). • There is no head to-head comparison to allow recommendation of TVR or BOC as preferred therapy • Patients with cirrhosis should never receive abbreviated treatment in BOC or TVR treatment regimens (recommendation B1) • Selected patients with high likelihood of SVR to PegIFN/ RBV or with contraindications to BOC or TVR can be treated with dual therapy • When lead-in is used to identify patients with IFN-α- sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment (recommendation B2) • Both pegylated IFN-α molecules, pegylated IFN-α2a (180 µg/wk) 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)

SIGN 2013: Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C. Edinburgh: SIGN; 2013.

SIGN guideline

Grundlage der Leitlinie: Methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at **www.sign.ac.uk/guidelines/fulltext/50/index.html.**

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

Empfehlungen

Treatment of chronic hepatitis C

- All treatment-naive patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy [A].
- All treatment-experienced patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy [A].
- Treatment-naive patients co-infected with HIV and HCV genotype 1 who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be considered for treatment with pegylated IFN and weight-based ribavirin for 48-72 weeks depending on viral response [B].

Wilkins 2013: British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013.

Leitlinie der British HIV Association (BHIVA)

Methodik

Grundlage der Leitlinie: BHIVA revised and updated the Association's guideline development manual in 2011. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations. The scope, purpose and guideline topics were agreed by the Committee and key questions concerning each guideline topic were drafted and a systematic literature review undertaken by an information scientist.

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

	disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with hepatic elastography or alternative non-invasive testing at least annually. Where there is confirmed progression of fibrosis, treatment initiation should be reconsidered.
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.	Department of Veterans Affairs Hepatitis C Resource Center Methodik Grundlage der Leitlinie: Grading system for recommendations adapted from the AASLD Practice Guidelines for the Diagnosis, Management, and Treatment of Hepatitis C. **Grading System for Recommendations** **Description** *Classification* Class I: Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy Class IIb: Usefulness/efficacy is less well established by evidence/opinion Class III: Conditions for which there is evidence and/or general agreement that a diagnostic evaluation procedure/treatment is not useful/effective, and in some cases, may be harmful *Level of evidence* Level A: Data derived from multiple RCT or meta-analyses Level B: Data derived from a single randomized trial, or nonrandomized studies Level C: Only consensus opinion of experts, case studies, or standard-of-care AASLD, American Association for the Study of Liver Diseases; RCT, randomized, controlled trials.
	Empfehlungen **Recommendations for PegIFN alfa with or without RBV treatment in genotype 1 patients:** • PegIFN alfa monotherapy may be used to treat patients with contraindications to RBV (Class I, Level A). • For patients who achieve RVR and have a low baseline viral load (HCV RNA < 400,000 IU / ml), 24-weeks of treatment with PegIFN – RBV may be sufficient (Class I, Level B). **Recommendations in patients with genotype 4 infection:** • Appropriate candidates with HCV genotype 4 infection should be treated with PegIFN alfa-2a 180 mcg per week or PegIFN alfa-2b 1.5 mcg / kg per week, plus RBV up to 1,400 mg per day for 48 weeks (Class I, Level A).

	Recommendations in patients with cirrhosis: • HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class < 7), adequate neutrophils (> 1.5 k/ mm 3), and adequate platelet counts (> 75 k/ mm 3) should be considered for treatment with BOC (for 44 weeks) or TVR (for 12 weeks) combined with PegIFN – RBV at standard doses for 48 weeks (Class I, Level B). • Patients with cirrhosis remain at risk for HCC and should undergo routine screening regardless of viral clearance status, in accordance with current guidelines (Class I, Level B). **Recommendations in patients with decompensated cirrhosis:** • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis (Class I, Level B). • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis (Class II, Level B). • IFN-based therapy in combination with RBV may be considered in patients awaiting liver transplantation with a Child-Pugh score < 7 and a MELD score ≤ 18 (Class I, Level A). • If antiviral therapy is undertaken, reduced IFN doses should be used and growth factors can be given to counteract treatmentassociated cytopenias (Class II, Level B).
	ANMERKUNGEN FBMED
	Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal Evidenzbasierte LL
NICE 2012: Telaprevir for the treatment of genotype 1 chronic hepatitis C.	Empfehlungen Telaprevir in combination with peginterferon alfa and ribavirin is recommended as an option for the treatment of **genotype 1 chronic hepatitis C** in adults with compensated liver disease: • who are previously untreated **or** • in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin has failed, including people whose condition has relapsed, has partially responded or did not respond. • Telaprevir plus peginterferon alfa and ribavirin was clinically more effective than peginterferon alfa and ribavirin alone in inducing a sustained virological response in previously untreated and previously treated patients.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2010: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.	Empfehlungen 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 FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
Brook 2010: European Guideline for the management of Hepatitis B and C virus infections.	British HIV Association guideline
	Methodik Grundlage der Leitlinie: The Writing Group used an evidence-based medicine approach to produce these guidelines. Level of Evidence: I = randomized controlled trial (RCT) or meta-analysis of several RCTs II = other good quality trial evidence III = observational studies/case reports IV= expert opinion
	Empfehlungen • Chronic HCV infection: Peginterferon alfa with ribavirin will cure chronic infection in approximately 50% of patients (Ia, A) • All other HCV genotypes (including 1 and 4) should be treated for 12-18 months. Treatment should be discontinued if there has not been a

	reduction in HCV viral load >2 log at week 12 of therapy or undetectable levels at week 24. Patients achieving undetectable viral load at week 4 (rapid virological responders) have the greatest chances of cure and may benefit from shorter courses of therapy. Patients are more likely to respond if they have less advanced liver fibrosis low serum HCV-RNA levels (<500,000 IU/ml), if they are infected with certain HCV genotypes (types 2 and 3) (Ib, A) • Patient selection for therapy depends mainly on HCV genotype and viral load. A liver biopsy is not necessary for making treatment decisions (1b, A)
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL

Leitlinien – Therapienaive Patienten

EASL 2014: EASL Clinical Practice Guidelines: Management of hepatitis C virus infection.	Leitlinie der European Association for the Study of the Liver (EASL) Methodik Grundlage der Leitlinie: The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in the CPG has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2). Evidence grading used in the EASL HCV Clinical Practice Guidelines (adapted from the GRADE system): **Evidence quality** / **Notes** / **Grading** High — Further research is very unlikely to change our confidence in the estimate of effect — A Moderate — Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate — B Low — Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain — C **Recommendation** / **Notes** / **Grading** Strong — Factors influencing the strenght of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost — 1 Weak — Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption — 2 Empfehlungen *Treatment-naïve patients with genotypes 2, 3, 4, 5, or 6:* • The combination of pegylated IFN-α and ribavirin is the approved standard of care for chronic hepatitis C genotype 2, 3, 4 ,5, and 6 (recommendation A1) • Ribavirin should be given at a weight-based dose of 15 mg/kg for genotypes 4, 5, and 6 and at a flat dose of 800 mg/day for genotypes 2 and 3 (recommendation A2) • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15 mg/kg (recommendation C2)
Leroy 2012: Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French	Guideline by the French Association for the Study of the Liver Methodik Grundlage der Leitlinie: The report of the meeting presented the position of FASL and included a rating of agreement on each item (level of agreement expressed as% of voters present in the room). The proposals were also classified according to the principles of the Grading of Recommendations, Assessment, Development and Evaluation working group system, which

Association for the Study of the Liver.	specifies three levels of evidence. Levels of evidence: A (high), B (moderate), C (low) and two grades of recommendation: 1 (strong), 2 (weak).
	Empfehlungen • Treatment-naive genotype 1 patients with predictive factors of poor response (non-CC genotypes of IL28B or fibrosis F3-F4) should receive triple therapy (PI plus PegIFN-RBV) as the first-line treatment (LoE: A; GoR: 1, level of agreement 84%).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office.	Department of Veterans Affairs Hepatitis C Resource Center
	Methodik (s. S. 40)
	Empfehlungen *Recommendations for therapy among treatment-naïve patients with genotype 1 infection:* • PegIFN alfa and RBV, in combination with BOC (800 mg orally every 7 – 9 h with food) or TVR (750 mg orally every 7 – 9 h with 20 g of fat) is the standard of care for most treatment-naïve genotype 1-infected patients (**Class I, Level A**). • If a TVR-containing regimen is used in treatment-naïve noncirrhotic patients who achieve eRVR, TVR should be discontinued at week 12 and PegIFN – RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1,000 IU/ ml at treatment week 4, and remains < 1,000 IU/ml or becomes undetectable by week 12, TVR should be discontinued at week 12, and PegIFN and RBV can be continued for another 36 weeks (**Class I, Level A**). • If a TVR-containing regimen is used in treatment-naïve cirrhotics • who achieve an HCV RNA that is undetectable or < 1,000 IU / ml at treatment weeks 4 and 12, TVR should be discontinued at week 12, and PegIFN – RBV can be continued for another 36 weeks (**Class I, Level A**). • If a BOC-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥ 1 log 10 during the 4-week lead-in, and HCV RNA is undetectable at weeks 8 – 24, 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 FBMED
	Evidenzbasierte LL

Leitlinien – Vorbehandelte Patienten und Nonresponder

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

<table>
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<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>
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</table>
</td></tr>
<tr><td>Empfehlungen

Triple therapy for genotype 1 patients who experienced virological failure during previous dual PegIFN/RBV therapy – results of phase III studies with BOC and TVR:

• Patients infected with HCV genotype 1 who failed to eradicate HCV on prior therapy with PegIFN/ RBV should be considered for re-treatment with the triple combination of PegIFN/RBV and a PI (recommendation A1)
• The previous response to IFN-based therapy is an important predictor of success of triple therapy, with relapsers having higher cure rates than partial responders, who in turn have higher cure rates than null responders. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy (recommendation A2)
• Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either PI (recommendation B2)
• Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated IFN-α, with or without ribavirin, can be re-treated with pegylated IFN-α and ribavirin (recommendation B2)</td></tr>
<tr><td rowspan="3">Leroy 2012:
Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French Association for the Study of the Liver.</td><td>Guideline by the French Association for the Study of the Liver</td></tr>
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Levels of evidence:
A (high), B (moderate), C (low) and two grades of recommendation: 1 (strong), 2 (weak).</td></tr>
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• Patients with PegIFN-RBV treatment failure should receive triple therapy</td></tr>
</table>

	with TVR or BOC and this should be the standard of care (LoE: C; GoR: 2, level of agreement 89%). • In patients who relapsed after PegIFN-RBV therapy, triple therapy should be quickly started in patients with severe fibrosis (F3–F4), is indicated for those with moderate fibrosis (F2) and should be discussed on a case-by-case basis in patients with minimal lesions (F0–F1) (LoE: B; GoR: 2, level of agreement 91%). • Patients who showed a partial response to PegIFN-RBV therapy but have severe fibrosis (F3–F4) should start triple therapy as soon as possible. For those with minimal to moderate fibrosis (_F2), treatment should be discussed on a case-by-case basis (LoE: B; GoR: 2, level of agreement 89%). • In null responders to PegIFN-RBV therapy with severe fibrosis, an SVR with triple therapy can be expected only in about 15% of F4 patients and 40% of F3 patients. • This treatment is indicated in the absence of any alternative (clinical trials). For F0–F2 patients, the chance of success is about 30% and the benefit–risk ratio should be evaluated on a case-by-case basis (LoE: B; GoR: 2, level of agreement 86%).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Yee 2012: Update on the Management and Treatment of Hepatitis C Virus Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office.	Department of Veterans Affairs Hepatitis C Resource Center
	Methodik (s. S. 40)
	Empfehlungen **Recommendations for retreatment of nonresponders and relapsers with genotype 1 infection:** • For patients who previously failed PegIFN – RBV, retreatment with BOC or TVR, and PegIFN – RBV may be considered, particularly in patients who were relapsers (**Class I, Level A**). • If a BOC-containing regimen is used for re-treatment of noncirrhotic prior partial responders or relapsers, the recommended treatment duration is 36 weeks if HCV RNA is undetectable from weeks 8 to 24. If HCV RNA is detectable at week 12, but < 100 IU / ml, and is undetectable from weeks 24 to 36, BOC can be discontinued at week 36 and PegIFN – RBV can be continued for an additional 12 weeks (**Class I, Level B**). • If a BOC-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU/ ml, and becomes undetectable from weeks 24 to 36 (**Class I, Level B**). • If a BOC-containing regimen is used for re-treatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but < 100 IU / ml, and become undetectable from weeks 24 to 36 (**Class II, Level C**). • If a TVR-containing regimen is used for re-treatment of prior relapsers and HCV RNA is undetectable from weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN – RBV should be continued for an additional 12 weeks. If HCV RNA is detectable, but < 1,000 IU / ml at week 4 and / or 12, TVR can be discontinued at week 12 and PegIFN – RBV can be continued for an additional 36 weeks (**Class I, Level B**). • If a TVR-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is < 1,000 IU / ml at weeks 4 and 12, TVR should be discontinued at week 12 and PegIFN alfa plus RBV should be continued for an additional 36 weeks (**Class I, Level B**).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL

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

DGVS 2014: Aktuelle Empfehlung der DGVS und des b*ng* zur Therapie der chronischen Hepatitis C.	Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten e.V.
	Methodik (siehe S. 31)
	Empfehlungen <u>HIV/HCV-Koinfektion</u> HIV/HCV Koinfektion Genotyp 1-6: • *Die antivirale Therapie sollte analog zu den Empfehlungen bei HCV monoinfizierten Patienten durchgeführt werden (Evidenzgrad IIb)* <u>Therapie vor und nach Lebertransplantation sowie bei dekompensierter Leberzirrhose</u> Für Patienten vor und nach Lebertransplantation werden unter Berücksichtigung der Interferonverträglichkeit folgende Therapieoptionen empfohlen: • *Sofosbuvir plus Ribavirin (Evidenzgrad IIb)* • *Sofosbuvir, PEG-Interferon und Ribavirin für 12 Wochen (Evidenzgrad IIb)* • *Sofosbuvir plus Simeprevir +/- Ribavirin für 12 Wochen (Evidenzgrad IIb)*
AASLD 2014: Recommendations for Testing, Managing, and Treating Hepatitis C.	Leitlinie der American Association For The Study Of Liver Diseases
	Methodik (siehe S. 32)
	Patients with HIV/HCV Coinfection *Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 infection who are eligible to receive IFN:* • Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype. Rating: Class I, Level B *Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN:* • Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive HIV/HCV-coinfected patients with HCV genotype 1 infection. Rating: Class I, Level B • Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily), with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for treatmentnaive and prior

PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.

Rating: Class IIa Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV nonresponse, regardless of IFN eligibility:

- Sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for prior PEG/RBV nonresponder, HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.

Rating: Class IIa, Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV plus telaprevir or boceprevir nonresponse:

- Treat as recommended for HCV-monoinfected individuals.

Recommended regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with genotype 2 and 3 infection:

- Use the same regimens as is recommended for persons with HCV monoinfection; specifically:
  - *For patients with genotype 2 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients. Patients who are prior nonresponders and have cirrhosis may benefit by extension of treatment to 16 weeks.*
    Rating: Class I, Level B
  - *For patients with genotype 3 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients.*
    Rating: Class I, Level B

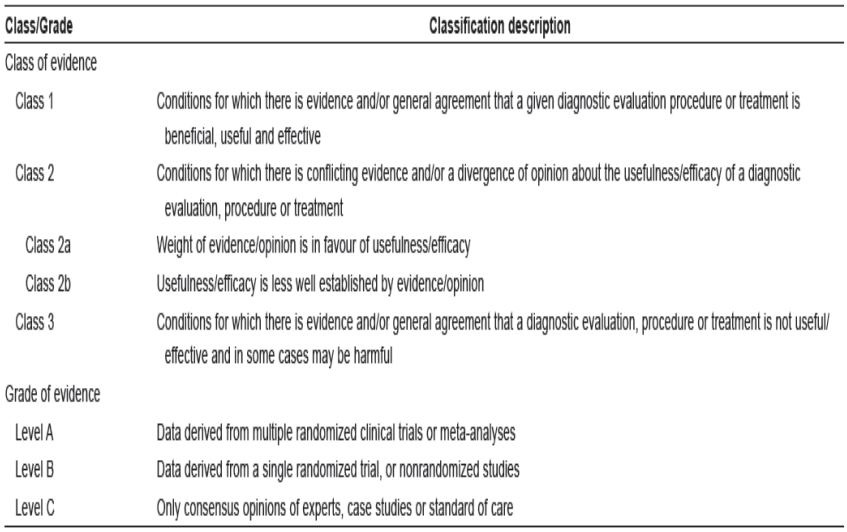
Alternative regimen(s) for treatment-naive or treatment-experienced (prior PEG/RBV relapse) HIV/HCV- coinfected patients with genotype 1 who are eligible to receive IFN:

- Simeprevir (150 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 24 weeks (for treatment-naive and treatment-experienced with prior relapse to PEG/RBV) is an acceptable regimen for IFN-eligible HIV/HCV-coinfected persons with either (1) HCV genotype 1b or (2) HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment. Simeprevir can only be used with the following antiretroviral drugs: raltegravir, rilpivirine, maraviroc, enfuvirtide tenofovir, emtricitabine, lamivudine, and abacavir.

Rating: Class IIa, Level B

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponders) HIV/HCV-coinfected patients with genotype 1 who are eligible for IFN:

- Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 1 infection,

	regardless of subtype. Rating: Class IIb, Level C *Alternative regimen(s) for treatment-naive and PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN:* • None *Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 1 who are ineligible to receive IFN:* • Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is an acceptable regimen for treatment-experienced (nonresponder) HIV/HCVcoinfected patients with HCV genotype 1 infection. Rating: Class IIb, Level C *Alternative regimen(s) for treatment-naive and PEG/RBV relapser, HIV/HCV-coinfected patients with genotype 2 or* *3 infection:* • None *Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 2 or 3 infection who are eligible to receive IFN:* • Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for treatment-experienced IFNeligible persons with HCV genotype 2 or 3 infection. Rating: Class IIa, Level C
	The following regimens are NOT recommended for treatment-naive or treatment-experienced HIV/HCV-coinfected patients: • PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks Rating: Class IIb, Level A • Monotherapy with PEG, RBV, or a DAA Rating: Class III, Level A
Hull 2013: CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of HIV/hepatitis C coinfection in adults.	Canadian Guideline for management and treatment of HIV/hepatitis C coinfection in adults
	Grading System for recommendation: 

Class/Grade	Classification description
Class of evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness/efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure or treatment is not useful/effective and in some cases may be harmful
Grade of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies or standard of care

	RECOMMENDATIONS 25. Genotype 1-infected HIV-HCV coinfected patients should be treated with either boceprevir or telaprevir in combination with pegylated interferon and ribavirin (Class 1, Level A). 26. Telaprevir should be used for the first 12 weeks, while boceprevir should begin after a four-week lead-in of pegylated interferon and ribavirin and continue for the remainder of therapy (Class 1, Level A). 27. At this time, a full 48-week course of pegylated interferon and ribavirin is recommended because there is no current evidence regarding response-guided therapy in coinfected patients (Class 1, Level C). 28. Standard stopping rules at weeks 4, 12 and 24 (telaprevir), or weeks 8, 12 and 24 (boceprevir) developed for monoinfection should be applied to the HIV-HCV coinfection context (Class 1, Level C).
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.	Department of Veterans Affairs Hepatitis C Resource Center
	Methodik (s. S. 40)
	Empfehlungen *Patienten mit HIV / HCV-Ko-Infektionen:* • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy (Class I, Level B). • Patients should be treated with PegIFN – RBV at doses similar to those with HCV monoinfection (Class I, Level B). • Patients should be treated with PegIFN – RBV for 48 weeks, regardless of genotype (Class I, Level A).
NICE 2012: Boceprevir for the treatment of genotype 1 chronic hepatitis C.	<u>Patients with HCV infection who are co-infected with HIV:</u> • The Committee considered the use of boceprevir plus peginterferon alfa and ribavirin in patients with HCV infection who are co-infected with HIV*. * Although these patients were not represented in the pivotal clinical trials, based on the current evidence available, the Committee concluded that there was no reason to make any different provision for these patients.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
NICE 2012: Telaprevir for the treatment of genotype 1 chronic hepatitis C.	<u>Patients with HCV infection who are co-infected with HIV:</u> The Committee considered what impact excluding from trials patients co-infected with HIV and intravenous drug users had on the generalisability of the results to the UK population. It concluded that although these patients were not represented in the pivotal clinical trials, based on the current evidence available, there was no reason to make any different provision for these patients.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal

NICE 2010: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.	Empfehlungen ***Peginterferon alfa-2a*** • People co-infected with HIV should also be treated for 48 weeks, regardless of genotype. ***Peginterferon alfa-2b*** • People co-infected with HIV should be treated for 48 weeks regardless of HCV genotype.
	ANMERKUNGEN FBMED
	• Systematische Literaturrecherche; LL wurde entwickelt anhand NICE single technology appraisal
Brook 2010: European Guideline for the management of Hepatitis B and C virus infections.	British HIV Association guideline
	Methodik Grundlage der Leitlinie: The Writing Group used an evidence-based medicine approach to produce these guidelines. Level of Evidence: I = randomized controlled trial (RCT) or meta-analysis of several RCTs II = other good quality trial evidence III = observational studies/case reports IV= expert opinion
	Empfehlungen • HIV-positive patients respond to treatment, although not as well as HIVnegative patients **(Ib, A)**. • Sustained virological response in those completing therapy is 11-29% for genotypes 1 or 4 and 43-73% for genotypes 2 or 3 **(1b, A)**
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL
Brook 2010: British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010.	British HIV Association guideline
	Methodik Grundlage der Leitlinie: The Writing Group used an evidence-based medicine approach to produce these guidelines. Level of Evidence: I = randomized controlled trial (RCT) or meta-analysis of several RCTs II = other good quality trial evidence III = observational studies/case reports IV= expert opinion
	Empfehlungen <u>Patients with HCV infection who are co-infected with HIV:</u> • Anti-HCV treatment should be started before the CD4 count falls below 350 cells/mL and before ART is started, if possible (LoE: I). • The aim of treatment is an SVR (undetectable viral load 24 weeks post treatment) (LoE: I). • An RVR (viral load undetectable) at 4 weeks of treatment predicts response. Lack of EVR (nondetectable viral load or 42 log10 fall at 12 weeks) or detectable viral load at 24 weeks of treatment predicts nonresponse and therapy should be stopped (LoE: I). • Any ART should be stabilized before anti-HCV therapy is commenced (LoE: I). • Careful assessment of liver fibrosis is recommended, especially for patients with HCV genotypes 1 and 4 or those with suspected cirrhosis (LoE: I).

	• For genotypes 1 a pretreatment liver biopsy is recommended, or a hepatic elastography if the biopsy is refused (LoE: I). • Consider treatment for all patients with genotypes 1/4, especially if there is significant liver fibrosis (Ishak grade F3 or more) (LoE: I). • Treatment in all genotypes should be with pegylated interferon weekly plus ribavirin at 1000–1200mg daily, supported by erythropoietin/growth factors if necessary (LoE: I). • Treat patients with genotypes 1 for 48 weeks if there is an RVR, or 72 weeks if there was a 2 log10 drop but detectable HCV RNA at week 12 and they become PCR negative at 24 weeks (LoE: I).
	ANMERKUNGEN FBMED
	• Evidenzbasierte LL

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NIHR Horizon Scanning Centre 2012: Sofosbuvir for chronic hepatitis C infection with compensated liver disease.

1. Trial

NEUTRINO, NCT01641640; sofosbuvir with peg-IFN and RBV; phase III.

Ziel: The primary efficacy objective of NEUTRINO was to determine the efficacy of treatment with SOF+PEG+RBV, as measured by the proportion of subjects with SVR12.

2. Methodik

Population: n=300 (planned); aged >18 years of age; HCV genotype 1, 4, 5 or 6 treatment naive.

Schedule: Sofosbuvir 400mg once daily in combination with RBV and peg-IFN.

Endpunkte: primary: SVR at week 12; secondary: Efficacy 4 and 24 weeks post dosing, HCV RNA during and post-treatment, viral resistance.

3. Ergebnisse (entnommen aus dem EPAR: Sovaldi)

Number of Subjects with SVR12 n, %
Treatment-naive

	SOF+PEG+RBV 12 Weeks (N = 327)
Overall SVR12	296/327 (90.5%)
No Cirrhosis	253/273 (92.7%)
Cirrhosis	43/54 (79.6%)
Genotype 1 (1a, 1b, 1a/1b)	262/292 (89.7%)
Genotype 1a	206/225 (91.6%)
Genotype 1b	55/66 (83.3%)
Genotypes 4, 5, or 6	34/35 (97.1%)

	Primary Analysis Treatment group: SOF + RBV + PEG for 12 weeks % of subjects with SVR12 (95% CI): 90.5 (86.8-93.5) Relapse rate (%): 8.6 Virologic failure rate (%): 8.6
NIHR Horizon Scanning Centre 2012: Sofosbuvir for chronic hepatitis C infection with compensated liver disease.	1. Trial QUANTUM, NCT014435044; Sofosbuvir and PSI-352938, PSI-352938 monotherapy, sofosbuvir, PSI-352938 and RBV or sofosbuvir and RBV; phase II
	2. Methodik (Randomised, placebo-controlled) Population: n=239 (planned) aged >18 years of age; chronic HCV infection; treatment naive. Arm 1: sofosbuvir 400mg with PSI-352938 300mg once daily for 12 weeks. Arm 2: PSI-352938 300mg once daily for 12 weeks. Arm 3: sofosbuvir with RBV 400mg once daily for 12 weeks. Arm 4: sofosbuvir 400mg with PSI-352938 300mg and RBV once daily for 12 weeks. Arm 5: PSI-352938 300mg once daily for 24 weeks. Arm 6: Sofosbuvir 400mg once daily with PSI-352938 300mg once daily for 24 weeks. Arm 7: sofosbuvir 400mg once daily with RBV for 24 weeks. Arm 8: sofosbuvir 400mg with PSI-352938 300mg and RBV once daily for 24 weeks. Arm 9: Placebo for 24 weeks followed by randomization through arms 1-8. Endpunkte: primary: Decreased HCV RNA at 24 weeks; secondary: AEs, HCV RNA, ALT normalisation, SVR at week 48, drug resistance
	3. Ergebnisse 25 participants randomised to 12 week treatment arms. At 4 weeks post-treatment results available for 17 genotype 1 participants: 59% (n=10) remained HCV RNA undetectable and 41% (n=7) experienced viral relapse. 7 participants who have reached 8 weeks post treatment period have remained HCV RNA undetectable. Adverse effects: Sofosbuvir was well tolerated, with no participants experiencing viral rebound and no discontinuation due to AEs.
NIHR Horizon Scanning Centre 2012: Sofosbuvir for chronic hepatitis C infection with	1. Trial NCT01054729; sofosbuvir 100 mg, 200 mg or 400 mg vs placebo both in combination with peg-IFN and RBV; phase II
	2. Methodik Population: n=64 (planned); 18-65 years of age; HCV genotype 1 Schedule:

compensated liver disease.	Arm 1: sofosbuvir 100mg or placebo once daily for 28 days, both with peg-IFN and RBV for 48 weeks. Arm 2: sofosbuvir 200mg or placebo once daily for 28 days with peg-IFN and RBV for 48 weeks. Arm 3:sofosbuvir 400mg or placebo once daily for 28 days with peg-IFN and RBV for 48 weeks. Endpunkte: primary: Safety and tolerability; secondary: HCV RNA
	3. Ergebnisse Sofosbuvir 100mg, 200mg, and 400mg were generally safe and well tolerated with no dose-dependent changes in the adverse event profile. Clinical efficacy was higher in the 200mg and 400mg dosing groups. Adverse effects: Sofosbuvir 100mg, 200mg, and 400mg were generally safe and well tolerated with no dose-dependent changes in the adverse event profile.
Horizon Scanning Centre 2013: Sofosbuvir with ledipasvir for hepatitis C, genotype 1.	1. Trial LONESTAR, NCT01726517, GS-US-337-0118; sofosbuvir/ledipasvir with and without ribavirin; phase II
	2. Methodik Population: n=100 (planned); aged 18 years and older; HCV infection; genotype 1; chronic; treatment naïve or experienced. Schedule: Treatment naïve participants sofosbuvir/ledipasvir, oral, 400mg/90mg once daily for 8 or 12 wks; or sofosbuvir/ledipasvir, oral, 400mg/90mg once daily, with ribavirin, 500mg or 600mg twice daily for 8 wks; Treatment experienced participants sofosbuvir/ledipasvir, oral, 400mg/90mg once daily for 12 wks; or sofosbuvir/ledipasvir, oral, 400mg/90mg once daily, with ribavirin, 500mg or 600mg twice daily for 12 wks Endpunkte: primary: SVR; safety and tolerability; secondary: Viral resistance to study drug; viral dynamics; pharmacokinetics.
	3. Ergebnisse For treatment naïve participants: sofosbuvir/ledipasvir 8wks, 12wks and sofosbuvir/ledipasvir with ribavirin respectively, 95% achieved SVR8a, 100% achieved SVR4b, 100% achieved SVR8; for treatment experienced participants: for sofosbuvir/ledipasvir and sofosbuvir/ledispavir with ribavirin respectively, 95% achieved SVR4, 95% achieved SVR4. Adverse effects: Not reported

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 17.07.2014

Schritt	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	#5 or #6 or #7
#9	#8 from 2009 to 2014

MEDLINE (PubMed) am 17.07.2014

Schritt	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 ("2009/07/01"[PDAT] : "2014/07/17"[PDAT])

MEDLINE (PubMed) nach Leitlinien am 17.07.2014

Schritt	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
#17	(#11) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title])
#18	(#17) AND ("2009/07/01"[PDAT] : "2014/07/17"[PDAT])

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