Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: Elvitegravir/ Cobicistat/ Emtricitabin/ Tenofoviralafenamid

Stand: März 2017

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

Elvitegravir/ Cobicistat/ Emtricitabin/ Tenofoviralafenamid
Geplantes Anwendungsgebiet (laut Beratungsanforderung):
HIV-Behandlung bei Kindern von 6 bis 11 Jahren.

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht II* Zugelassene Arzneimittel im Anwendungsgebiet
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	Es liegen keine Beschlüsse vor
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:	
Elvitegravir/ Cobicistat/ Emtricitabin/ Tenofoviralafenamid J05AR18 Genvoya®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Genvoya wird zur Behandlung von Erwachsenen, Jugendlichen und **Kindern (ab 6 Jahren und mit einem Körpergewicht von mindestens 25 kg)** angewendet, die mit dem humanen Immundefizienzvirus 1 (HIV-1) infiziert sind. Die HI-Viren dieser Patienten dürfen keine bekanntermaßen mit Resistenzen gegen die Klasse der Integrase-Inhibitoren, Emtricitabin oder Tenofovir verbundenen Mutationen aufweisen.
Proteasehemmer (PI)	
Ritonavir (RTV) J05AE03 Norvir®	Ritonavir ist in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von HIV-1-infizierten Patienten (Erwachsene und **Kinder von 2 Jahren** und älter) angezeigt.
Fosamprenavir (FPV) J05AE07 Telzir®	Telzir in Kombination mit niedrig dosiertem Ritonavir ist zur Behandlung von mit dem humanen Immundefizienz-Virus Typ 1 (HIV-1) infizierten Erwachsenen, Jugendlichen und **Kindern ab 6 Jahren** in Kombination mit anderen antiretroviralen Arzneimitteln angezeigt. Bei antiretroviral mäßig vorbehandelten Erwachsenen konnte nicht belegt werden, dass Telzir in Kombination mit niedrig dosiertem Ritonavir gleich wirksam ist wie die Kombination aus Lopinavir/Ritonavir. Es wurden keine Vergleichsstudien bei Kindern oder Jugendlichen durchgeführt. Bei stark vorbehandelten Patienten ist die Anwendung von Telzir in Kombination mit niedrig dosiertem Ritonavir nicht ausreichend untersucht. Bei mit Proteasehemmern (PI) vorbehandelten Patienten sollte die Wahl von Telzir unter Berücksichtigung des individuellen viralen Resistenzmusters und der Vorbehandlung des Patienten erfolgen.
Atazanavir (ATV) J05AE08 Reyataz®	REYATAZ Kapseln in Kombination mit niedrig dosiertem Ritonavir sind in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von HIV-1-infizierten Erwachsenen und **Kindern ab 6 Jahren** indiziert. Basierend auf den vorhandenen virologischen und klinischen Daten von Erwachsenen ist für Patienten mit Stämmen, die gegen mehrere Proteaseinhibitoren (≥4 PI-Mutationen) resistent sind, kein Nutzen zu erwarten. Es liegen nur sehr begrenzte Daten zu Kindern im Alter von 6 bis unter 18 Jahren vor. Die Entscheidung für REYATAZ sollte bei Erwachsenen und Kindern, die bereits antiretroviral vorbehandelt sind, auf individuellen viralen Resistenztests und der Krankengeschichte des Patienten basieren.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Darunavir (DRV) J05AE10 Prezista®	PREZISTA zusammen mit niedrig dosiertem Ritonavir eingenommen ist indiziert in Kombination mit anderen antiretroviralen Arzneimitteln zur Therapie bei Patienten mit Infektionen mit dem humanen Immundefizienzvirus (HIV-1). PREZISTA 150 mg Tabletten können zur Erreichung der geeigneten Dosis angewendet werden (siehe Abschnitt 4.2): • Zur Therapie der HIV-1-Infektion bei antiretroviral (ART) vorbehandelten Erwachsenen, einschließlich derer, die mehrfach vorbehandelt wurden. • Zur Behandlung der HIV-1-Infektion bei **pädiatrischen Patienten ab 3 Jahren** und mindestens 15 kg Körpergewicht. Die Entscheidung für einen Therapiebeginn mit PREZISTA bei solchen ART- vorbehandelten Patienten, und zum Einsatz von PREZISTA sollte auf Basis der Daten einer Genotypisierung getroffen werden.
Nukleosidale und nukleotidale Inhibitoren der Reversen Transkriptase (NRTI)	
Zidovudin (AZT) J05AF01 Generisch	Retrovir zur oralen Anwendung ist angezeigt in der antiretroviralen Kombinationstherapie zur Behandlung von Erwachsenen und **Kindern**, die mit dem humanen Immundefizienz- Virus (HIV) infiziert sind. Die Chemoprophylaxe mit Retrovir ist angezeigt bei HIV-positiven Schwangeren (nach der 14. Schwangerschaftswoche) zur Prävention der materno-fetalen HIV-Transmission und zur Primärprophylaxe einer HIV Infektion bei Neugeborenen.
Didanosin (ddI) J05AF02 Videx®	VIDEX ist in Kombination mit anderen antiretroviralen Arzneimitteln für die Behandlung von HIV-1-infizierten **Patienten** angezeigt, nur wenn andere antiretrovirale Arzneimittel nicht angewendet werden können.
Stavudin (D4T) J05AF04 Zerit®	Zerit ist in Kombination mit anderen antiretroviralen Arzneimitteln für die Behandlung von HIV-infizierten erwachsenen Patienten und **Kindern (über 3 Monate)** nur dann indiziert, wenn andere antiretrovirale Arzneimittel nicht angewendet werden können. Die Dauer der Behandlung mit Zerit sollte auf den kürzest möglichen Zeitraum begrenzt werden.
Lamivudin (3TC) J05AF05 Generisch	Lamivudin ist als Teil einer antiretroviralen Kombinationstherapie zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV) bei Erwachsenen und **Kindern** angezeigt.
Abacavir (ABC) J05AF06 Generisch	Das Arzneimittel ist angezeigt in der antiretroviralen Kombinationstherapie zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV) bei Erwachsenen, Jugendlichen und **Kindern**. Hinweise zu den Anwendungsgebieten - Der Wirksamkeitsnachweis von des Arzneimittels basiert hauptsächlich auf Ergebnissen von Studien mit zweimal täglicher Verabreichung, die bei nicht vorbehandelten erwachsenen Patienten in Form einer Kombinationstherapie durchgeführt wurden. - Vor Beginn der Behandlung mit Abacavir sollte unabhängig von der ethnischen Zugehörigkeit jeder HIV-infizierte Patient auf das Vorhandensein des HLA-B*5701-Allels hin untersucht werden. Patienten, bei denen bekannt ist, dass sie das HLA-B*5701-Allel tragen, sollten Abacavir nicht anwenden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Tenofovirdisoproxil (TDF) J05AF07 Viread®	Viread 123 mg Filmtabletten werden in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung HIV-1-infizierter **pädiatrischer Patienten im Alter von 6 bis < 12 Jahren mit einem Körpergewicht von 17 kg bis unter 22 kg** angewendet, bei denen der Einsatz von First-Line-Arzneimitteln aufgrund einer Resistenz gegenüber NRTI oder aufgrund von Unverträglichkeiten ausgeschlossen ist. Die Entscheidung für Viread zur Behandlung von antiretroviral vorbehandelten Patienten mit HIV-1-Infektion sollte auf viralen Resistenztests und/oder der Behandlungshistorie der einzelnen Patienten basieren.
Emtricitabin (FTC) J05AF09 Emtriva®	Emtriva wird in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung HIV-1-infizierter Erwachsener und **Kinder im Alter von 4 Monaten und darüber** angewendet. Diese Indikation beruht auf Studien an nicht vorbehandelten Patienten und an vorbehandelten Patienten mit stabiler virologischer Kontrolle. Es liegen keine Erfahrungswerte über die Anwendung von Emtriva bei Patienten vor, deren gegenwärtige Therapie versagt oder die ein mehrfaches Therapieversagen aufweisen. Bei der Entscheidung über ein neues Behandlungsschema für Patienten, bei denen eine antiretrovirale Therapie versagt hat, müssen die Mutationsmuster der verschiedenen Arzneimittel und vorangegangene Therapien beim einzelnen Patienten sorgfältig berücksichtigt werden. Ein Resistenztest – sofern verfügbar – könnte angebracht sein.
Nicht-nukleosidale Inhibitoren der reversen Transkriptase (NNRTI)	
Nevirapin (NVP) J05AG01 generisch	in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von HIV-1-infizierten Erwachsenen, Jugendlichen und **Kindern jeden Alters** indiziert. Die meisten Erkenntnisse beziehen sich auf Nevirapin in Kombination mit nukleosidischen Reverse-Transkriptase-Hemmern (NRTIs). Die Entscheidung, welche Therapie nach einer Behandlung mit Nevirapin gewählt wird, sollte auf klinischer Erfahrung und Resistenztestung basieren.
Efavirenz (EFV) J05AG03 Generisch	Efavirenz ist zur antiviralen Kombinationsbehandlung von humanem Immundefizienz- Virus Typ 1 (HIV-1)-infizierten Erwachsenen, Jugendlichen und **Kindern ab 3 Jahre** angezeigt. Efavirenz wurde bei Patienten mit fortgeschrittener HIV-Erkrankung, das heißt bei Patienten mit CD4-Zahlen von <50 Zellen/ mm^3 oder nach Versagen von Schemata, die einen Proteaseinhibitor (PI) enthalten, nicht ausreichend untersucht. Eine Kreuzresistenz von Efavirenz mit Pis wurde nicht dokumentiert. Gegenwärtig liegen keine ausreichenden Daten über die Wirksamkeit der sich anschließenden Anwendung einer auf PI-basierenden Kombinationstherapie nach Versagen der Efavirenz enthaltenden Schemata vor. Eine Zusammenfassung der klinischen und pharmakodynamischen Informationen siehe Abschnitt 5.1.
Etravirin (ETV) J05AG04 Intelence®	INTELENCE in Kombination mit einem geboosterten Protease-Inhibitor und anderen antiretroviralen Arzneimitteln ist indiziert für die Behandlung von Infektionen mit dem humanen Immundefizienz-Virus 1 (HIV-1) bei antiretroviral vorbehandelten erwachsenen Patienten und bei antiretroviral vorbehandelten **pädiatrischen Patienten ab 6 Jahren** (siehe Abschnitte 4.4, 4.5 und 5.1). Die Indikation bei Erwachsenen basiert auf den Analysen der 48. Woche von 2 Phase- III-Studien bei in hohem Maße vorbehandelten Patienten, in denen INTELENCE in Kombination mit einer optimierten Basistherapie (optimised background regimen/ OBR), die Darunavir/Ritonavir einschloss, untersucht wurde. Die Indikation bei pädiatrischen Patienten basiert auf 48-Wochen-Analysen einer einarmigen Phase-II-Studie bei antiretroviral vorbehandelten pädiatrischen Patienten (siehe Abschnitt 5.1).
Integrase-Inhibitoren (INI)	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Raltegravir (RAL) J05AX08 Isentress®	ISENTRESS® ist angezeigt in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung einer Infektion mit dem Humanen Immundefizienzvirus (HIV-1) bei Erwachsenen, Jugendlichen, **Kindern, Kleinkindern und Säuglingen** ab 4 Wochen.
Antivirale Mittel zur Behandlung von HIV Infektionen, Kombinationen	
Lamivudin und Zidovudin J05AR01 Generisch	ist angezeigt in der antiretroviralen Kombinationstherapie zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV) (siehe Abschnitt 4.2).
Abacavir und Lamivudin J05AR02 Generisch	Kivexa ist angezeigt in der antiretroviralen Kombinationstherapie zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV) bei Erwachsenen, Jugendlichen und **Kindern mit einem Körpergewicht von mindestens 25 kg**. Vor Beginn der Behandlung mit Abacavir sollte unabhängig von der ethnischen Zugehörigkeit jeder HIV-infizierte Patient auf das Vorhandensein des HLA-B*5701-Allels hin untersucht werden. Patienten, bei denen bekannt ist, dass sie das HLA-B*5701-Allel tragen, sollten Abacavir nicht anwenden, außer wenn basierend auf der Behandlungsgeschichte und den Ergebnissen der Resistenztestung keine andere Therapieoption für diese Patienten verfügbar ist .
Lopinavir und Ritonavir J05AR10 Kaletra®	Kaletra ist in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von mit dem humanen Immundefizienz-Virus (HIV-1) infizierten **Kindern über 2 Jahre**, Jugendlichen und Erwachsenen angezeigt. Bei bereits mit Proteasehemmern vorbehandelten HIV-1-infizierten Erwachsenen sollte die Anwendung von Kaletra auf einer individuellen virologischen Resistenzuntersuchung und der Behandlungsvorgeschichte des Patienten beruhen.
Andere antivirale Mittel	
Enfuvirtid (ENF) J05AX07 Fuzeon®	Fuzeon wird in Kombination mit anderen antiretroviralen Arzneimitteln angewendet bei HIV-1-infizierten **Patienten**, die eine Behandlung erhalten haben und ein Therapieversagen gezeigt haben mit Regimen, welche zumindest je ein Arzneimittel aus jeder der antiretroviralen Substanzklassen Proteasehemmer, nicht-nukleosidische Reverse-Transkriptase-Hemmer und nukleosidische Reverse-Transkriptase-Hemmer enthielten, oder die eine Unverträglichkeit gegenüber vorangegangenen antiretroviralen Behandlungsregimen haben. Bei der Entscheidung über ein neues Behandlungsregime für Patienten, die gegenüber einem antiretroviralen Regime ein Therapieversagen zeigten, sollen die Behandlungsgeschichte des individuellen Patienten und die Mutationsmuster in Verbindung mit den verschiedenen Arzneimitteln besonders beachtet werden. Sofern verfügbar, können Resistenzuntersuchungen angemessen sein.

Quellen: Fachinformationen, Lauer-Taxe (Stand 14.03.2017)

Abteilung Fachberatung Medizin

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

Vorgang: 2017-B-009 (Elvitegravir/Cobicistat/Emtricitabin/Tenofoviralafenamid)

Auftrag von: Abt. AM

bearbeitet von: Abt. FB Med

Datum: 16.02.2017

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *Infektionen mit Humanen Immundefizienzvirus (HIV)* durchgeführt. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Erstrecherche ergab 832 Quellen und umfasste den Zeitraum: 01.04.2011 bis 25.04.2016. Die Folgerecherche deckte den Zeitraum vom 25.04.2016 bis 01.02.2016 (Cochrane Reviews) respektive 06.02.2016 (Leitlinien, Systematische Reviews und Handsuche) ab und ergab 95 Treffer.

Die Treffer wurden in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Für die Synopse wurden nur die Quellen der letzten 5 Jahre berücksichtigt. Insgesamt ergab dies 44 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

zur Behandlung von Erwachsenen, Jugendlichen und Kindern (ab 6 Jahren und mit einem Körpergewicht von mindestens 25 kg) angewendet, die mit dem humanen Immundefizienzvirus 1 (HIV-1) infiziert sind. Die HI-Viren dieser Patienten dürfen keine bekanntermaßen mit Resistenzen gegen die Klasse der Integrase-Inhibitoren, Emtricitabin oder Tenofovir verbundenen Mutationen aufweisen.

Abkürzungen:

3TC	Lamivudin
ABC	Abacavir
ART	Anti-Retroviral Therapy
ARV	antiretroviral
ATV/r	Atazanavir/ritonavir-boosted

AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
AZT	Azidothymidin (Zidovudin)
CCR5	CC-Motiv-Chemokin-Rezeptor 5
cobi	cobicistat
CrCl	creatinine clearance
d4T	Stavudin
DAHTA	Deutsche Agentur für Health Technology Assessment
ddI	Didanosin
DRV/r	Darunavir/ritonavir-boosted
DTG	dolutegravir
EFV	Efavirenz
EVG/c	Elvitegravir/cobicistat-boosted
FPV	Fosamprenavir
FTC	Emtricitabin
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HAART	Highly Active Anti-Retroviral Therapy
IDV	Indinavir
INI	Integrase-Inhibitor
INSTI	integrase strand transfer inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LPV/r	Lopinavir/ritonavir-boosted
MD	Mean differences
MVC	Maraviroc
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NNRTI	Nicht-nukleosidaler Reverse-Transkriptase-Inhibitor
NRTI	Nukleosidaler/nukleotidaler Reverse-Transkriptase-Inhibitor
NVL	Nationale VersorgungsLeitlinien
NVP	Nevirapin
OBT	Optimierte Hintergrundtherapie (Optimized Background Therapy)
PI	Protease-Inhibitor
PI/r	Protease-Inhibitor geboostert mit Ritonavir
RAL	Raltegravir
RPV	Rilpivirin
RTV	Ritonavir
SIGN	Scottish Intercollegiate Guidelines Network
TDF	Tenofovirdisoproxil(fumarat)
TRIP	Turn Research into Practice Database
VL	Viral load
WHO	World Health Organization
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ZDV	Zidovudin

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2016 [16]. 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 – Emtricitabin/Tenofoviralafenamid siehe auch: IQWiG, 2016 **[28].**	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 21. April 2016):** Descovy wird in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg) angewendet, die mit dem humanen Immundefizienzvirus Typ 1 (HIV-1) infiziert sind. a) nicht antiretroviral vorbehandelte (therapienaive) Erwachsene **Zweckmäßige Vergleichstherapie:** NRTI-Backbone: Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin in Kombination mit dem NRTI-Backbone sollen wirkstoffgleiche dritte Kombinationspartner (Efavirenz oder Rilpivirin oder Dolutegravir) über die Studienarme gleich verteilt eingesetzt werden. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Efavirenz oder Rilpivirin oder Dolutegravir in Kombination mit Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin:** Ein Zusatznutzen ist nicht belegt. b) nicht antiretroviral vorbehandelte (therapienaive) Jugendliche ab 12 Jahren **Zweckmäßige Vergleichstherapie:** Efavirenz in Kombination mit Abacavir plus Lamivudin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Efavirenz in Kombination mit Abacavir plus Lamivudin:** Ein Zusatznutzen ist nicht belegt. c) antiretroviral vorbehandelte (therapieerfahrene) Erwachsene **Zweckmäßige Vergleichstherapie:** Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer individuellen antiretroviralen Therapie:** Ein Zusatznutzen ist nicht belegt. d) antiretroviral vorbehandelte (therapieerfahrene) Jugendliche ab 12 Jahren **Zweckmäßige Vergleichstherapie:** Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer individuellen antiretroviralen Therapie:** Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [11]. 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 – Elvitegravir/Cobicistat/Emtricitabin/Tenofoviralafenamid siehe auch: IQWiG, 2016 **[26] &** IQWiG, 2016 **[25].**	**Zugelassenes Anwendungsgebiet [laut Zulassung vom19. November 2015]:** Genvoya wird zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg) angewendet, die mit dem humanen Immundefizienzvirus 1 (HIV-1) infiziert sind. Die HI-Viren dieser Patienten dürfen keine bekanntermaßen mit Resistenzen gegen die Klasse der Integrase-Inhibitoren, Emtricitabin oder Tenofovir verbundenen Mutationen aufweisen. a) nicht antiretroviral vorbehandelte (therapienaive) Erwachsene **Zweckmäßige Vergleichstherapie:** Efavirenz oder Rilpivirin oder Dolutegravir jeweils in Kombination mit zwei Nukleosid-/Nukleotidanaloga (Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Wirkstoff (oder ggf. der zweckmäßigen Vergleichstherapie):** Ein Zusatznutzen ist nicht belegt b) nicht antiretroviral vorbehandelte (therapienaive) Jugendliche ab 12 Jahren **Zweckmäßige Vergleichstherapie:** Efavirenz in Kombination mit Abacavir und Lamivudin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Wirkstoff (oder ggf. der zweckmäßigen Vergleichstherapie):** Ein Zusatznutzen ist nicht belegt c) antiretroviral vorbehandelte (therapieerfahrene) Erwachsene **Zweckmäßige Vergleichstherapie:** Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Wirkstoff (oder ggf. der zweckmäßigen Vergleichstherapie):** Ein Zusatznutzen ist nicht belegt d) antiretroviral vorbehandelte (therapieerfahrene) Jugendliche ab 12 Jahren **Zweckmäßige Vergleichstherapie:** Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Wirkstoff (oder ggf. der zweckmäßigen Vergleichstherapie):** Ein Zusatznutzen ist nicht belegt
G-BA, 2016 [17]. 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 – Rilpivirin (neues Anwendungsgebiet) Siehe auch: IQWiG, 2016 **[30].**	**Zugelassenes Anwendungsgebiet (laut Zulassung vom20. November 2015):** Edurant® in Kombination mit anderen antiretroviralen Arzneimitteln ist indiziert für die Behandlung von Infektionen mit dem humanen Immundefizienz-Virus Typ 1 (HIV-1) bei antiretroviral nicht vorbehandelten Patienten ab 12 Jahren mit einer Viruslast von ≤ 100.000 HIV-1-RNA-Kopien/ml. [Erweiterung des bisherigen Anwendungsgebiets um den Altersbereich von 12 bis einschließlich 17 Jahren] Antiretroviral nicht vorbehandelte Jugendliche im Altersbereich von 12 bis einschließlich 17 Jahren mit einer Viruslast von ≤ 100.000 HIV-1-RNA-Kopien/ml **Zweckmäßige Vergleichstherapie:** Efavirenz in Kombination mit Abacavir plus Lamivudin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2017 [13]. Beschluss des Gemeinsamen	**Zugelassenes Anwendungsgebiet (laut Zulassung vom21. Juni 2016):** Odefsey wird zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg) mit HIV-1-Infektion

Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Emtricitabin/Rilpivirin/Tenofoviralafenamid siehe auch: IQWiG, 2016 **[27].**	(Infektion mit dem Humanen Immundefizienzvirus 1) und einer Viruslast von ≤ 100.000 HIV-1-RNA-Kopien/ml angewendet, bei denen HIV-1 keine Mutationen aufweist, die bekanntermaßen mit Resistenzen gegen die Klasse der nichtnukleosidischen Reverse-Transkriptase-Inhibitoren (NNRTI), Tenofovir oder Emtricitabin assoziiert sind (siehe Abschnitte 4.2, 4.4 und 5.1 der Fachinformation). a) nicht antiretroviral vorbehandelte (therapienaive) Erwachsene **Zweckmäßige Vergleichstherapie:** Efavirenz oder Rilpivirin oder Dolutegravir jeweils in Kombination mit zwei Nukleosid- /Nukleotidanaloga (Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt b) nicht antiretroviral vorbehandelte (therapienaive) Jugendliche ab 12 Jahren **Zweckmäßige Vergleichstherapie:** Efavirenz oder Rilpivirin oder Dolutegravir jeweils in Kombination mit Abacavir plus Lamivudin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Efavirenz in Kombination mit Abacavir plus Lamivudin:** Ein Zusatznutzen ist nicht belegt c) antiretroviral vorbehandelte (therapieerfahrene) Erwachsene **Zweckmäßige Vergleichstherapie:** Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt d) antiretroviral vorbehandelte (therapieerfahrene) Jugendliche ab 12 Jahren **Zweckmäßige Vergleichstherapie:** Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt
G-BA, 2015 [10] 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 – Dolutegravir/Abacavir/ Lamivudin Vgl. IQWiG, 2014 [23]	Anwendungsgebiet: Triumeq ist angezeigt zur Behandlung von Infektionen mit dem Humanen Immundefizienz-Virus (HIV) bei Erwachsenen und Jugendlichen im Alter von über 12 Jahren, die mindestens 40 kg wiegen. Vor Beginn der Behandlung mit Abacavir-haltigen Arzneimitteln sollte unabhängig von der ethnischen Zugehörigkeit jeder HIV-infizierte Patient auf das Vorhandensein des HLA-B*5701-Allels hin untersucht werden. Patienten, bei denen bekannt ist, dass sie das HLA-B*5701-Allel tragen, sollten Abacavir nicht anwenden. **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) nicht antiretroviral vorbehandelte (therapienaive) Erwachsene Zweckmäßige Vergleichstherapie: Efavirenz in Kombination mit zwei Nukleosid-/Nukleotidanaloga (Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Efavirenz in Kombination mit Tenofovirdisoproxil plus Emtricitabin:** Hinweis für einen beträchtlichen Zusatznutzen. b) nicht antiretroviral vorbehandelte (therapienaive) Jugendliche ab 12 Jahren Zweckmäßige Vergleichstherapie: Efavirenz in Kombination mit Abacavir plus

	Lamivudin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Efavirenz in Kombination mit Abacavir plus Lamivudin:** Ein Zusatznutzen ist nicht belegt. c) antiretroviral vorbehandelte Erwachsene, für die eine Kombinationsbehandlung mit einem Integrase-Inhibitor die erste Therapieoption darstellt Zweckmäßige Vergleichstherapie: Raltegravir in Kombination mit einer individuellen Backbone-Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. Die jeweilige Zulassung der Präparate ist zu beachten. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Raltegravir in Kombination mit einer individuellen Backbone-Therapie:** Ein Zusatznutzen ist nicht belegt. d) antiretroviral vorbehandelte Erwachsene, für die eine Kombinationsbehandlung mit einem Integrase-Inhibitor eine nachrangige Therapieoption darstellt und e) antiretroviral vorbehandelte Jugendliche ab 12 Jahren Zweckmäßige Vergleichstherapie: Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. Die jeweilige Zulassung der Präparate ist zu beachten. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer individuellen antiretroviralen Therapie:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2014 [14] 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 – Emtricitabin/ Rilpivirin/ Tenofovirdisoproxil (neues Anwendungsgebiet), 19. Juni 2014 Vgl. IQWIG, 2014 [32]	Zugelassenenes Anwendungsgebiet: ⇒ Emtricitabin/Rilpivirin/Tenofovirdisoproxil (Eviplera®) wird zur Behandlung von Erwachsenen mit HIV-1-Infektion (Infektion mit dem Humanen Immundefizienzvirus Typ 1) und einer Viruslast von ≤ 100.000 HIV-1-RNA-Kopien/ml angewendet, bei denen HIV-1 keine Mutationen aufweist, die bekanntermaßen mit Resistenzen gegen die Klasse der nichtnukleosidischen Reverse-Transkriptase-Hemmer (NNRTI), Tenofovir oder Emtricitabin assoziiert sind. Zweckmäßige Vergleichstherapie: ⇒ Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. Die jeweilige Zulassung der Präparate ist zu beachten Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer individuellen antiretroviralen Therapie: Ein Zusatznutzen ist **nicht belegt**
G-BA, 2014 [9] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII -	Eckpunkte der Entscheidung: ⇒ Maßgeblicher Zeitpunkt gemäß 5. Kapitel § 8 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) für das erstmalige Inverkehrbringen des Wirkstoffs Dolutegravir ist der 15. Februar 2014. Zugelassenes Anwendungsgebiet von Dolutegravir (Tivicay ®) gemäß

Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Dolutegravir, 7. August 2014 Vgl. IQWIG, 2014 [22]	Fachinformation: ⇒ Dolutegravir (Tivicay®) ist angezeigt in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV) bei Erwachsenen und bei Jugendlichen im Alter von über 12 Jahren. Zweckmäßige Vergleichstherapie & Ausmaß Zusatznutzen: a) **nicht antiretroviral vorbehandelte (therapienaive) Erwachsene** ⇒ *zVT* = Efavirenz in Kombination mit zwei Nukleosid-/Nukleotidanaloga (Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin) ⇒ *Ausmaß Zusatznutzen* = Beleg für einen **beträchtlichen Zusatznutzen** b) **nicht antiretroviral vorbehandelte (therapienaive) Jugendliche ab 12 J.** ⇒ *zVT* = Efavirenz in Kombination mit Abacavir plus Lamivudin ⇒ *Ausmaß Zusatznutzen* = Ein Zusatznutzen ist **nicht belegt.** c) **antiretroviral vorbehandelte Erwachsene, für die eine Behandlung mit einem Integrase-Inhibitor die erste Therapieoption darstellt** ⇒ *(1) zVT* = Raltegravir in Kombination mit einer individuellen Backbone-Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. ⇒ *(1) Ausmaß Zusatznutzen* = Hinweis auf einen **geringen Zusatznutzen** ⇒ *(2) zVT* = Individuelle antiretrovirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. *(2) Ausmaß Zusatznutzen* = Ein Zusatznutzen ist **nicht belegt.**
G-BA, 2014 [8] 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 – Cobicistat, 18. September 2014	Zugelassenes Anwendungsgebiet: ⇒ Cobicistat (Tybost®) wird als pharmakologischer Verstärker (Booster) von Atazanavir 300 mg einmal täglich oder Darunavir 800 mg einmal täglich im Rahmen einer antiretroviralen Kombinationstherapie bei Erwachsenen angewendet, die mit dem humanen Immundefizienzvirus 1 (HIV-1) infiziert sind. Zweckmäßige Vergleichstherapie: ⇒ Die zweckmäßige Vergleichstherapie für die pharmakokinetische Verstärkung (Booster) für Atazanavir 300 mg einmal täglich oder Darunavir 800 mg einmal täglich in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von mit dem Humanen Immundefizienzvirus 1 (HIV-1) infizierten Erwachsenen ist: Ritonavir Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer individuellen antiretroviralen Therapie: Ein Zusatznutzen ist **nicht belegt**
G-BA, 2013 [12] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die	Zugelassenenes Anwendungsgebiet: ⇒ Elvitegravir, Cobicistat, Emtricitabin, Tenofovirdisoproxil (Stribild®) zur Behandlung der Infektion mit dem Humanen Immundefizienzvirus 1 (HIV-1) bei Erwachsenen, die nicht antiretroviral vorbehandelt sind oder bei denen HIV-1 keine Mutationen aufweist, die bekanntermaßen mit Resistenzen gegen einen der drei antiretroviralen Wirkstoffe von Stribild® assoziiert

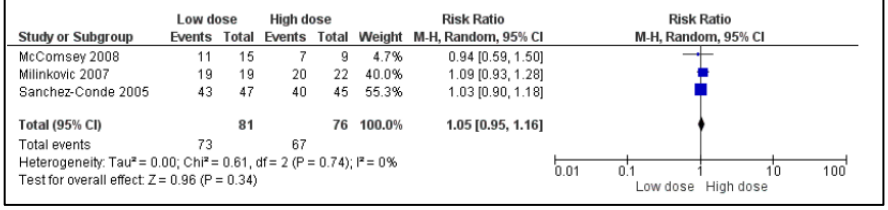
Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V –Elvitegravir/ Cobicistat/ Emtricitabin/ Tenofovir-disoproxil, 05. Dezember 2013 Vgl. IQWiG, 2013 [24]	sind. Zweckmäßige Vergleichstherapie & Ausmaß Zusatznutzen: a) **Therapienaive Patienten** ⇒ *zVT* = Efavirenz in Kombination mit zwei Nukleosid-/Nukleotidanaloga (Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin) ⇒ *Ausmaß Zusatznutzen* = Ein Zusatznutzen ist **nicht belegt.** b) **Therapieerfahrene Patienten, bei denen HIV-1 keine Mutationen aufweist, die bekanntermaßen mit Resistenzen gegen einen der drei antiretroviralen Wirkstoffe von Stribild® assoziiert sind** ⇒ *zVT* = Individuelle Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. Die Zulassung der Präparate ist jeweils zu beachten. *Ausmaß Zusatznutzen* = Ein Zusatznutzen ist **nicht belegt.**
G-BA, 2012 [15] 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 - Emtricitabin, Rilpivirin, Tenofovirdisoproxil, 5. Juli 2012. Vgl. IQWiG 2012 [31] und [21]	Zugelassenenes Anwendungsgebiet ⇒ Eviplera® wird zur Behandlung von Infektionen mit dem Humanen Immundefizienz-virus Typ 1 (HIV-1) bei antiretroviral nicht vorbehandelten erwachsenen Patienten mit einer Viruslast von ≤ 100.000 HIV-1-RNA-Kopien/ml angewendet. Zweckmäßige Vergleichstherapie: ⇒ Efavirenz in Kombination mit zwei Nukleosid-/Nukleotidanaloga (Tenofovir plus Emtricitabin oder Abacavir plus Lamivudin) Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Efavirenz in Kombination mit Tenofovir plus Emtricitabin: Beleg für einen **geringen Zusatznutzen.**
G-BA, 2012 [18] 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 – Rilpivirin, 05. Juli 2012 Vgl. IQWiG 2012 [29]	Zugelassenenes Anwendungsgebiet: ⇒ Edurant® in Kombination mit anderen antiretroviralen Arzneimitteln ist indiziert für die Behandlung von Infektionen mit dem humanen Immundefizienz-Virus Typ 1 (HIV-1) bei antiretroviral nicht vorbehandelten erwachsenen Patienten mit einer Viruslast von ≤ 100.000 HIV-1-RNA-Kopien/ml. Zweckmäßige Vergleichstherapie: ⇒ Efavirenz in Kombination mit zwei Nukleosid-/Nukleotidanaloga (Tenofovir plus Emtricitabin oder Abacavir plus Lamivudin) Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Efavirenz in Kombination mit Tenofovir plus Emtricitabin oder Abacavir plus Lamivudin: Beleg für einen **geringen Zusatznutzen**.

Cochrane Reviews

Mbuagbaw L et al., 2016 [38]. Efavirenz or nevirapine in three-drug combination therapy with two nucleoside or nucleotide-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naïve individuals.	1. Fragestellung To determine which non-nucleoside reverse transcriptase in- hibitor, either EFV or NVP, is more effective in suppressing viral load when given in combination with two nucleoside reverse tran- scriptase inhibitors as part of initial antiretroviral therapy for HIV infection in adults and children.
	2. Methodik Population: We included adults and children infected with HIV and with- out prior exposure to antiretroviral therapy (ART), and women who had received short courses of NNRTIs for the prevention of mother-to-child transmission. Intervention / Komparator: We considered triple-drug antiretroviral combination regimens for initial therapy containing two NRTIs plus either EFV or NVP at any dose (EFV + 2NRTIs versus NVP + 2NRTIs). Endpunkte: • Primäre Endpunkte: The percentage of participants achieving undetectable plasma HIV RNA concentration (viral load) over time (virological success), Mortality, Progression to AIDS (clinical), all severe adverse events and discontinuation rate • Sekundäre Endpunkte: Change in mean CD4 cell count (immunological response), Treatment failure, Prevention of sexual transmission of HIV, Development of ART drug resistance, individual adverse events Suchzeitraum (Aktualität der Recherche): bis 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): Twelve RCTs, which included 3278 participants Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung Qualität der Studien: This body of evidence includes twelve RCTs (3278 participants). The main methodological limitation in the included studies was the lack of blinding. Only one study was blinded (van den Berg-Wolf 2008). In most instances, this did not affect our rating of the quality of evidence for outcomes unlikely to be affected by a lack of blinding such as virological success, mortality and progression to AIDS. In two studies reported as abstracts, risk of bias was unclear in almost all the domains (Mateelli 2013; Sow 2006). The cut-off point used to define virological success also differed across studies, but this was related to the quality of the equipment available and did not seem to introduce any hetero- geneity in measures of virological success. We did not downgraded for this. We downgraded when adverse events were graded using different scales, the definition of treatment failure varied across studies, industry funded studies contributed most of the data for certain outcomes and confidence intervals were too wide. Overall the quality of the evidence ranged from high to very low. • no difference between EFV and NVP in virological success (RR 1.04, 95% CI

	0.99 to 1.09; 10 trials, 2438 participants; *high quality evidence*), probably little or no difference in mortality (RR 0.84, 95% CI 0.59 to 1.19; 8 trials, 2317 participants; *moderate quality evidence*) and progression to AIDS (RR 1.23, 95% CI 0.72 to 2.11; 5 trials, 2005 participants; *moderate quality evidence*). • No difference in severe adverse events (RR 0.91, 95% CI 0.71 to 1.18; 8 trials, 2329 participants; *very low quality evidence*). • no difference in discontinuation rate (RR 0.93, 95% CI 0.69 to 1.25; 9 trials, 2384 participants; *moderate quality evidence*) and change in CD4 count (MD −3.03; 95% CI −17.41 to 11.35; 9 trials, 1829 participants; *moderate quality evidence*). • no difference in treatment failure (RR 0.97, 95% CI 0.76 to 1.24; 5 trials, 737 participants; *low quality evidence*). • Development of drug resistance is stat. significantly less in the EFV arms (RR 0.76, 95% CI 0.60 to 0.95; 4 trials, 988 participants; *moderate quality evidence*). • No studies were found that looked at sexual transmission of HIV. • adverse events individually: EFV is associated with more people with impaired mental function (7 per 1000) compared to NVP (2 per 1000; RR 4.46, 95% CI 1.65 to 12.03; 6 trials, 2049 participants; *moderate quality evidence*) but fewer people with elevated transaminases (RR 0.52, 95% CI 0.35 to 0.78; 3 trials, 1299 participants; *high quality evidence*), fewer people with neutropenia (RR 0.48, 95% CI 0.28 to 0.82; 3 trials, 1799 participants; *high quality evidence*), and fewer people withrash (229 per 100 with NVP versus 133 per 1000 with EFV; RR 0.58, 95% CI 0.34 to 1.00; 7 trials, 2277 participants; *moderate quality evidence*). No difference in gastrointestinal adverse events (RR 0.76, 95% CI 0.48 to 1.21; 6 trials, 2049 participants; *low quality evidence*), pyrexia (RR 0.65, 95% CI 0.15 to 2.73; 3 trials, 1799 participants; *low quality evidence*), raised alkaline phosphatase (RR 0.65, 95% CI 0.17 to 2.50; 1 trial, 1007 participants; *low quality evidence*), raised amylase (RR 1.40, 95% CI 0.72 to 2.73; 2 trials, 1071 participants; *low quality evidence*) and raised triglycerides (RR 1.10, 95% CI 0.39 to 3.13; 2 trials, 1071 participants; *low quality evidence*). No difference in serum glutamic oxaloacetic transaminase (SGOT; MD 3.3, 95% CI -2.06 to 8.66; 1 trial, 135 participants; *moderate quality evidence*), serum glutamic- pyruvic transaminase (SGPT; MD 5.7, 95% CI -4.23 to 15.63; 1 trial, 135 participants; *moderate quality evidence*) and raised cholesterol (RR 6.03, 95% CI 0.75 to 48.78; 1 trial, 64 participants; *moderate quality evidence*). • subgroup analyses revealed that NVP increases mortality when given once daily (RR 0.34, 95% CI 0.13 to 0.90; 3 trials, 678 participants; *high quality evidence*). No differences in the primary outcomes for patients who were concurrently receiving treatment for tuberculosis.
	4. Fazit der Autoren: EFV and NVP are similarly effective in viral suppression, preventing HIV progression and reducing mortality. EFV is more likely to affect mental function, while NVP is more likely to cause signs of liver damage, reduced white blood cells and rash.
Magula N, Dedicoat M, 2015 [37]	1. Fragestellung ⇒ Evaluate the evidence supporting the effects of stavudine at dosages that are

Low dose versus high dose stavudine for treating people with HIV infection (Review)	lower than standard dosage and the applicability of available data in resource-limited settings where stavudine use plays a critical role. ⇒ Compare the safety and virologic efficacy of low dose versus high dose stavudine for treating HIV-1 infection.
	2. Methodik **Types of studies:** blinded and non-blinded RCTs **Population:** HIV infected adults treated with combination ART **Intervention:** Low dose stavudine ⇒ *Low dose stavudine* is described as the stavudine dosage of 30 mg BD or less for patients with a BW of 60 kg or more and less than 30 mg BD for patients with a BW of less than 60 kg **Komparator:** high dose stavudine ⇒ *High dose stavudine* is described as the standard dosage of 40 mg BD or greater for patients with a body weight of 60 kg or more and 30 mg BD dosage for those with a body weight of less than 60 kg **Endpunkt:** ⇒ *Primary Outcomes:* Viral load < 200 copies/ml; Major side-effects leading to drug discontinuation such as lactic acidosis, pancreatitis or severe peripheral neuropathy ⇒ *Secondary Outcomes:* Less severe side-effects e.g. mild peripheral neuropathy, lipodystrophy, rash, etc. **Suchzeitraum:** 1996 to 2008 (conducted on 10 Sep. 2008); searches were repeated on 5 June 2009 for 2008 to 2009, on 23 November 2012 for 2009 to 2012 and on 5 February 2014 for 2012-2014. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 3 (n=157) **Qualitätsbewertung der Studien:** ⇒ Cochrane Collaboration tool (Higgins 2008) for assessing the risk of bias for each individual study Using comprehensive search strategies, which included searching scientific literature from a wide range of databases, published or unpublished, written in any language to minimized the potential for reporting bias
	3. Ergebnisdarstellung • studies were at a high risk of selection, performance/detection and selective outcome reporting biases **Primary Outcomes** **Viral load < 200 copies/ml** ⇒ cut-off for viral load suppression is reported at different levels in each of the studies: o The trials of McComsey 2008 & Sanchez-Conde 2005 using a cut-off of 50 copies/mL o Milinkovic 2007 using a cut-off of 200 copies/mL.

	Figure 4. Forest plot of comparison: 2 Low dose vs high dose stavudine, outcome: 2.1 Proportion of participants with HIV-1 RNA < 200 copies/ml.  **Major side-effects** ⇒ There were no differences in lactic acidosis between the low dose and high dose stavudine arms and no reported major side-effects that led to discontinuation of treatment in all three trials. ⇒ There were no associated significant changes in body fat composition. In the Milinkovic 2007 and McComsey 2008 there was an increase in limb fat in both the low dose arms and a reduction in both high dose arms, however the changes were not statistically significant.
	4. Anmerkungen/Fazit der Autoren ⇒ The most significant finding of this review is that in all three trials, participants were all ART experienced and had sustained virologic suppression at the time of enrolment. ⇒ This systematic review identified only three small trials that evaluated virologic efficacy and safety of high dose versus low dose stavudine. ⇒ All three trials were conducted in developed countries and none reported from developing countries yet stavudine remains a component of ART combination therapy in many developing countries. ⇒ It was not possible to perform a meta-analysis on these trails. Individual results from the trials were imprecise and have not identified a clear advantage in virologic efficacy or safety between low and high dose stavudine. Furthermore, enrolled participants were treatment experienced with sustained virologic suppression and so existing data cannot be generalized to settings where stavudine is currently used in ART naive patients with high viral loads. Stavudine dose reduction trials in ART naive patients, in developing countries where stavudine is still being used are warranted as the phasing out of stavudine that is recommended by WHO may not be immediately universally feasible.
Cruciani M et al., 2013 [4] Abacavir-based triple nucleoside regimens for maintenance therapy in patients with HIV	1. Fragestellung ⇒ The aim of this review is to combine randomised, controlled trials to examine whether in patients with undetectable viraemia simplification treatment with ABC-based triple-nucleoside combinations has similar rates of efficacy and tolerability compared with a continued PI regimen or simplification with NNRTIs (efavirenz or nevirapine) containing regimen. Meanwhile, it offers the opportunity to address the risk of cardiovascular disease in ABC-treated patients and comparators.
	2. Methodik **Population:** Chronically HIV-infected adult patients treated with a PI-containing regimen (PI or boosted PI), with undetectable viral load (HIV-1 RNA below the cut-off value as defined in individual studies).

	Intervention/Komparator: 1. Continue the PI regimen or switch to a simplification maintenance regimen, including 2. Switch to a NNRTI (EFV or NVP) containing regimen, or 3. Switch to a triple-NRTI regimen (ABC-AZT-3TC (Trizivir®)) 1 and 2 are controls, 3 is the experimental intervention. If a trial had all three options, we compared the experimental group to each of the 2 control groups (1 vs 3, and 2 vs 3); in this case, to avoid double-counts in the experimental group, we split the 'shared' group (3 NRTI) into two groups with smaller sample size, and include two independent comparisons. **Endpunkte** ⇒ *Primary Outcomes:* Proportion of patients discontinuing or switching antiretroviral therapy due to virologic failure; Rates of patients with adverse events requiring treatment interruption or switching, or both; Overall rates of treatment interruption or switching, or both; Death (all cause); Occurrence of myocardial infarction and cardiovascular disease; Occurrence of new **Suchzeitraum:** bis 2012 (Recherche in 2009, Update in 2012) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 (n=1675) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias, GRADE
	3. Ergebnisdarstellung ⇒ low risk of bias trials in most of the domains considered ⇒ All the studies included HIV-1 infected patients virologically suppressed after a successful treatment with PI containing ART. ⇒ <u>Overall failure</u> (8 studies, n=1.606); Triple nucleoside combination (N=693 participants) vs PI continuation (n=466) vs. NNRTI simplification (n=477): no significant difference between triple nucleoside combination and controls (RR 0.88, 95%CI 0.74 to 1.04), either PI-based (RR 0.80, 95%CI 0.62 to 1.03) or NNRTI based (RR 0.99, 95% CI 0.79 to 1.24). There was some degree of heterogeneity, and a random effect model was applied. ⇒ <u>Virologic Failure</u> (8 studies, n=1,587); Triple nucleoside combination (n=689) vs. PI continuation (n=461) vs. NNRTI simplification (n=437): no significant difference triple nucleoside combination and controls (RR 1.39, 95% CI 0.95 to 2.02), either PI-based (RR 1.49, 95% CI 0.72 to 3.08) or NNRTI based (RR 1.32, 95% CI 0.89 to 1.97), though the test for overall effect (p=0.09) was closed to the level of significance, thus suggesting a weak evidence of higher incidence of virologic failure in the 3NRTI group compared to controls. A random effect model was applied (I2 = 18 %). ⇒ <u>Discontinuation for Adverse Events</u> (8 studies, n=1,597); Triple nucleoside combination (n=689) vs. PI continuation (n=461) or to NNRTI simplification (n=447): no significant difference between triple nucleoside combination and controls (RR 0.68, 95% CI 0.44 to 1.07), either PI-based (RR 0.77, 95% CI 0.39 to 1.53) or NNRTI based (RR 0.63, 95% CI 0.34 to 1.18), the test for overall effect (p=0.09) was closed to the level of significance, thus suggesting a weak evidence of lower incidence of side effects in the experimental group. There was substantial heterogeneity (I2 =57%), and a random effect model was applied. ⇒ <u>Change in lipids and in CD4 cells</u> from baselines were reported in 7 studies, but

	inconsistency in reporting these data did not allow quantitative analysis.
	4. Anmerkungen/ Fazit der Autoren ⇒ The strategy of switching to triple nucleoside regimens shows weak evidence of lower incidence of side effects and a higher incidence of virologic failure in the 3NRTI group compared to controls. ⇒ Simplification with 3NRTI holds the advantages of preserving other classes of antiretroviral drugs, to lower blood lipids, and to be cost effective and simple to administer. Thus, simplification with triple nucleoside regimens AZT + 3TC + ABC should be still considered for individuals who are unable to tolerate or have contraindications to NNRTI or PI based regimens. ⇒ Though studies in the current review were conducted between 2001 and 2010, the large majority of patients from studies analysed received old PI regimens (e.g., indinavir, ritonavir, nelfinavir, saquinavir) no longer recommended by International Guidelines.
Shey MS et al., 2013 [42]. Co-formulated abacavir-lamivudine-zidovudine for initial treatment of HIV infection and AIDS	1. Fragestellung The primary objective of this review was to evaluate the antiviral efficacy of co-formulated zidovudine-lamivudine-abacavir for initial treatment of HIV infection. The secondary objectives were to evaluate the safety and tolerability of the triple nucleoside combination.
	2. Methodik **Population:** HIV-infected, antiretroviral-naive patients (> 13 year) **Intervention/Komparator:** Treatment of HIV infection with co-formulated abacavir-lamivudine-zidovudine as initial therapy vs. treatment based on PIs or NNRTIs **Endpunkte:** • *Primary Outcomes:* suppression of viral activity; • *Secondary Outcomes:* CD4 cell count, Severe adverse events, Clinical lipodystrophy manifestations, Total cholesterol, Triglyceride level, Treatment adherence **Suchzeitraum der systematischen Literaturrecherche:** bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n=2247) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias, GRADE
	3. Ergebnisdarstellung <u>Virological failure</u> (3 trials, n=1687) o no significant difference between NRTIs and those on either PI-based or NNRTI-based therapy (RR 1.14, 95% CI 0.56 to 2.32), moderate quality of evidence o There was significant heterogeneity between the included trials. o 2 studies (n=540) did not find a significant difference in the incidence of virological failure between participants on NRTIs and those on a PI (i.e. nelfinavir or atazanavir) (RR 0.82, 95% CI 0.50 to 1.36; heterogeneity P= 0.21, I2=35%). o 1 Study (n=1147) found that participants on NRTIs had a significantly higher incidence of virological failure than did those on the NNRTI

	efavirenz (RR 1.93, 95% CI 1.46 to 2.55). Virological suppression (4 studies, n=2247) o No significant difference between NRTI and controls (RR 0.97 [95% CI 0.75;1.12], moderate quality of evidence) o There was significant heterogeneity between the four studies. o 3 Studies finding no significant differences between comparison groups and 1 study finding NRTIs to be inferior to efavirenz. CD4+ cell counts: no significant differences between NRTIs and either PIs or NNRTIs (3 trials, n=1687: mean difference -0.01, 95% CI -0.11 to 0.09, I^2=0%, moderate quality of evidence), Severe adverse events: no significant difference (4 trials; n=2247: RR 1.22, 95% CI 0.78 to 1.92, I^2=62%, moderate quality of evidence) Hypersensitivity reactions: no significant difference (4 trials, ; n=2247, RR 4.04, 95% CI 0.41 to 40.02, I^2=72%, moderate quality of evidence).
	4. Anmerkungen/ Fazit der Autoren • We found that co-formulated abacavir-lamivudine-zidovudine remains a viable option for initiating anti-retroviral therapy, especially in HIV-infected patients with pre-existing hyperlipidaemia and those who do not tolerate ritonavir. The varied geographical locations of the included trials augment the external validity of our findings. • We are moderately confident in our estimate of the treatment effects of the triple NRTI regimen as initial therapy for HIV infection. In the context of the GRADE approach, such moderate quality of evidence implies that the true effects of the regimen are likely to be close to the estimate of effects found in this review.

Systematische Reviews

Jiang J et al., 2016 [33]. Dolutegravir (DTG, S/GSK1349572) combined with other ARTs is superior to RAL- or EFV-based regimens for treatment of HIV-1 infection: a meta-analysis of randomized controlled trials	1. Fragestellung The purpose of this study is to review the evidence for DTG use in clinical settings, including its efficacy and safety.
	2. Methodik Population: therapy-naive HIV-positive patients Intervention / Komparator: DTG (INI) versus EFV (NNRTI) and RAL(INI) Endpunkt: virological and immunological responses, clinical and laboratory adverse events (AEs) Suchzeitraum (Aktualität der Recherche): bis Juli 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): Four unique studies were included with the use of DTG in antiretroviral therapy-naive patients. Qualitätsbewertung der Studien: GRADE and Jadad Score
	3. Ergebnisdarstellung Qualität der Studien: Alle Studien hatten einen Jadad Score von 5. DTG combined with abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) resulted in a signicantly better virological outcome with a mITT relative risk (RR)of 1.07 (95 % confidence interval (95 % CI 1.03–1.12). Evidence further supported use of DTG had a better virological suppression in the 50 mg once daily group (mITT RR 1.07; 95 % CI 1.03–1.12) as well as in the sub-analysis in dolutegravir/efavirenz(DTG/EFV) and dolutegravir/ raltegravir (DTG/RAL) groups (RR 1.09, 95 % CI 1.03–1.15; RR 1.06, 95 % CI 0.98–1.15, respectively). In the matter of safety of DTG-based regimen, the risk of any event was RR 0.98 (95 % CI 0.94–1.01), the risk of serious adverse events (AEs) was RR 0.84 (95 % CI 0.62–1.15), and the risk of drug-related serious AEs was RR 0.33 (95 % CI 0.13–0.79).
	4. Fazit der Autoren: Tese results show that DTG 50 mg given once daily combined with an active background drug provides supe- rior virological control and fewer adverse reactions com- pared with raltegravir 400 mg or efavirenz 600 mg given twice daily.
Li Sl et al., 2014 [36] Effectiveness and Safety of Rilpivirine, a Non-Nucleoside Reverse Transcriptase Inhibitor, in Treatment-Naive Adults lnfected with HIV-1: A Meta-analysis	1. Fragestellung The aim of this study was to determine the effectiveness and safety of rilpivirine in treatment-naive adults lnfected wlth HIV-1
	2. Methodik **Population:** treatment-naive adults infected with HIV-1 **Intervention:** RPV (Rilpivirine) **Komparator:** EFV (Efavirenz) **Endpunkt:** effectiveness and safety **Suchzeitraum (Aktualität der Recherche):** to October 2013 in Medline, EMBASE, CINAHL, the Cochrane Controlled Trial Register database, CBMdisc, and Chinese Medical Current Contents (CMCC)

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 (n=2522) **Qualitätsbewertung der Studien:** Jadad Score
	3. Ergebnisdarstellung • Included studies with high quality (weighted Jadad score =4,0) • No significant difference in the viral Ioad between the RPV group and the EFV group (RR, 1.03; 95% CI, 0.99-1.07; I^2=0%) • No sign. differences in mean changes from baseline in CD4 cell counts at week 48 between RPV group and EFV group (RR, 1.04; 95% CI, 0.85-1.24; I^2=70,6%). • higher risk of virological failure at week 48 for RPV (RR, 1.70; 95% CI, 1.21-2.38; I^2=0%) • lower risk of rash (any grade) at week 48 for RPV than for EFV (RR, 0.11; 95% CI, 0.03-0.33; I^2=37,4%) • lower incidence of neurological events of interest with RPV than with EFV (RR, 0.52; 95% CI, 0.45, 0.60; I^2=29,8%)
	4. Anmerkungen/Fazit der Autoren • The overall meta-analysis results demonstrated that non-inferior antiviral efficacy was observed in viral Ioad comparable with EFV at 48 weeks (P > .05) • RPV is effective and safe for HIV-1-infected patients. However, only 4 trials and 2,522 patients were included in this meta-analysis, so more patients and higher quality, Ionger intervention randomized controlled trials are required to clarify the issues of the safety and efficacy of RPV in patients with HIV-1 infection.
Hemkens LG et al., 2015 [20] Comparative effectiveness of tenofovir in treatment-naive HIV-infected patients: systematic review and meta-analysis	1. Fragestellung To assess effectiveness of tenofovir disoproxil fumarate (TDF)-based treatments, including commonly used fixed dose co-formulations, on various patient-important outcomes and surrogate markers in ART-naive patients
	2. Methodik **Population:** adult HIV-infected patients without prior exposure to antiretroviral therapy **Intervention:** TDF based treatment **Komparator:** any other ART without TDF **Endpunkte:** • mortality, AIDS-defining events, virological failure, • fractures, cardiovascular events, renal failure, rash, • quality of life, • CD4 cell count, HDL-, LDL-, total cholesterol, triglycerides, estimated glomerular filtration rate (eGFR), proteinuria, bone mineral density (BMD), and body fat change. **Literatursuche:** up to 01/2015 in Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, Science Citation Index, andthe WHO Global Health Library **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 22 trials (8297 patients) **Qualitätsbewertung der Studien:** Cochrane risk of bias tool
	3. Ergebnisse *Study quality*

	• High risk of bias in 17 of 22 studies due to open study design, unclear randomization process and high attrition bias (large proportions of randomized patients not or not clearly included in analyses) • Low risk of bias in 2 studies • Unclear risk of bias in 3 studies *Results: TDF-based regimens versus other regimens* • Clinical events and deaths (18 studies): no sign. differences o RR for death: 0.88 (95%CI 0.60 to 1.30), I^2=0% o RR for AIDS: 0.82 (95%CI 0.58 to 1.16), I^2=0% o RR for fractures: 0.97 (95%CI 0.68 to 1.37), I^2=0% o Effects similar in studies comparing TDF/FTC with ABC/3TC. • no outcome data on quality of life • Data on cardiovascular events, renal failure, proteinuria, and rash were very inconsistently reported using very heterogeneous definitions and were therefore not pooled • Virological failure at 48 weeks (16 trials): no sign. differences o RR for "free of virological failure" (HIV-1-RNA levels <50 copies/ml) 1.03 (95%CI 0.99–1.07), I^2=50% o Similar effects in trials comparing TDF/FTC with ABC/3TC (RR 1.02; 0.95–1.10), I^2= 79% • CD4 cell count (14 trials): no sign. difference o mean difference (MD ;95%CI): 0.55 cells/ml (-15.24 to 16.33); I^2=72% • Lipid levels (8 trials): significantly decreased with TDF-based regimens versus other regimens: MD (95%CI): o LDL-cholesterol -9.53 mg/dl (-12.16 to -6.89); I^2=14% o HDL-cholesterol -2.97 mg/dl (-4.41 to -1.53); I^2=39% o total cholesterol -18.42 mg/dl (-22.80 to -14.04); I^2=54% o triglycerides -29.77 mg/dl (-38.61 to -20.92);I^2=0% o Similar effects in trials comparing TDF/FTC-based regimens with ABC/3TC-based regimens. • Estimated glomerular filtration rate (8 trials) o Renal function significantly decreased over 48 weeks with TDF-based regimens vs other regimens: mean difference (95%CI): -3.47 ml/minute (-5.89 to -1.06); I^2=74% • Bone mineral density (4 trials) o greater relative decrease with TDF-containing treatments: MD (95%CI): hip: -1.41% (-1.87 to -0.94; I^2=0%); lumbar spine: -1.26% (-1.84 to -0.68; I^2=0%);) o Similar effects in trial (n=1) comparing TDF/FTC with ABC/3TC • Body fat (2 studies):No significant difference in changes of trunk and limb fat, no heterogeneity between trials
	4. Fazit der Autoren: This analysis found no different comparative effects of TDF-based and non-TDF-based treatments on mortality, AIDS-defining events, fractures, CD4 cell count, and virological failure. Tenofovir disoproxil fumarate-based regimens were associated with more favorable lipid levels, but reduced BMD and eGFR. Effects were similar in trials comparing TDF/FTC versus ABC/3TC-based regimens, in particular for virological failure in relation to baseline viral load 5. Hinweise durch FBMed Eingeschränkte Ergebnissicherheit aufgrund des hohen Verzerrungspotentials der Einzelstudien und der z.T. hohen Heterogenität zw. den Studien

Kryst J et al., 2015 [35] Efavirenz-Based Regimens in Antiretroviral-Naive HIV-Infected Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials	1. Fragestellung Systematic review and meta-analysis of RCT in order to establish differences between efavirenz-based regimens and other regimens recommended by clinical experts to be used in HIV-infected patients previously untreated with antiretroviral therapy
	2. Methodik **Population:** adult HIV-infected patients without prior exposure to antiretroviral therapy **Intervention:** efavirenz **Komparator:** any other, commonly used treatment (studies assessing placebo as a comparator were excluded) **Endpunkte:** • progression of disease or death, • virological response to treatment, • safety profile (defined as risk of adverse events and discontinuation of the treatment due to adverse events). **Suchzeitraum:** up to December 2013 in Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Trip Database **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 34 RCTs included in SR (26 RCTs included in MA) **Qualitätsbewertung der Studien:** Jadad score (0-5) + allocation concealment
	3. Ergebnisse *Methodological quality of included studies:* • Jadad scores ranged from 1 to 4, mostly due to a lack of blinding and insufficient data about randomization methods used • Only four of the included studies provided information about allocation concealment. *Efavirenz vs non-nucleoside reverse transcriptase inhibitor (NNRTI) added to the background regimen (10 studies)* • NNRTI: o nevirapine in 5 studies o rilpivirine in 3 studies o etravirine in 1 study + lersivirine in 1 study (not included in MA) • No statistically significant differences in o death (RR 1.06; 95% CI: 0.66–1.68; p>0.05, I^2=0%), or o composite outcome—disease progression or death (RR 1.28; 95% CI: 0.86–1.90; p>0.05, I^2=46%). • No stat. sign. differences in proportion of patients with virological response at weeks 48–52 (plasma VL below 50 copies/ml: RR 1.00; 95% CI: 0.96–1.04; p>0.05, I^2=0%). • Risk of discontinuation due to intolerance: RR 1.01; 95% CI: 0.82–1.24; p>0.05, I^2=68%) *Efavirenz vs integrase strand transfer inhibitor (InSTI) added to the background regimen (6 studies)* • InSTI: o raltegravir in 2 trials o elvitegravir in combination with cobicistat in 2 trials o dolutegravir in 2 trials • no statistically significant differences in

	o death (RR 1.24; 95% CI: 0.33–4.61; p>0.05, I^2=15%) o proportion of patients with pVL<50 copies/ml at week 96 (RR 1.04; 95% CI: 0.99–1.09; p>0.05, I^2=5%). • Stat. sign. higher proportion of patients with pVL<50 copies/ml at week 48 with InSTI (RR 1.06; 95% CI: 1.03–1.10; p<0.05, I^2=0%), • higher risk of discontinuation of therapy due to AE for efavirenz-based regimens (RR 2.30; 95% CI: 1.60–3.31; p<0.05, I^2=22%), *Efavirenz vs ritonavir-boosted protease inhibitor (bPI) added to the background regimen (15 studies)* • PI: o Lopinavir and atazanavir in 8 and 5 trials, respectively, o amprenavir, indinavir and fosamprenavir in single studies, • Note: 4 studies additionally included patients with a limited previous exposure to HAART therapy • No statistically significant differences in o death (RR 1.05; 95% CI: 0.84– 1.32; p>0.05, I^2=0%) o disease progression defined in 3 studies as an occurrence of AIDS-defining events (RR 1.18; 95% CI: 0.88–1.58; p>0.05, I^2=0%). o proportion of patients with plasma viral loads < 50 copies/ml at weeks 48–52 (RR 0.94; 95% CI: 0.86–1.04; p>0.05, I^2=73%) and at weeks 96–104 (RR 0.98; 95% CI: 0.80–1.19; p>0.05, I^2=76%), o risk of discontinuation of treatment due to its intolerance (RR 1.16; 95% CI: 0.87–1.55; p>0.05, I^2=24%) o risk of grade 3/4 AE (RR 0.85; 95% CI: 0.57–1.25; p>0.05, I^2=78%) *efavirenz vs CC chemokine receptor type 5 (CCR5) antagonist added to the background regimen* <u>Vicriviroc (1 study):</u> • higher rates of virologic failure in vicriviroc groups (25 mg and 50 mg once a day) compared with efavirenz group <u>Maraviroc: 1study</u> • no statistically significant differences in o disease progression defined as an occurrence of C category events indicating a development of AIDS (RR 1.99; 95% CI: 0.76–5.26; p>0.05) at week 48. o death at 96-week (RR 1.50; 95% CI: 0.25–8.90; p>0.05). o virological outcomes: plasma VL below 50 copies/ml at week 48 (RR 0.94; 95% CI: 0.85–1.04; p>0.05) and at week 96 (RR 0.94; 95% CI: 0.83–1.07; p>0.05). o risk of grade 3/4 AE at week 48 (RR 1.23; 95% CI: 0.94–1.61; p>0.05) and at week 96 (RR 1.16; 95% CI:0.91–1.47; p>0.05), • significantly higher risk of discontinuation of therapy due to AE for efavirenz-based regimen (RR 3.26; 95% CI: 1.86–5.70; p<0.05), which was confirmed for both 48 and 96-week follow-up.
	4. Fazit der Autoren: Results of the present meta-analysis support the current clinical guidelines for antiretroviral-naive, HIV-infected patients. Efavirenz-based therapy should be considered as one of the most preferred treatment options in ART-naive patients, however it should be prescribed with caution in patients with underlying psychiatric conditions. Results of recent studies suggests good efficacy and beneficial safety profile of drugs from new classes of antiretroviral agents (integrase inhibitors, CCR5 antagonists) compared with other initial regimens used nowadays in clinical practice for the treatment of HIV-infected patients, however more data

	from further, reliable RCTs are needed to confirm above results. 5. Hinweise durch FBMed Studien weisen je nach Endpunkt z.T. beträchtliche Heterogenität auf
Pillay P et al., 2013 [41] Outcomes for Efavirenz versus Nevirapine-Containing Regimens for Treatment of HIV-1 Infection: A Systematic Review and Meta-Analysis	1. Fragestellung To review virological outcomes in HIV-1 infected, treatment-naive patients on regimens containing EFV versus NVP from randomised trials and observational cohort studies
	2. Methodik: SR of RCTs and observational cohort studies **Population:** adult HIV-infected patients not previously treated with ART **Intervention:** Efavirenz containing regimens in a combination of three antiretroviral drugs only **Komparator:** Nevirapine containing regimens in a combination of three antiretroviral drugs only **Endpunkte:** • Virologic outcomes: plasma HIV-1 RNA • Treatment termination/discontinuation (any cause) • mortality **Literaturrecherche:** up to May 2013 in Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 38 (10 RCTs, 15 prospective cohort studies, 13 retrospective cohort studies) **Qualitätsbewertung der Studien:** • Risk of bias assessment: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), selective reporting (reporting bias),comparability of baseline groups, application of intent-to-treat analysis, and proportion lost to follow up • Overall quality of evidence using GRADE • Where sufficient studies were available, publication bias was assessed visually using funnel plots. **Heterogenität** examined using the x^2 statistic with a significance level of >0.10, and the I^2 statistic with an I^2 estimate greater than 50% was considered indicative of moderate to high levels of heterogeneity
	3. Ergebnisse *Study characteristics* • "Third drug" comparison: o majority of studies: EFV 600mg once daily vs NVP 200mg twice daily. o 1 study: weight adjusted EFV dose o 2 studies: NVP 400 mg once daily o 15 studies did not report NVP dosage, and were all assumed to use 200 mg twice daily • Backbone: NRTI used differed between studies: o Stavudine (d4T)/3TC in 21 studies; 9 studies did not use this NRTI backbone at all. o AZT/3TC in 21 studies; 9 studies did not use this backbone at all.

	○ TDF/3TC or TDF/FTC was used less frequently, in only 7 studies. ○ 7 studies did not report on NRTI backbones. • Risk of bias: ○ RCTs: all open label, only 2 of 10 reported on allocation concealment, 5 of 10 reported loss to follow up • Quality of evidence: ○ <u>evidence from RCTs</u> was considered to be high quality for critical outcomes: no evidence of serious risk of bias, inconsistency, imprecision or indirectness ○ <u>evidences from observational studies:</u> very low quality, mainly due to risk of bias (lack of random sampling, baseline imbalances, and retrospective design), and inconsistency in the direction and imprecision in CI around the point estimates. *Results: EFV vs NVP* Virologic failure • data from RCT (n=6): RR 0.85 [0.73– 0.99], I^2 = 0% • data from observational studies (n=9): RR 0.65 [0.59–0.71]; I^2 =54% Virologic success • data from RCT (n=8): 1.04 [95%CI 1.00–1.08], I^2 = 0% • data from observational studies (n=13): 1.06 [1.00– 1.12]; I^2 =68% Mortality • data from RCT (n=4):RR 0.81[0.47, 1.37] I^2 = 30% • data from observational studies (n=8): RR 0.76 [0.67–0.87], I^2= 0% Treatment discontinuation (any cause) • data from RCT (n=5): RR 0.83 [0.55–1.25] I^2: k.A • data from observational studies (n=7): RR=0.89 [0.73–1.08], I^2: k.A.
	4. Fazit der Autoren: EFV-based first line ART is significantly less likely to lead to virologic failure compared to NVP-based ART. 5. Hinweise durch FBMed Evidenz aus RCTs wurde mit hoch bewertet, obwohl alle Studien ein offenes Design aufwiesen und größtenteils keine Informationen zu allocation concealment gegeben wurden
Kawalec P et al., 2013 [34] Nevirapine-Based Regimens in HIV-Infected Antiretroviral-Naive Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials	1. Fragestellung To compare effectiveness of nevirapine-based regimens with other antiretroviral schedules used as an initial treatment of HIV-infected antiretroviral-naive subjects
	2. Methodik **Population:** adult HIV-infected patients not previously treated with antiretroviral therapy. **Intervention:** nevirapine **Komparator:** any other, commonly used treatment schedule (studies assessing placebo as a comparator were excluded). **Endpunkte:** • clinical progression of disease or death, • virological response (defined as undetectable plasma HIV RNA), • risk of AE ; discontinuation of study because of AE **Suchzeitraum:** up to December 2012 in Medline, EMBASE, the Cochrane Central

	Register of Controlled Trials (CENTRAL), and the Trip Database **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 **Qualitätsbewertung der Studien:** Jadad score (0-5) + Allocation concealment **Heterogenität:** Clinical heterogeneity was assessed by examining the characteristics of the featured studies, whereas the statistical heterogeneity was assessed using the chi-square test, with a significance level of p<0.10. A fixed effects model was used when no statistical heterogeneity was detected; otherwise the random effects model was used.
	3. Ergebnisdarstellung Methodological quality of included RCTs was poor • 3 RCT with Jadad-Score =1 • 8 RCT with Jadad Score =2 • 1 RCT with Jadad Score =3 <u>Effectiveness of adding nevirapine vs one nonnucleoside reverse transcriptase inhibitor (NNRTI) to the background regimen</u> comparison of nevirapine vs efavirenz as NNRTI • (Inclusion of 1 study with patients with previous limited exposure of antiretroviral therapy) • no stat. sign. difference in disease progression or death (3 studies, RR 0.78; 95% CI: 0.53-1.16; p>0.05; I^2=46%), • no stat. sign. difference in virological response (plasma VL below 400 copies/ml (2 studies): RR 1.00; 95% CI: 0.95-1.05; p>0.05; I^2=21% and below 50 copies/ml (3 studies): RR 1.03; 95% CI: 0.95-1.11; p>0.05; I^2=0%) in weeks 48-52 • risk of assigned treatment discontinuation due to intolerance was comparable in both arms (4 studies, RR 1.25; 95% CI: 0.99-1.60;p>0.05; I^2=31%); <u>Effectiveness of adding nevirapine vs ritonavir-boosted protease inhibitor (bPI) to the background regimen</u> • 3 trials included truly antiretroviral naive patients; 4 other studies recruited patients with limited prior antiretroviral exposure. • no stat. sign. differences in disease progression or death (3 studies, RR 1.01; 95% CI: 0.65-1.58; p>0.05; I^2=52%), • no stat. sign. differences in proportions of patients with plasma VL <50 copies/ml at week 48 (RR 0.90; 95% CI: 0.77-1.06; p>0.05; I^2=62%). • no stat. sign.differences in AE of grade 3/4 (3 studies, RR 1.34; 95% CI: 0.68-2.66; p>0.05; I^2=69%) • stat. sign. higher risk of treatment discontinuation due to AE in nevirapine group compared to the 2 PI-based regimen (7 studies, RR 3.10; 95% CI: 1.14-8.41; I^2=71%);
	4. Anmerkungen/Fazit der Autoren Our data demonstrate the comparable efficacy of nevirapine-based therapy versus other regimens recommended as initial therapy for HIV-infected patients (PI-based and efavirenz-based treatments). Concerning safety, special groups of patients can achieve significant clinical benefits from nevirapine-based regimens. 5. Hinweise FBMed z.T. beträchtliche Heterogenität
Messiaen P et al.,	1. Fragestellung

2013 [39] Clinical Use of HIV Integrase Inhibitors: A Systematic Review and Meta-Analysis	To review the evidence for integrase inhibitor use in clinical settings.
	2. Methodik **Population:** HIV-infected patients (antiretroviral therapy-naive patients and treatment-experienced patients with either virological failure or switching to integrase inhibitors while virologically suppressed.) **Intervention:** integrase inhibitors(INI; raltegravir, elvitegarvir, dolutegravir) **Komparator:** others than INI **Endpunkte: efficacy** **Suchzeitraum:** April 2006 - November 2012 **Studiendesign:** inclusion of RCTs, non-RCTs, retrospective analysis of these trials, cohort studies or cross-sectional studies **Anzahl eingeschlossene Studien/Patienten (Gesamt):**48 (davon 59% RCTs); 16 RCTs included in MA **Qualitätsbewertung der Studien:** GRADE
	3. Ergebnisdarstellung Hier Ergebnisse der MA *Characteristics of the included studies →Tab. 3*

Table 3. Study characteristics of studies included in meta-analysis (n = 16): regimens, population size, timepoint of analysis and virological outcome data are enlisted.

	INI (n =)	CTR (n =)	Regimen	Analysis time point (w)
ART-naive patients				
STARTMRK [16]	281	282	RAL 400 mg bd + TDF/FTC vs. EFV + TDF/FTC	48
Protocol 004 [21]	160	38	RAL 100, 200, 400 or 600 mg bd + TDF/3TC vs. EFV + TDF/3TC	48
GS-236-014 [26]	48	23	EVG/COBI single tablet qd+ TDF/FTC vs. EFV + TDF/FTC	48
GS-236-0102 [25]	348	352	EVG/COBI/FTC/TDF qd vs EFV/TDF/FTC	48
SPRING-1 [28]	155	50	DTG 10,25 or 50 mg + TDF/FTC or ABC/3TC vs. EFV + TDF/FTC or ABC/3TC	48
SINGLE [14]	414	419	DTG 50 mg + ABC/3TC vs. EFV/TDF/FTC	48
GS-236-0103 [31]	353	355	EVG/COBI/FTC/TDF qd vs ATV/r + TDF/FTC	48
SPARTAN [13]	63	31	RAL 400 mg bd + ATV vs. ATV/r + TDF/FTC	24
PROGRESS [32]	101	105	RAL 400 mg bd + LPV/r vs. LPV/r + TDF/FTC	24
RADAR [33]	40	40	RAL 400 mg bd + DRV/r vs. DRV/r + TDF/FTC	24
ART-experienced patients with virological failure				
BENCHMRK 1 and 2 [2]	461	237	RAL 400 mg bd + NNRTI + NRTI vs. Placebo + NNRTI + NRTI	24
Protocol 005 [36,37]	134	45	RAL 200, 400 or 600 mg bd + optimized BR vs. placebo + optimized BR	24
GS-183-105 [38]	205	73	EVG/RIT 20, 50 or 125 mg bd + optimized BR vs. PI/r + optimized BR	24
ART-experienced patients switching suppressive therapy				
SWITCHMRK 1 and 2 [48]	353	354	RAL 400 mg bd + BR − LPV/r vs. BR	24
SPIRAL [49]	139	134	RAL 400 mg bd + BR − PI/r vs. BR	32
EASIER ANRS 138 [50]	85	85	RAL 400 mg bd + BR − T20 vs. BR +− T20 or RAL (>24w)	24

INI-containing treatment arm is underlined.
ART = antiretroviral treatment; INI = integrase inhibitor; CTR = control arm; VL<50 = viral load or HIV RNA <50 copies/ml; RAL = raltegravir; EFV = efavirenz; EVG = elvitegravir; COBI = cobicistat; DTG = dolutegravir; ATV = atazanavir; DRV = darunavir; TDF/FTC = tenofovir/emtricitabine; ABC/3TC = abacavir/lamivudine; LPV = lopinavir; r = ritonavir; (N)NRTI = (non-)nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; BR = background regimen; T20 = enfurvirtide.
doi:10.1371/journal.pone.0052562.t003

Results of MA for virological outcome (number of patients achieving HIV RNA below 50 copies/ml)

→Figure

A: treatment naïve patients

B + C: treatment experienced patients

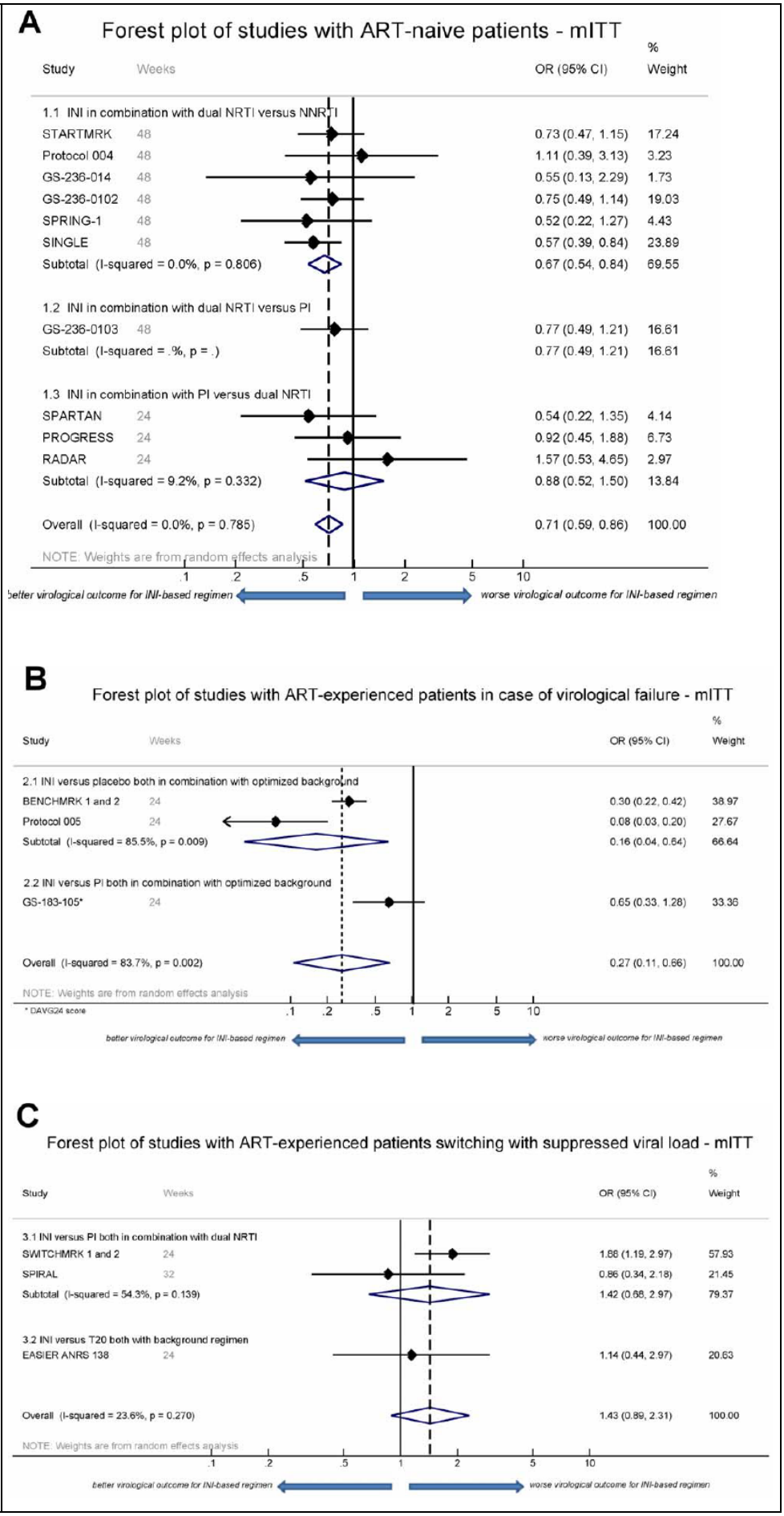
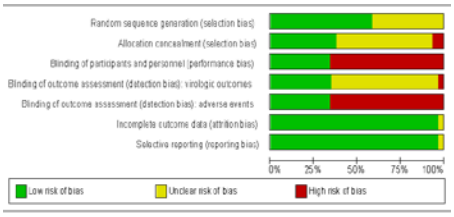

A
Forest plot of studies with ART-naive patients - mITT
Study
Weeks
OR (95% CI)
% Weight
1.1 INI in combination with dual NRTI versus NNRTI
STARTMRK 48 0.73 (0.47, 1.15) 17.24
Protocol 004 48 1.11 (0.39, 3.13) 3.23
GS-236-014 48 0.55 (0.13, 2.29) 1.73
GS-236-0102 48 0.75 (0.49, 1.14) 19.03
SPRING-1 48 0.52 (0.22, 1.27) 4.43
SINGLE 48 0.57 (0.39, 0.84) 23.89
Subtotal (I-squared = 0.0%, p = 0.806) 0.67 (0.54, 0.84) 69.55
1.2 INI in combination with dual NRTI versus PI
GS-236-0103 48 0.77 (0.49, 1.21) 16.61
Subtotal (I-squared = .%, p = .) 0.77 (0.49, 1.21) 16.61
1.3 INI in combination with PI versus dual NRTI
SPARTAN 24 0.54 (0.22, 1.35) 4.14
PROGRESS 24 0.92 (0.45, 1.88) 6.73
RADAR 24 1.57 (0.53, 4.65) 2.97
Subtotal (I-squared = 9.2%, p = 0.332) 0.88 (0.52, 1.50) 13.84
Overall (I-squared = 0.0%, p = 0.785) 0.71 (0.59, 0.86) 100.00
NOTE: Weights are from random effects analysis
.1 .2 .5 1 2 5 10
better virological outcome for INI-based regimen
worse virological outcome for INI-based regimen
B
Forest plot of studies with ART-experienced patients in case of virological failure - mITT
Study
Weeks
OR (95% CI)
% Weight
2.1 INI versus placebo both in combination with optimized background
BENCHMRK 1 and 2 24 0.30 (0.22, 0.42) 38.97
Protocol 005 24 0.08 (0.03, 0.20) 27.67
Subtotal (I-squared = 85.5%, p = 0.009) 0.16 (0.04, 0.64) 66.64
2.2 INI versus PI both in combination with optimized background
GS-183-105* 24 0.65 (0.33, 1.28) 33.36
Overall (I-squared = 83.7%, p = 0.002) 0.27 (0.11, 0.66) 100.00
NOTE: Weights are from random effects analysis
* DAVG24 score
.1 .2 .5 1 2 5 10
better virological outcome for INI-based regimen
worse virological outcome for INI-based regimen
C
Forest plot of studies with ART-experienced patients switching with suppressed viral load - mITT
Study
Weeks
OR (95% CI)
% Weight
3.1 INI versus PI both in combination with dual NRTI
SWITCHMRK 1 and 2 24 1.88 (1.19, 2.97) 57.93
SPIRAL 32 0.86 (0.34, 2.18) 21.45
Subtotal (I-squared = 54.3%, p = 0.139) 1.42 (0.68, 2.97) 79.37
3.2 INI versus T20 both with background regimen
EASIER ANRS 138 24 1.14 (0.44, 2.97) 20.63
Overall (I-squared = 23.6%, p = 0.270) 1.43 (0.89, 2.31) 100.00
NOTE: Weights are from random effects analysis
.1 .2 .5 1 2 5 10
better virological outcome for INI-based regimen
worse virological outcome for INI-based regimen

	Figure 3. Forest Plot of mITT meta-analyses. Panel A: Forest plot showing the meta-analysis of mITT data extracted from studies with therapy-naïve patients. Besides an overall analysis, three sub-analyses for three different comparisons are depicted. The black line indicates OR = 1, signifying no benefit of the INI arm compared to the non-INI arm. The dotted line shows the odds ratio of all included studies. The individual odds ratios as well as the proportionate weight in the overall analysis are shown in the right column. Panel B: Forest plot showing the meta-analysis of mITT data extracted from studies with ART-experienced patients in case of virological failure. Panel C: Forest plot showing the meta-analysis of mITT data extracted from studies with ART-experienced patients switching with suppressed viral load. mITT = modified intention-to-treat; ART = antiretroviral treatment; INI = integrase inhibitor; (N)NRTI = (non-)nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; T20 = enfuvirtide: OR = odds ratio. Summary: Therapy-naive patients: • favorable odds ratios (OR) for integrase inhibitor-based regimens were observed, (OR 0.71, 95% CI 0.59–0.86), high quality • Integrase inhibitors combined with protease inhibitors only did not result in a significant better virological outcome, moderate quality Treatment experienced patients: • Evidence supported integrase inhibitor use following virological failure (OR 0.27; 95% CI 0.11–0.66), moderate quality • switching to integrase inhibitors from a high genetic barrier drug during successful treatment was not supported (OR 1.43; 95% CI 0.89–2.31), low quality
	4. Anmerkungen/Fazit der Autoren Based on the meta-analyses, treatment with INIs in combination with dual NRTI showed to be more beneficial for treatment-naive patients compared to other currently used treatment strategies. Also in treatment-experienced patients with virological failure, use of INIs proved to be beneficial as well. However, in successfully treated patients with a history of therapy failure, switching a high genetic barrier drug towards an INI was not supported.
Cruciani M et al., 2014 [3] Virological efficacy of abacavir: systematic review and meta-analysis	1. Fragestellung To review the available evidence on efficacy of abacavir (ABC)
	2. Methodik **Population**: HIV-infected adults (treatment naive as well as antiretroviral-experienced participants) **Intervention:** abacavir-containing ART **Komparator:** non-abacavir-containing ART **Endpunkte:** • Primary: rates of patients with VL below the pre-defined cut-off (<50 copies/mL and/or 200–500 copies/mL) at 48 w and/or at 96 w. • Secondary: AE requiring treatment interruption and/or switching **Suchzeitraum**: up to June 2014 (update of search performed for Cruciani 2011) **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 31 **Qualitätsbewertung der Studien**: Cochrane Risk of Bias Tool **Heterogenität:** assessment of statistical heterogeneity using Tau^2, Cochran's Q and I^2 statistics.
	3. Ergebnisdarstellung • Risk of bias:



- no stat- sign. differences in proportions of subjects with VL <50 copies/ mL (siehe Tab 2)
- occurrence of AE requiring discontinuation of treatment:
  - no stat sign. differences between ABC and tenofovir (RR 1.26; 95% CI 0.99–1.61),
  - superiority of abacavir- versus non-tenofovir- containing regimens (RR 0.68, 95% CI 0.56–0.83)

o

Table 2. *Abacavir versus controls; summary of the pooled outcome data*

Outcome or subgroup	Studies	Participants	Effect estimate, RR (95% CI)	*P*	Heterogeneity (I^2), %
Rates of patients with HIV RNA below the cut-off					
<50 copies/mL, 48 weeks					
ABC versus TDF	5	3321	0.99 (0.94–1.05)	0.81	54
ABC versus other	14	3936	0.99 (0.89–1.09)	0.76	65
<50 copies/mL, 96 weeks					
ABC versus TDF	4	1877	0.99 (0.90–1.09)	0.82	0
ABC versus other	9	2457	not performed[a]		83
<200–500 copies/mL, 48 weeks					
ABC versus TDF	2	718	not performed[a]		93
ABC versus other	12	3746	not performed[a]		80
<200–500 copies/mL, 96 weeks					
ABC versus TDF	3	1430	0.98 (0.92–1.05)	0.61	30
ABC versus other	11	3304	0.99 (0.92–1.06)	0.76	63
ABC versus TDF according to baseline VL					
48 weeks					
overall	6	4118	0.98 (0.94–1.03)	0.50	54
<100000 copies/mL	5	2202	1.01 (0.99–1.03)	0.19	0
>100000 copies/mL	5	1916	0.96 (0.90–1.03)	0.22	36
96 weeks					
overall	4	2003	0.98 (0.93–1.03)	0.73	0
<100000 copies/mL	4	1272	0.99 (0.93–1.04)	0.62	1
>100000 copies/mL	3	731	0.97 (0.87–1.08)	0.54	0
Discontinuation for adverse events					
ABC versus TDF	7	3051	1.26 (0.99–1.61)	0.06	0
ABC versus other	16	4778	0.68 (0.56–0.83)	0.0001	27

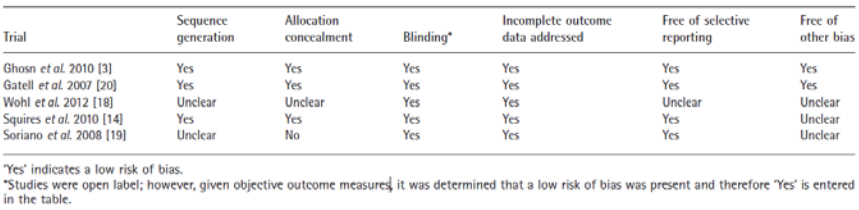
ABC, abacavir; TDF, tenofovir.
Results are provided for all possible comparisons and separately for subgroups of studies comparing ABC with TDF or with other cART regimens.
[a]Not performed due to the high heterogeneity ($I^2 > 75\%$).

4. Fazit der Autoren: Our cumulative, cross-sectional data suggest a similar virological efficacy of abacavir/lamivudine and tenofovir/emtricitabine regardless of the baseline VL.

5. Hinweise durch FBMed

	• Review differenziert nicht nach Therapielinie • z.T. hohe Heterogenität zwischen den Studien
Sprenger HG et al., 2014 [43] A systematic review of a single-class maintenance strategy with nucleoside/nucleotide reverse transcriptase inhibitors in HIV/AIDS	1. Fragestellung To assess the antiviral efficacy of maintenance therapy with NRTI-only regimens and to evaluate the metabolic effects of this strategy
	2. Methodik **Population:** HIV infected patients treated successfully in induction phase with three- or four-drug standard cART (patients could be ART-naive or experienced at beginning of induction regimen) **Intervention:** NRTI only regimens (mainly ABC/3TC/ZDV) **Komparator:** PI or NNRTi-based cART **Endpunkte:** o Primary: virological failure, o Secondary: change in CD4+ T-cell count, lipid profile and SAE **Suchzeitraum:** up to 03/2013 in Medline, Embase **Anzahl eingeschlossene Studien/Patienten (Gesamt):**)11 RCT + 3 observational studies **Qualitätsbewertung der Studien:** Jadad score, New-Ottawa Scale
	3. Ergebnisdarstellung *Study quality* o 4 of 11 RCT with good methodological quality based on Jaded score, none of the trials was blinded o 1 of 3 observational studies with good quality based on New-Ottawa Scale *NRTI-only maintenance therapy after suboptimal regimens* • none of the RCTs showed a significant higher rate of virological failure in the triple-NRTI arm compared to a PI arm or NNRTI arm • in some studies there was a trend toward a higher failure rate in the NRTI-only arm, especially in patients with earlier exposure to NRTI mono- or dual therapy • note: most studies used a high HIV-a RNA threshold (>400 copies/ml) for virological failure; majority of PI used in all studies were unboosted *Maintenance therapy after successful first line ART therapy in ART naïve subjects* <u>NRTI-only maintenance compared to a PI-based regime</u>: • 3 RCT demonstrate that maintenance therapy with triple-NRTI is treatment option compared to continuation of a PI-based regimen (based on virological failure) <u>NRTI-only maintenance compared to an NNRTI-based regimen</u> • Triple NRTI maintenance is non-inferior to an NNRTI-based regimen based on virological failure (3 RCTs) • Better lipid profil with triple NRTI
	4. Anmerkungen/Fazit der Autoren: Triple-NRTI maintenance regimens appear to be non-inferior compared to standard two-class triple (or even quadruple) regimens, whether PI or NNRTi-based.

	5. Hinweise durch FBMed Keine Meta-Analyse durchgeführt
Baril J et al., 2014 [1] A meta-analysis of the efficacy and safety of unboosted atazanavir compared with ritonavir-boosted protease inhibitor maintenance therapy in HIV-infected adults with established virological suppression after induction	1. Fragestellung To evaluate the efficacy and safety of switching from a ritonavir (RTV)-boosted PI to unboosted ATV compared with continuing on an RTV-boosted PI regimen in adult HIV-1-positive patients after patients showed established virological suppression through an induction phase of PI/RTV-based highly active antiretroviral therapy (HAART).
	2. Methodik **Population:** HIV-1-infected adults (treatment experienced: i.e., during an induction phase, they had received a regimen including an RTV boosted PI and had achieved and maintained virological suppression). **Intervention** unboosted ATV (400 mg per day) **Komparator:** RTV boosted ATV (300 mg ATV and 100 mg RTV per day) or another RTV-boosted PI **Endpunkte**: • maintenance of virological suppression (defined as the proportion of patients maintaining HIV-1 RNA levels below specified thresholds [i.e. <50 and < 400 HIV-1 RNA copies/mL] during the study maintenance phase • change in CD4 cell counts • safety: mean lipid levels [i.e. total cholesterol, triglycerides, low-density lipoprotein (LDL) and highdensity lipoprotein (HDL)], renal function parameters (e.g. creatinine) and the occurrence of hyperbilirubinaemia (i.e. grades 2−4), jaundice and scleral icterus. **Literaturrecherche:** up to August 2012 in PubMed, EMBASE, CENTRAL, Cochrane Reviews and DARE, additionally search for proceedings from International AIDS Society, Interscience Conference on Antimicrobial Agents and Chemotherapy and the Conference on Retroviruses and Opportunistic Infections **Anzahl eingeschlossene Studien/Patienten (Gesamt):** n=5 (1249 patients) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Funding by Bristol-Myers Squibb
	3. Ergebnisse *Study characteristics* • 2 studies compared PI/RTV combination (lopinavir/RTV; or lopinavir/RTV, indinavir/RTV or saquinavir/RTV) vs. unboosted ATV • 3 studies compared ATV/RTV vs. unboosted ATV • NRTI backbone: lamivudine and abacavir regimen commonly used; tenofovir much less frequently used • length of maintenance: 24-48 weeks *Risk of bias* • 3 studies: adequate quality; 2 studies: acceptable

	Table 2 Qualitative risk of bias assessment summary  'Yes' indicates a low risk of bias. *Studies were open label; however, given objective outcome measures, it was determined that a low risk of bias was present and therefore 'Yes' is entered in the table. *Efficacy results* • virological efficacy: unboosted ATV vs PI/RTV: → n.s. o HIV RNA < 50 copies/mL: RR 1.04; 95% CI 0.99-1.10 ; I^2=0% o HIV RNA < 400 copies/mL: RR 1.05; 95% CI 0.99-1.11;I^2=0% • change in CD4 counts: MD14.10; 95% CI −13.27-41.48; I^2=53% *Safety results* • lipid parameters: unboosted ATV vs PI/RTV o significant reduction in total cholesterol (MD −14.7 mg/ dL; 95% CI −20.96 to −8.49; P < 0.00001), o triglycerides (MD −51.15 mg/dL; 95% CI −78.36 to −23.94; P = 0.0002) o LDL cholesterol (MD = −5.56 mg/dL; 95% CI −9.71 to −1.41; P = 0.009) o No significant differences in HDL cholesterol • Sign. lower risk of grade 2−4 hyperbilirubinaemia with unboosted ATV compared with ATV/RTV (RR 0.43; 95% CI 0.21 to 0.89; P = 0.02; I^2 = 0%)
	4. Fazit der Autoren: The meta-analysis demonstrated that switching patients with virological suppression from an RTV-boosted PI to unboosted atazanavir leads to improvements in safety (i.e. blood parameter abnormalities) without sacrificing virological efficacy.
Ford N et al., 2013 [6] Comparative Efficacy of Lamivudine and Emtricitabine: A Systematic Review and Meta-Analysis of Randomized Trials	1. Fragestellung To assess the comparative efficacy of lamivudine and emtricitabine as a core component of the nucleoside reverse transcriptase inhibitor backbone
	2. Methodik **Population:** treatment-naïve or treatment-experienced HIV-positive adult patients **Intervention/ Komparator:** lamivudine (3TC) and emtricitabine (FTC) as part of combination antiretroviral therapy • Inclusion of trials where partner drugs in the regimen were identical or could be considered to be comparable. • We allowed for comparisons between tenofovir and abacavir provided the study population did not begin treatment with a viral load ≥100,000 copies/ml, as trials have concluded comparable efficacy for these two drugs below this threshold **Endpunkte**: virological success and virological failure **Suchzeitraum:** up to March 31 2013/June 30 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 **Qualitätsbewertung der Studien:** • study quality assessed following criteria developed by the Cochrane Collaboration. • overall quality of the evidence was assessed using GRADE

	3. Ergebnisdarstellung • 5 studies were done in treatment-naive patients, 7 studies in treatment-experienced patients • 3 trials had the same backbone regimens; the rest compared tenofovir and abacavir. (siehe Anhang: Tab.1 Study characteristics) Treatment success was not significantly different in any of the 12 trials: • In the three trials that directly compared lamivudine and emtricitabine (with identical backbone) the relative risk for achieving treatment success was non-significant for both trials (RR 1.03, 95%CI 0.96– 1.10; P = 0.3). • pooled relative risk for treatment success (from trials with identical and comparable backbone) was non-significant (RR 1.00, 95% CI 0.97–1.02; I^2 =0). This result was not different in any of the pre-defined subgroups (test for heterogeneity for all subgroups: p=0.1), or if random-effects methods were used to pool the data (RR 0.99, 95%CI 0.96–1.01). Treatment failure: all but one study found no difference in the risk of treatment failure: • pooled relative risk was not statistically significant (RR 1.08, 95%CI 0.94–1.22; I^2 = 3.4%), • Subgroup differences were not apparent (p=0.1 for all subgroups). Two of the three trials with identical backbone regimens provided data on AE: • In trial FTC302, no difference in the incidence of any grade 3 or 4 adverse event was reported. • In trial FTC-303/350, 4% of patients discontinued treatment due to adverse events in the FTC arm and there were no discontinuations in the 3TC arm. **Validity of results** • GRADE assessment rated the quality of the evidence overall to be moderate: o Risk of bias was judged to be low o no evidence of publication bias (p = 0.3 using Egger's test for funnel plot asymmetry). o Results of all studies were consistent for the critical outcomes of virological suppression and failure. Concern was noted with respect to possible indirectness resulting from the inclusion of trials with nonidentical backbone regimens but the direction of this bias would be expected to favour emtricitabine.
	4. Anmerkungen/Fazit der Autoren: The results of this review should not be understood as definitive evidence of equivalence. Nevertheless, the overall findings provide supportive evidence for the recommendations of current international and national treatment guidelines to treat emtricitabine and lamivudine as interchangeable and reassurance to countries that, for reasons of affordability or availability have opted for lamivudine as part of first line antiretroviral therapy. 5. Hinweise durch FBMed Keine Differenzierung nach Vorbehandlung
Ford N et al., 2015 [7] Comparative Safety	1. Fragestellung To evaluate the safety of EFV compared with other antiretroviral agents in first-line therapy and to describe the frequency of neuropsychiatric adverse events among patients exposed to EFV

and Neuropsychiatric Adverse Events Associated With Efavirenz Use in First-Line Antiretroviral Therapy: A Systematic Review and Meta-Analysis of Randomized Trials	2. Methodik Durchführung des SR nach einem a priori definierten Protokoll **Population:** antiretroviral-naive HIV-positive adults and children. **Intervention:** EFV irrespective of dose **Komparator:** non-EFV–based regimens as part of an identical backbone combination therapy **Endpunkte:** • Primary: drug discontinuation due to adverse event o Secondary: o severe (grade, 3–4) clinical adverse events, o severe laboratory adverse events, and o toxicity-related mortality. o proportion of patients experiencing neuropsychiatric adverse events **Suche:** from inception to October 2014 in MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 42 trials **Qualitätsbewertung:** Cochrane Risk of Bias Tool auf Einzelstudienebene; GRADE für studienübergreifende Bewertung der Quality of Evidence
	3. Ergebnisdarstellung *Study quality* • 81% of studies failed to report on approach to allocation concealment; only 33% of the studies blinded participants and patients;Loss to follow-up was less than 10% for 74% of the studies and in most instances was nondifferential (79%); and for the majority of trials (86%), there was no evidence of selection bias or outcome reporting (86%). • some statistical evidence of publication bias (0.06 using Egger test for funnel plot asymmetry). *Results* <u>Discontinuations due to AE</u> (moderate quality of evidence) • lower risk with EFV compared to nevirapine (9 studies: RR: 0.7, 95% CI: 0.53 to 0.98; I^2= 34,10%; RD: -3.6, 95% CI: -6.6 to -0.6). • higher risk with EFV compared to: o low-dose EFV (1 study: RR: 3.1, 95% CI: 1.3 to 7.7; RD: 4.0, 95% CI: 1.0 to 7.0), o rilpivirine (4 studies: RR: 2.0, 95% CI: 1.0 to 3.8; I^2=71,8%; RD: 4.1, 95% CI: 1.3 to 6.8), o tenofovir (1 study: RR: 3.6, 95% CI: 1.4 to 9.6;RD: 7.7, 95% CI: 2.4 to 13.0), o atazanavir (5 studies: RR: 1.4, 95% CI: 1.1 to 1.8, I^2=0%; RD: 2.6, 95% CI: 0.6 to 4.6), o maraviroc (1 study: RR: 3.3,95% CI: 1.9 to 5.7; RD: 9.4, 95% CI: 5.3 to 13.5). o dolutegravir (2 studies: RR: 4.3, 95% CI: 2.2 to 8.3, I^2=0%; absolute risks not significantly different) and o raltegravir (3 studies: RR: 2.7, 95% CI: 1.1 to 6.9, I^2=0%; absolute risks not significantly different) <u>Severe clinical AE</u>

	No sign. differences for any drug comparison Severe laboratory AE • lower risk comparing EFV with atazanavir/r (RD: -77.1, 95% CI: -91.9 to -62.4; relative differences were not significant) • higher risk comparing EFV with dolutegravir (2.8, 95% CI: 0.2 to 5.3, relative differences were not significant) • other differences were observed. Severe neuropsychiatric AE • Higher risk for EFV compared with o atazanavir/ r (RR: 2.4, 95% CI: 1.5 to 3.8; RD: 3.7, 95% CI: 1.8 to 5.5), o dolutegravir (RR: 16.7, 95% CI: 2.0 to 137.8; RD: 3.0, 95% CI: 1.4 to 4.6), o maraviroc (RR: 5.3, 95% CI: 1.6 to 18.1; RD: 3.6, 95% CI: 1.3 to 5.9), • absolute differences were higher for EFV compared with abacavir (RD: 6.0, 95% CI: 2.4 to 9.6). • No other differences were observed
	4. Anmerkungen/Fazit der Autoren: EFV use is associated with a higher risk of treatment discontinuation compared with a number of other antiretroviral drugs, with a greater (and expected) frequency of CNS events. Although most CNS events were mild, and suicide ideation is rare, even mild adverse events are a concern from a public health perspective because they may lead to decreased adherence to treatment. Future decisions about keeping or replacing EFV in first-line therapy, particularly in low- and middle-income settings, should take into account other factors, such as the good virological efficacy, low cost, availability as once-daily combination, compatibility with tuberculosis drugs, and wide experience of using this antiretroviral drug. 5. Hinweise durch FBMed für die sekundäre Endpunkten liegen keine Informationen bzgl. zugrundeliegender Studienanzahl und GRADE-Bewertung vor

Leitlinien

BHIVA 2016 [2]

British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)

Guideline of the British HIV Association:

To provide guidance on best clinical practice in the treatment and management of adults with HIV infection with antiretroviral therapy (ART).

Methodik: Update der Leitlinienversion von 2013

Grundlage der Leitlinie:

- syst. Literaturrecherche/-bewertung
- Konsensusprozess
- Beteiligung von 2 Patientenvertretern an der LL-Entwicklung
- öffentl. Stellungnahmeverfahren

Literaturrecherche:

- October 2011 – August 2014 in Medline, Embase, The Cochrane library
- Abstracts from selected conferences were searched between 1 January 2011 and July 2015
- For the 2016 interim update the panel reviewed newly licensed products and the writing panel developed a consensus opinion based on critic endpoints; appropriate sections were updated. Formal GRADE analysis of these products will be included in the 2017 update. Small changes were made to the virological failure section. All 2016 amendments are highlighted.

LoE/GoR: BHIVA has adopted the modified GRADE system for its guideline development.

Strength of recommendation

Grade 1	A Grade 1 recommendation is a strong recommendation to do (or not do) something, where the benefits clearly outweigh the risks (or vice versa) for most, if not all patients. (‘we recommend’)
Grade 2	A Grade 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. (‘we suggest’)
Quality of Evidence	
Grade A	Grade A evidence means high-quality evidence that comes from consistent results from well-performed RCTs, or overwhelming evidence of some other sort (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	Grade B evidence means moderate-quality evidence from randomized trials that suffer from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with special strengths such as observational studies with consistent effects and exclusion of most potential sources of bias.
Grade C	Grade C evidence means low-quality evidence from controlled trials with several very serious limitations or observational studies with limited evidence on effects and exclusion of most potential sources of bias.
Grade D	Grade D evidence on the other hand is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there is likely to be little confidence in the effect estimate.

In addition to graded recommendations, good practice points (GPP) were formulated, which are recommendations based on the clinical judgement and experience of the working group

The guidelines will be next fully updated and revised in 2017

Hinweis: Detaillierte Darstellung der Methodik sowie die Bewertung der Evidenz nach

GRADE findet sich in den Appendixes der Leitlinie verfügbar

Empfehlungen

Adults

What to start

- We recommend that therapy-naïve PLWH start ART containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir-boosted protease inhibitor (PI/r), nonnucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) (1A).

Table 5.1. Summary recommendations for choice of ART

	Preferred	Alternative
NRTI backbone	Tenofovir-DF and emtricitabine	Abacavir and lamivudine[a,b]
	Tenofovir-AF and emtricitabine	
Third agent (alphabetical order)	Atazanavir/r	Efavirenz
	Darunavir/r	
	Dolutegravir	
	Elvitegravir/c[c]	
	Raltegravir	
	Rilpivirine[d]	

/r: boosted with ritonavir; /c: boosted with cobicistat

[a] Abacavir is contraindicated if an individual is HLA-B*57:01 positive

[b] Use recommended only if baseline viral load is ⍰100,000 copies/mL except when initiated in combination with dolutegravir in which case abacavir/lamivudine can be used at any baseline viral load.

[c] Tenofovir-DF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in individuals with creatinine clearance <70 mL/min; tenofovir-AF/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in patients with CrCl <30 mL/min

[d] Use recommended only if baseline viral load is ⍰100,000 copies/mL

NB. The viral load advice for abacavir/lamivudine and rilpivirine applies only to initiating these agents in individuals with a detectable viral load – when these agents are used as a switch option in the context of viral load suppression the baseline viral load can be disregarded.

Which nucleoside reverse transcriptase inhibitor backbone

- We recommend therapy-naïve individuals start combination ART containing tenofovir-DF and emtricitabine or tenofovir-AF and emtricitabine as the preferred NRTI backbone (1A).
- We suggest abacavir and lamivudine is an acceptable alternative NRTI backbone in therapy-naïve individuals. In those with a baseline viral load >100,000, it should be used with caution if there are clinical reasons to prefer it over alternative NRTI backbones (2A).

The caution regarding baseline viral load does not apply if abacavir/lamivudine is used with dolutegravir (2A).

- Abacavir must not be used in individuals who are HLA-B*57:01-positive (1A).

Which third agent

recommend therapy-naïve individuals start combination ART containing atazanavir/r, navir/r, dolutegravir, elvitegravir/c, raltegravir or rilpivirine as the third agent (1A).

Which third agent?

- We recommend therapy-naïve patients start combination ART containing

	atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), dolutegravir, elvitegravir/c, raltegravir or rilpivirine as the third agent (1A). • We suggest that for therapy-naïve patients, efavirenz is an acceptable alternative third agent (1A). *Erläuterungen Zusammenfassung:* When selecting a third agent from either the preferred or alternative options, factors such as potential sideeffects, dosing requirements, dosing convenience, individual preference, co-morbidities, drug interactions and cost should be considered. In summary, efavirenz should no longer remain a preferred third agent and should now be considered an alternative. Because of similar critical treatment outcomes, atazanavir/r, darunavir/r, dolutegravir elvitegravir/c, raltegravir and rilpivirine are all recommended as preferred third agents (with the caveat that rilpivirine is only recommended within its licence in individuals with a baseline viral load less than 100,000 copies/mL). **Novel antiretroviral therapy strategies** • We recommend against the use of PI monotherapy as initial therapy for treatment-naïve patients (1C). • We suggest the use of darunavir/r-based dual ART regimen with raltegravir in treatmentnaïve patients with CD4 count >200 cells/μL and viral load <100,000 copies/mL where there is need to avoid abacavir, tenofovir-DF or tenofovir-AF (2A). • We recommend against the use of PI-based dual ART with a single NNRTI, NRTI or CCR5 receptor antagonist for treatment-naïve patients (1B). **Individuals with no or limited drug resistance** • We recommend for individuals experiencing virological failure on first-line ART with wild-type virus at baseline and without emergent resistance mutations at failure, switch to a PI/r- or PI/c-based combination ART regimen is the preferred option (1C). • We recommend individuals experiencing virological failure on first-line ART with wild-type virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure, switch to a new PI/r- or PI/c-based regimen with the addition of at least one, preferably two, active drugs (1C). • We recommend individuals experiencing virological failure on first-line PI/r or PI/c plus two-NRTI based regimens, with limited major protease mutations, switch to a new active PI/r or PI/c with the addition of at least one, preferably two, active agents of which one has a novel mechanism of action (1C). • We recommend against switching a PI/r or PI/c to an INI or NNRTI as the third agent in individuals with historical or existing reverse transcriptase mutations associated with NRTI resistance or past virological failure on NRTIs (1B). **Individuals with multiple class virological failure with or without extensive drug resistance** • We recommend individuals with persistent viraemia and with limited options to construct a fully suppressive regimen are discussed at an MDT inclusive of a virologist /referred for expert advice (or through virtual clinic referral) (GPP). • We recommend individuals with extensive drug resistance are switched to a new ART regimen containing at least two and preferably three fully active agents with at least one active PI/r such as twice-daily darunavir/r and one agent with a novel mechanism (an INI, maraviroc or enfuvirtide) with etravirine an option based on viral susceptibility (1C). • We recommend in individuals without DRV resistance associated mutations, boosted-DRV can be given once daily (1C) • We recommend individuals with extensive drug resistance including reduced darunavir susceptibility receive dolutegravir as the INI (1C). • We suggest that consideration on an individual basis should be given to whether

inclusion of NRTIs with reduced activity on genotypic testing will provide additional antiviral activity if the regimen

- includes three fully active drugs including a boosted PI (2C).
- We recommend all individuals receive intensive adherence support at the start and at regular intervals to support them on their new ART combination (GPP).

Individuals with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed

- We recommend accessing newer agents through research trials, expanded access and named individual programmes (GPP).
- We suggest that consideration, on an individual basis, should be given to whether inclusion of NRTIs with reduced activity on genotypic testing will provide additional antiviral activity – this may well be the case where it is difficult to construct a regimen with three fully active drugs including a boosted PI (see Section 7.4) (2C).
- We recommend against discontinuing or interrupting ART (1B).
- We recommend against adding a single, fully active ARV because of the risk of further resistance (1D).
- We recommend against the use of maraviroc to increase the CD4 cell count when there is evidence for X4 or dual tropic virus (1C).
- We recommend in the context of triple class failure, where darunavir is being used as the boosted PI, it should be given with ritonavir twice-daily
- We recommend that in the context of triple-class failure and raltegravir/elvitegravir selected integrase resistance, twice-daily dolutegravir should be included as part of a new regimen where there is at least one fully active agent in the background regimen (1C).

Adolescents

Adolescents include all young people defined by WHO as those aged between 10 and 19 years , and young adults aged between 20 and 24 years [1]. For the purposes of these guidelines we will consider adolescents living with HIV by route of transmission: perinatally acquired HIV infection (PaHIV) and behaviourally infected HIV (BaHIV).

For behaviourally infected young people >18 years of age, the management of their HIV disease and associated considerations should be in accordance with BHIVA adult guidelines. The management of adolescents aged less than 16 years within paediatric care should be in accordance with Children's HIV Association (CHIVA) guidelines (http://www.chiva.org.uk/professionals/health/guidelines/index.html) and the Paediatric European Network for Treatment of AIDS (PENTA) treatment guidelines [2]. There are limited data and no randomised controlled trial data on long-term complications of PaHIV and ART exposure throughout physical maturity, and the following recommendations are based on pragmatic and good clinical practice.

8.9.1 Recommendations for management of HIV, ART and sexual and reproductive health specifically for perinatally acquired HIV

- Avoid standard-dose (600mg) efavirenz-based regimens in any young person <50kg, with any history of mental health or psychological or neurocognitive problems.

Young adults and adolescents (YAA) represent a uniquely vulnerable group who have poor health outcomes compared to younger children and older adults living with the same condition. This is a feature of lifestyle, adolescent behaviour, lack of engagement in health care services and primary care and often lack of social support. As such, any service providing care for YAA living with HIV must offer appropriate youth-centred services, with an open-door policy, non-judgemental care provision, and opening hours consistent with educational commitments.

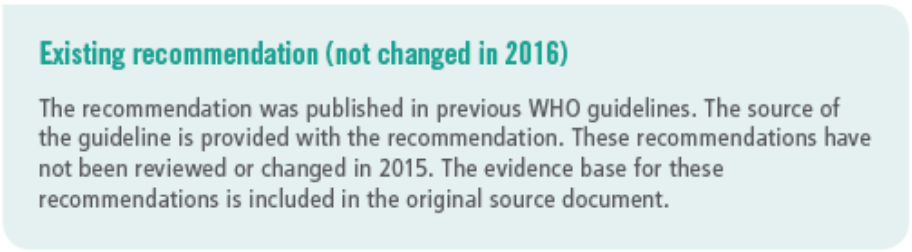
	8.9.2 UK Epidemiology for YAA with PaHIV With antiretroviral therapy, the significant fall in HIV-associated morbidity and mortality for perinatally infected children has resulted in increasing numbers entering adolescence and transitioning towards adult services [3,4]. Over 90% of children diagnosed in the UK and reported to the National study of HIV and Pregnancy (NSHPC) are followed prospectively in the Collaborative HIV Paediatric Study (CHIPS; www.chipscohort.ac.uk). Data to the end of March 2014 shows that of 1873 children ever reported, 595 have already transferred to adult services, at a median age of transfer of 17 years [4]. **8.9.3 Transition Process for YAA with PaHIV** Transfer to adult services had been associated with increased disease-related morbidity and mortality for a wide range of chronic conditions of childhood prompting the National Service Framework (NSF) 2004 to set standards for the healthcare of young people [5]. Subsequently the Department of Health (DH) has produced a wealth of resources to guide the development of transitional care services [6–8]. Transition is defined as 'A planned, purposeful, process resulting in the point of transfer to adult services'. While several different transition models are described, the key to a successful transition is communication, forward planning and maintaining a young person-centred approach [9,10]. HIV-specific transitional care guidance is available through CHIVA and set within the CHIVA Standards (www.chiva.org.uk) [10]. **8.9.4 UK Epidemiology for YAA with BaHIV** Public Health England (PHE) surveillance data reveals 736/5,967 (12%) of new HIV diagnoses in 2013 were in young adults aged 15–24 years. Routes of transmission were: sex between men (*n*=462); heterosexual contact (*n*=152); and IVDU (*n*=4). Both the proportion and number of new HIV diagnoses among MSM aged 15–24 years have increased over the past decade, from 8.7% (250/2,420) in 2004 to 16% (460/2,950) in 2013 [11]. **8.9.5 Neurocognitive impact of HIV in YAA** The neurocognitive impact of living with HIV on the developing adolescent brain is becoming increasingly apparent, with poorer school performance, increased psychiatric diagnoses and particular difficulties in executive functioning for PaHIV YAA [12–14]. Recent data suggest that more than two-thirds of treatment-naïve BaHIV YAA meet criteria for a diagnosis of HIV-associated neurocognitive disorders, with the most common deficits being in memory and fine motor skills [15]. Optimising virological control with further investigation and referral to expert neurology HIV clinics is recommended. **8.9.6 Antiretroviral therapy** **8.9.6.2 Toxicity** At standard dose, increased efavirenz toxicity associated with higher plasma drug levels has been reported in adults of lower weight, a weight band that will include many YAA [19]. Additionally, reports of a potential increase in suicidal risk associated with efavirenz is of concern in an age group where suicide is the second most common cause of death in the UK, and is more than three times as common in males when compared to females [20]. Rates of suicide more than double in those aged 20–24 compared with those aged 15–19; suicide has been reported in PaHIV YAA in adult care [20,21]. Prolonged ART exposure resulting in lipodystrophy, at an age when body image is so important, may have a negative impact on psychological wellbeing and a potential impact on adherence to ART [22,23]. Growth stunting and delayed puberty in PaHIV YAA and dermatological conditions associated with HIV, such as scaring from shingles, molluscum contagiosum and seborrhoeic dermatitis may further exacerbate issues around body image and self worth. Multidisciplinary team assessment that includes dietetics, psychology and where appropriate, referral for cosmetic surgery is required.
WHO, 2016 [44] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (Second edition, 2016)	These consolidated guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the care of people living with HIV and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection.
	Methodik: Update der Leitlinienversion von 2013 **Grundlage der Leitlinie:** • syst. Literaturrecherche, • Konsensusprozess **(Such)zeitraum:** This edition updates the 2013 consolidated guidelines on the use of antiretroviral drugs following an extensive review of evidence and consultations in mid-2015, shared at the end of 2015, and now published in full in 2016. **LoE & GoR:** Bewertung der Evidenz sowie Stärke der Empfehlung nach GRADE Weitere Dokumente zur Methodik und Bewertung der Evidenz finden sich auf der WHO Internetseite.
	Empfehlungen

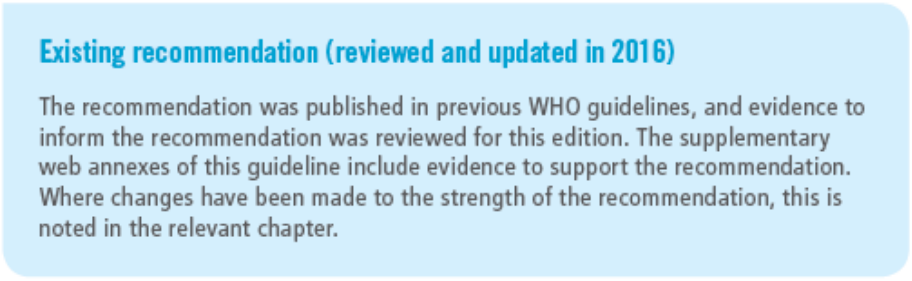
Age groups and populations

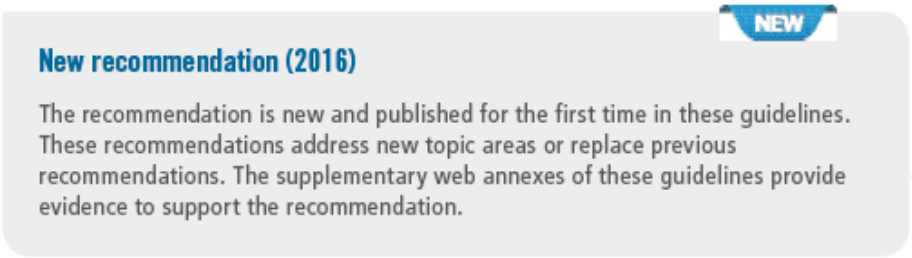
The following definitions for adults, adolescents, children and infants are used in these guidelines for the purpose of implementing recommendations for specific age groups. It is acknowledged that countries may have other definitions under national laws:

[…]

- An **adolescent** is a person 10–19 years of age inclusive.
- A **child** is a person 1 to younger than 10 years of age.
- An **infant** is a child younger than 1 year of age.







What to start: First-line ART

Table 4.1. First-line ART regimens for adults, pregnant or breastfeeding women, adolescents and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a,b]
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG[c] TDF + 3TC (or FTC) + EFV_{400}[c,e] TDF + 3TC (or FTC) + NVP
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG[c,d] TDF (or ABC) + 3TC (or FTC) + EFV_{400}[c,d,e] TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

[a] For adults and adolescents, d4T should be discontinued as an option in first-line treatment.

[b] ABC or boosted protease inhibitors (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

[c] Safety and efficacy data on the use of DTG and EFV_{400} in pregnant women, people with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available.

[d] Conditional recommendation, moderate-quality evidence.

[e] EFV at lower dose (400 mg/day).

3TC lamivudine, ABC abacavir, AZT zidovudine, DRV darunavir, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, TDF tenofovir.

First-line ART for adults

Recommendations

- First-line ART for adults[a] should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI).
- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
- If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following alternative options is recommended:
  - AZT + 3TC + EFV
  - AZT + 3TC + NVP
  - TDF + 3TC (or FTC) + NVP

  (strong recommendation, moderate-quality evidence).
- **TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternative options to initiate ART (conditional recommendation, moderate-quality evidence).** NEW
- Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).

[a] Adults include pregnant and breastfeeding women, for whom additional guidance is found in Box 4.3.

3TC lamivudine, AZT zidovudine, d4T stavudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, TDF tenofovir

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

First-line ART for adolescents

Recommendations

First-line ART for adolescents should consist of two NRTIs plus an NNRTI or an INSTI:

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, low-quality evidence).
- **TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV_{400}[a] may be used as alternative options to initiate ART (conditional recommendation, low-quality evidence).** NEW

If preferred regimens are contraindicated or not available, one of the following alternative options is recommended (strong recommendation, moderate-quality evidence):

ABC + 3TC + EFV
ABC + 3TC + NVP
AZT + 3TC + EFV
AZT + 3TC + NVP
TDF + 3TC (or FTC) + NVP

[a] EFV at a lower dose (400 mg/day).

First-line ART for children 3–10 years of age

Recommendations

For children 3 to less than 10 years of age, the NRTI backbone should be one of the following, in preferential order (conditional recommendation, moderate-quality evidence[a]):

- ABC + 3TC
- AZT or TDF + 3TC (or FTC).

For children 3 years and older, EFV is the preferred NNRTI for first-line treatment and NVP is the preferred alternative (strong recommendation, low-quality evidence).

[a] Strength of evidence reviewed in 2015.

What ART regimen to switch to (second- and third-line ART)

Table 4.15. Preferred second-line ART regimens for adults, adolescents, pregnant women and children

Population		Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r[c]
		2 NRTIs + DTG		
Pregnant or breastfeeding women		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r
Children	Less than 3 years	2 NRTIs + LPV/r	2 NRTIs[b] + RAL	Maintain the failing LPV/r-based regimen and switch to 2 NRTIs[b] + EFV at 3 years of age
		2 NRTIs + NVP	2 NRTIs[b] + LPV/r	2 NRTIs[b] + RAL[d]
	3 years to less than 10 years	2 NRTIs + LPV/r[a]	2 NRTIs[b] + EFV	2 NRTIs[b] + RAL[d]
		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + LPV/r	2 NRTIs[b] + ATV/r[d]

[a] ATV/r can be used as an alternative PI for children older than 3 months of age.

[b] If ABC+ 3TC or TDF + 3TC (or FTC) was used in the first-line failing regimen, AZT + 3TC should be used in second-line and vice versa.

[c] RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

[d] DRV/r can be used as an alternative PI option in special situations.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, RAL raltegravir.

Second-line ART for adults and adolescents

Recommendations

- Second-line ART in adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a ritonavir-boosted protease inhibitor (PI).
- The following sequence of second-line NRTI options is recommended:
  - After failure on a TDF + 3TC (or FTC)-based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.
  - After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC (or FTC) as the NRTI backbone in second-line regimens.
- Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach (strong recommendation, moderate-quality evidence).
- Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART (strong recommendation, moderate-quality evidence).
- **Heat-stable fixed-dose combinations of DRV/r can be used as an alternative boosted PI option for second-line ART (conditional recommendation, low-quality evidence).** NEW
- **A combination of RAL plus LPV/r can be used as an alternative second-line ART regimen (conditional recommendation, low-quality evidence).** NEW

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Second-line ART for children

<table>
<tr>
<td></td>
<td>
Recommendations
• After failure of a first-line LPV/r-based regimen, children younger than 3 years should be switched to a RAL-based second-line regimen (conditional recommendation, very low-quality evidence). NEW
• After failure of a first-line LPV/r-based regimen, children older than 3 years should be switched to a second-line regimen containing two NRTIs plus EFV or RAL (conditional recommendation, very low-quality evidence). NEW
• After failure of a first-line NNRTI-based regimen, children should be switched to a boosted PI-based regimen. LPV/r or ATV/r are preferred (conditional recommendation, very low-quality evidence).
• After failure of a first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is AZT + 3TC (strong recommendation, low-quality evidence).
• After failure of a first-line regimen containing AZT or d4T + 3TC (or FTC), the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC (or FTC) (strong recommendation, low-quality evidence).
Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

Third-line ART
Recommendations
• National programmes should develop policies for third-line ART (conditional recommendation, low-quality evidence).
• Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs (conditional recommendation, low-quality evidence).
• Patients on a failing second-line regimen with no new ARV drug options should continue with a tolerated regimen (conditional recommendation, very low-quality evidence).
Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection:r ecommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).
</td>
</tr>
<tr>
<td rowspan="2">Gunthard HF et al., 2016 [19]
Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2016 Recommendations of the International Antiviral Society–USA Panel</td>
<td>Zielsetzung/Fragestellung

To provide updated recommendations for the use of antiretroviral therapy in adults (aged≥18 years) with established HIV infection, including when to start treatment, initial regimens, and changing regimens, along with recommendations for using ARVs for preventing HIV among those at risk, including pre-exposure and post-exposure prophylaxis.</td>
</tr>
<tr>
<td>Methodik

Grundlage der Leitlinie:
• internationale Expertengruppe,
• syst. Literaturrecherche,
• Konsensusprozesse

Suchzeitraum: Comprehensive literature searcheswere conducted in the PubMed and EMBASE databases through April 2016.

Weitere Kriterien für die Qualität einer Leitlinie: Finanzierung durch die „IAS–USA - a not-for-profit, mission-based, nonmembership, educational organization“, CoI erfasst und</td>
</tr>
</table>

bewertet, Empfehlungen hervorgehoben aber nicht mit Literatur verknüpft

Strength of recommendation:

A	Strong support for the recommendation
B	Moderate support for the recommendation
C	limited support for the recommendation

Quality of evidence:

Ia	Evidence from 1 or more RCT published in the peer-reviewed literature
Ib	Evidence from 1 or more RCT presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies published in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel´s analysis of the accumulated available evidence

Empfehlungen

Recommendations for When to Start Antiretroviral Therapy[a]

- Antiretroviral therapy (ART) is recommended for all viremic patients with established HIV infection, regardless of CD4 cell count (evidence rating A Ia).
- Initiation of ART is recommended as soon as possible in the setting of acute HIV infection *(evidence rating B III).*
- Planned discontinuation of early ART after a specific duration of treatment is not recommended outside a research setting *(evidence rating A Ia).*[b]
- Initiation of ART is recommended for individuals who have persistent *undetectable viral load without ART but have declining CD4 cell counts (evidence rating B III).*

[a] See text for essential details and cautions.

[b] The recommendation or the evidence rating has not changed substantially since the 2014 report.

Recommendations for Initial ART Regimens[a]

- Recommended initial regimens (listed in alphabetic order by InSTI component):
  - Dolutegravir/abacavir/lamivudine (evidence rating AIa)
  - Dolutegravir plus TAF/emtricitabine (evidence rating AIa)[b]
  - Elvitegravir/cobicistat/TAF/emtricitabine (evidence rating AIa)[b]
  - Raltegravir plus TAF/emtricitabine (evidence rating AIII)
- HLA-B*5701 testing should be performed prior to abacavir use (evidence rating AIa); those who test positive should not be given abacavir (evidence rating AIa).
- Tenofovir disoproxil fumarate is not recommended for individuals with or at risk of kidney or bone disease (osteopenia or osteoporosis) (evidence rating BIII).
- Recommended initial regimens for individuals in whom an InSTI is not an option (listed in alphabetic order by non-InSTI component):
  - Darunavir (boosted) plus TAF (or TDF)/emtricitabine or abacavir/lamivudine (evidence rating AIa)[b]
  - Efavirenz/TDF/emtricitabine (evidence rating AIa)
  - Rilpivirine/TAF (or TDF)/emtricitabine (evidence rating AIa)[b]
- Initial 2-drug regimens are recommended only in rare situations in which a patient cannot take abacavir, TAF, or TDF (evidence rating BIa).
- HIV-infected pregnant women should initiate ART for their own health and to reduce the likelihood of HIV transmission to their infant (evidence rating AIa).[c]
- For HIV-infected patients with hepatitis B virus coinfection should initiate ART that contains TDF or TAF (evidence rating AIa), lamivudine or emtricitabine, and a third component (evidence rating AIa).
- Entecavir may be used to treat hepatitis B virus infection (evidence rating AIII). If HIV RNA is not suppressed, entecavir should be avoided because it can select for drug-resistant HIV (evidence rating AIII).
- HIV-infected patients with hepatitis C virus coinfection should start an ART regimen with drugs that do not have significant drug interactions with hepatitis C virus therapies (evidence rating AIIa).
- Tenofovir disoproxil fumarate is not recommended for patients with osteopenia or osteoporosis (evidence rating BIII).
- Monitoring for development of kidney disease with estimated glomerular filtration rate, urinalysis, and testing for glycosuria and albuminuria or proteinuria is recommended when ART is initiated or changed and every 6 months (along with HIV RNA) once HIV RNA is stable (evidence rating BIII).
- Tenofovir disoproxil fumarate should be avoided or dose adjusted in patients with a creatinine clearance rate below 60 mL/min (evidence rating AIa).
- Tenofovir alafenamide is not recommended in patients with a creatinine clearance rate below 30 mL/min (evidence rating AIa).
- Tenofovir disoproxil fumarate or TAF should be discontinued if a patient's renal function worsens, particularly if there is evidence of proximal tubular dysfunction (evidence rating AIIa).
- HIV-infected patients with end-stage renal disease should be evaluated for kidney transplantation with expectation of high rates of patient and graft survival (evidence rating AIIa).

Abbreviations: ART, antiretroviral therapy; InSTI, integrase strand transfer; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a] See text for essential details and cautions. Components separated with a slash (/) indicate that they are available as coformulations.

[b] TDF may be substituted for TAF if TAF is not available for the patient.

[c] The recommendation or the evidence rating has not changed substantially since the 2014 report.

Ergänzende Dokumente

Deutsche AIDS-Gesellschaft (DAIG), Pädiatrische Arbeitsgemeinschaft AIDS (PAAD), 2013 [5] *(Hinweis: neuer Stand: 17.03.2013, gültig bis 16.03.2018 aber keine inhaltlichen Änderungen)*

Leitlinien zur antiretroviralen Therapie bei Kindern und Jugendlichen

Leitlinie der Deutschen AIDS Gesellschaft (DAIG) und der Pädiatrischen Arbeitsgemeinschaft AIDS (PAAD)

Anmerkung:

- Leitlinie entspricht nicht einer S3-Leitlinie, wurde jedoch aufgrund der limitierten Evidenz in der Patientenpopulation unter 18 Jahre als deutsche Leitlinie ergänzend dargestellt;
  im AWMF-Leitlinienregister als S1-Leitlinie klassifiziert; Recherche und Auswahl der Literatur unklar, Methodik der Konsensfindung nicht beschrieben
- Zielpopulation hinsichtlich Altersobergrenze nicht klar definiert (Kinder [im Alter von 0-14 Jahren?] oder auch Jugendliche [bis 18J.?]; Diskrepanz zwischen Leitlinientitel und formulierter Fragestellung)

Fragestellung: Einsatz antiretroviraler Therapie im Kindesalter

Methodik:

Empfehlungen basieren auf folgenden Grundlagen:
1) Diskussionen in der PAAD
2) Literaturrecherche in Medline nach RCTs bei Kindern im März 2011
3) Empfehlungen der US-amerikanischen Gesellschaft für kinderärzte vom August 2010, die akutellen europäschen Therapieempfehlungen der PENTA 2009
4) Studienergebnisse zur ART bei Erwachsen

Graduierung der Evidenz und Empfehlungen:

Tab. 1 Graduierung der Evidenz.

Graduierung	Evidenz
I	≥1 randomisierte kontrollierte Studie
II	≥1 kontrollierte, aber nicht-randomisierte Studie Kohorten- oder Fallkontrollstudien bevorzugt von mehr als einer Forschungsgruppe oder von mehr als einem Zentrum Beobachtung von sehr deutlichen Effekten innerhalb unkontrollierter Studien
III	Expertenmeinung, klinische Erfahrung oder deskriptive Studien

Tab. 2 Graduierung der Empfehlungen.

Grad	Empfehlung
A	gute Evidenz *für* die Durchführung der Maßnahme/Therapie
B	mäßige Evidenz *für* die Durchführung der Maßnahme/Therapie
C	wenig Evidenz *für* die Durchführung der Maßnahme/Therapie
D	mäßige Evidenz *gegen* die Durchführung der Maßnahme/Therapie
E	gute Evidenz *gegen* die Durchführung der Maßnahme/Therapie

Empfehlungen

Tabelle 4: Empfehlungen zur Initialtherapie

Empfehlungen zu Arzneimittelkombinationen in der Initialtherapie
Kombinationstherapie
1 PI/r + 2 NRTI
1 NNRTI + 2 NRTI

Tabelle 5: Therapieempfehlungen in Abhängigkeit vom Alter

Empfehlungen zur Medikamentenkombination in der Initialtherapie in Abhängigkeit vom Alter		
	Kombinationstherapie	Bemerkung
2 NRTI + 1 PI/r		
<6 Jahren	LPV/r + 2NRTI	Zulassung erst ab 2 Jahren, Dosisangaben nach FDA, TDM, nicht bei Frühgeborenen
	NFV + 2 NRTI	Mögliche Alternative, Zulassung erst ab 3 Jahren, TDM, geschmacklich besser
>6 Jahren	LPV/r + 2 NRTI	
	ATV/r + 2 NRTI	
	FPV/r + 2 NRTI	
2 NRTI + 1 NNRTI		
<3 Jahre	NVP + 2 NRTI	nicht bei NVP exponierten Kindern
>3 Jahre	NVP + 2 NRTI	nicht bei NVP exponierten Kindern, bei Jugendlichen CD4-Grenzen beachten [49, 50]
	EFV + 2 NRTI	Zulassung ab 3 Jahren
3 NRTI + 1 NNRTI		
<1 Jahr	NVP + AZT + 3TC + ABC	in Ausnahmefällen möglich [53]

Abkürzung: ABC –Abacavir, ATV – Atazanavir; FPV – Fosamprenavir, LPV/r - Lopinavir/Ritonavir,NFV – Nelfinavir, EFV- Efavirenz

Hintergrund: Vergleich NNRTI vs PI

<u>Vergleichsstudie im Kindesalter „PENPACT1“:</u>

- therapienaive Kinder und Jugendliche zu 1 NNRTI oder 1 PI + jeweils 2 NRTI randomisiert – und bei Therapieversagen mit dem jeweils anderen Regime behandelt
- kein Unterschied zwischen den Studienarmen hinsichtlich Therapieerfolg.
- Unter den Therapieversagern einer Therapie mit NNRTI + 2 NRTI traten jedoch mehr NRTI-Mutationen auf als bei den Therapieversagern mit PI + 2 NRTI.

Babiker et al. First-line anti- retroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial . Lancet Infect Dis 2011 ; 11 : 273 – 283

Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, (PAGAA), 2016 [40]

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Fragestellung/Zielsetzung: Provide guidance to HIV care practitioners on the optimal use of ARV agents in HIV-infected infants, children, and adolescents (through puberty) in the United States.

These updated Guidelines for the Use of Antiretroviral Agents Pediatric HIV Infection address the use of antiretroviral therapy (ART) for HIV-infected infants, children, and adolescents. In general, these guidelines are appropriate for the care and management of youth with sexual maturity rating (SMR, formerly Tanner staging) I-III, whereas the guidelines developed by the Panel on Antiretroviral Guidelines for Adults and Adolescents are suitable for the care and management of adolescents in late puberty (SMR IV-V).

Methodik

Grundlage der Leitlinie

The Panel is composed of approximately 32 voting members who have expertise in management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, ex officio member of the Panel. The US government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment.

A standardized review of recent relevant literature related to each section of the guidelines is performed by a representative of the François-Xavier Bagnoud Center and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.

Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed with ballots to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (by email or teleconference) for additional review, discussion, and further modification to reach a final version acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.

LoE / GoR

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials in children[a] with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints plus accompanying data in children[a] from one or more well-designed, non randomized trials or observational cohort studies with long-term clinical outcomes **II:** One or more well-designed, non-randomized trials or observational cohort studies in children[a] with long-term clinical outcomes **II*:** One or more well-designed, non-randomized trials or observational cohort studies in adults with long-term clinical outcomes plus accompanying data in children[a] from one or more smaller non-randomized trials or cohort studies with clinical outcome data **III:** Expert opinion

[a] Studies that include children or children and adolescents, but not studies limited to postpubertal adolescents

Developer: Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children—a working group of OARAC

Funding Source: Office of AIDS Research, NIH and HRSA Financial Disclosure: All

	members of the Panel submit a financial disclosure statement in writing annually, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. *Sonstige methodische Hinweise* […] Because licensure of drugs in children often is based on extrapolation of efficacy data from adult trials in addition to safety and PK data from studies in children, recommendations for ARV drugs often rely, in part, on data from clinical trials or studies in adults. Pediatric drug approval may be based on evidence from adequate and well-controlled investigations in adults if: 1. The course of the disease and the effects of the drug in the pediatric and adult populations are expected to be similar enough to permit extrapolation of adult efficacy data to pediatric patients; 2. Supplemental data exist on PKs of the drug in children indicating that systemic exposure in adults and children are similar; and 3. Studies are provided that support the safety of the drug in pediatric patients. […] <u>Anmerkung FBMed</u>: Die LL weist methodische Mängel insbesondere der Beschreibung/Darstellung zur Literaturrecherche auf. Es finden sich keine Informationen zu relevanten Angaben wie z.B. den genutzten/durchsuchten Datenbanken oder den Suchzeiträumen. Daher kann nicht abschließend beurteilt werden, ob dieser LL eine systematische Recherche zugrunde liegt. Aufgrund der insgesamt geringen Evidenzlage zur relevanten Population, wurde die LL jedoch als ergänzende Quelle aufgenommen.
	Empfehlungen **What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children** • Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**. • For treatment-naive children, the Panel recommends initiating antiretroviral therapy with three drugs, including either a boosted protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor plus a dual nucleoside/nucleotide reverse transcriptase inhibitor backbone. **(kein LoE/GoE angegeben)** *<u>Evidenzgrundlage für die Wahl zwischen INSTI, NNRTI oder PI/r (‘Choosing Among an Integrase Strand Transfer Inhibitor-Based, a Non-Nucleoside Reverse Transcriptase Inhibitor-Based, or a Boosted Protease Inhibitor-Based Initial Regimen’):</u>* Preferred regimens for initial therapy include INSTI-, NNRTI-, or boosted PI-based regimens. The choice of regimen should be based on patient characteristics, especially age, results of viral drug resistance testing, drug efficacy and adverse events (AEs), patient and family preference, pill size, and dosing frequency. Clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a PI-based regimen for initial therapy. Three pediatric studies have

compared an NNRTI-based regimen to a PI-based regimen and results varied based on age of the population studied and specific drug within the class.

- The **P1060 study** demonstrated superiority of a lopinavir/ritonavir (LPV/r)-based regimen compared to a nevirapine-based regimen in HIV-infected infants and children aged 2 months to 35 months, regardless of prior maternal or infant exposure to peripartum single-dose nevirapine prophylaxis (21.7% vs. 39.6% death, virologic failure, or toxicity by Week 24 with prior nevirapine exposure and 18.4% vs. 40.1% with no prior exposure).
  Anmerkung FBMed: Kinder zwischen 2 bis 35 Monaten!

- Those in the nevirapine group demonstrated greater, but not statistically significant, improvements in immunologic status and growth. Similar improved immune and growth parameters were also demonstrated in the **NEVEREST study** where children switched to a nevirapine regimen versus those who continued on a rito LPV/r regimen after achieving virologic control.
  Anmerkung FBMed: Kinder zwischen 6 Wochen und 2 Jahren!

- **PENPACT-1 (PENTA 9/PACTG 390)** compared a PI-based regimen and a NNRTI-based regimen in HIV-infected treatment-naive children aged 30 days to <18 years (the study did not dictate the specific NNRTI or PI initiated). In the PI-based group, 49% of children received LPV/r and 48% received nelfinavir; in the NNRTI-based group, 61% of children received efavirenz and 38% received nevirapine. After 4 years of follow-up, 73% of children randomized to PI-based therapy and 70% randomized to NNRTI-based therapy remained on their initial ART regimen. In both groups, 82% of children had viral loads <400 copies/mL.3
  Anmerkung FBMed: Population zwischen 30 Tagen und <18 Jahren!

- The **PROMOTE-pediatrics trial** demonstrated comparable virologic efficacy among children randomized to receive either an NNRTI or LPV/r-based ART.4 Children were aged 2 months to <6 years and had no perinatal exposure to nevirapine. Selection of NNRTI was based on age (children aged <3 years received nevirapine and those aged >3 years primarily received efavirenz). At 48 weeks, the proportion with HIV RNA level <400 copies/mL at 48 weeks was 80% in the ritona LPV/r arm versus 76% in the NNRTI arm, a difference of 4% and not statistically significant (95% CI: -9% to +17%).
  Anmerkung FBMed: Kinder zwischen 2 Monaten bis <6 Jahren!
- Clinical investigation of INSTI-based regimens in children has been limited to non-comparative studies demonstrating safety, tolerability, and PKs. The recommendation for an INSTI as part of an initial regimen is based largely on efficacy, tolerability and fewer drug-drug interactions in adult comparative trials showing superiority of INSTI-containing compared to PI-containing and NNRTI-containing regimens and small studies in ART-naive adolescents. […]

Integrase Strand Transfer Inhibitor-Based Regimens (Integrase Strand Transfer Inhibitor plus Two-Nucleoside Reverse Transcriptase Inhibitor Backbone): Three INSTIs—dolutegravir, elvitegravir and raltegravir—are licensed for the treatment of ARV-naive HIV infected adults. These agents have quickly become the preferred regimen in adults because of their virologic efficacy, lack of drug-drug interactions and favorable toxicity profile. Raltegravir is licensed for treatment of HIV-infected children as young as age 4 weeks.

Dolutegravir is approved for use in adolescents aged ≥12 years and studies in younger children are under way. Elvitegravir has been studied in adolescents in two, fixed-dose combination regimens and in combination with two NRTIs and ritonavir boosting. At this time, only one fixed-dose combination has sufficient experience in adolescents to recommend

Raltegravir

Raltegravir is FDA-approved for treatment of HIV-infected children aged ≥4 weeks and weighing ≥3 kg. It is available in film-coated tablets, chewable tablets, and single packets of granules for oral suspension.

Efficacy in Clinical Trials:

- Raltegravir has been evaluated in three large randomized clinical trials (RCTs) in adults, STARTMRK, SPRING-2, and ACTG A5257. In STARTMRK, a raltegravir-containing regimen was compared to an efavirenz-containing regimen. At 48 weeks, raltegravir was non-inferior. However, with longer follow up of 4 and 5 years, more patients discontinued efavirenz and raltegravir was found to be superior.[16-18] SPRING-2 compared raltegravir to dolutegravir and demonstrated non-inferiority of dolutegravir.[5] ACTG A5257 compared raltegravir to ATV/r and DRV/r; all regimens had equivalent virologic efficacy but raltegravir had better tolerability.[19]
- Raltegravir has been studied in infants, children and adolescents in an open-label trial, IMPAACT P1066, to evaluate PK, safety, tolerability, and efficacy. In children and adolescents (96 treated at final dose of raltegravir), aged 2 through 18 years, who were mostly drug-experienced, 79.1% of the patients achieved a favorable viral load (HIV viral load <400 copies/mL or ≥1 $\log_{10}$ decline in viral load). Infants and toddlers aged ≥4 weeks to <2 years were also enrolled in P1066 and received treatment with raltegravir oral suspension. At weeks 24 and 48, 61% of the infants (14 of 23 infants) had an HIV viral load <400 copies/mL.[20-22]

Adverse Events:

- Raltegravir has a favorable safety profile.
- In P1066, drug-related adverse AEs included one child each with psychomotor hyperactivity and insomnia, rash, and elevated transaminases.

Table 7 *(siehe unten)* provides a list of Panel-recommended regimens that are "Preferred," "Alternative" or for "Use in Special Circumstances;" recommendations vary by age, weight, and sexual maturity rating.

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children

[…]

Preferred Regimens, continued	
Children Aged ≥3 Years to <12 Years	Two NRTIs **plus** ATV/r
	Two NRTIs **plus** twice daily DRV/r
	Two NRTIs **plus** EFV[c]
	Two NRTIs **plus** LPV/r
	Two NRTIs **plus** RAL[b]

Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs

Children Aged ≥3 Months and <12 Years	ABC **plus** (3TC **or** FTC)
	ZDV **plus** (3TC **or** FTC)

Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs

Children Aged ≥2 Weeks	ddI **plus** (3TC **or** FTC)
	ZDV **plus** ddI
Children Aged ≥3 Months	ZDV **plus** ABC
Adolescents at SMR III	TDF **plus** (3TC **or** FTC)

Detaillierte Darstellung der Recherchestrategie

Erstrecherche:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 25.04.2016

#	Suchfrage
#1	MeSH descriptor: [HIV-1] explode all trees
#2	MeSH descriptor: [Drug Therapy] explode all trees
#3	#1 and #2
#4	MeSH descriptor: [HIV Infections] explode all trees
#5	MeSH descriptor: [HIV Infections] explode all trees and with qualifier(s): [Drug therapy - DT, Therapy - TH]
#6	("HIV 1" or "hiv i" or "hiv1" or "hivi" or "human immunodeficiency virus 1" or "human immunodeficiency virus i" or "human immunodeficiency virus type 1" or "human immunodeficiency virus type i"):ti,ab,kw
#7	(treat* or therap* or monotherap* or polytherap* or pharmacotherap* or effect* or efficacy or management or drug*):ti,ab,kw
#8	#1 or #6
#9	#8 and #7
#10	#3 or #5 or #9 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only) and Other Reviews
#11	#1 or #4 or #6 Publication Year from 2011 to 2016, in Technology Assessments

SR, Meta-Analysen, HTAs in Medline (PubMed) am 25.04.2016

#	Suchfrage
#1	Search ("hiv 1"[MeSH Major Topic]) AND "drug therapy"[MeSH Terms]
#2	Search "hiv infections/drug therapy"[MeSH Major Topic]
#3	Search (((((("hiv 1"[Title/Abstract]) OR "hiv i"[Title/Abstract]) OR "hiv1"[Title/Abstract] OR "hivi"[Title/Abstract] OR "human immunodeficiency virus 1"[Title/Abstract]) OR "human immunodeficiency virus i"[Title/Abstract]) OR "human immunodeficiency virus type 1"[Title/Abstract]) OR "human immunodeficiency virus type i"[Title/Abstract]
#4	Search "hiv 1"[MeSH Major Topic]
#5	Search #3 OR #4
#6	Search ((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
#7	Search #5 AND #6
#8	Search #1 OR #2 OR #7
#9	Search (#8) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#10	Search (#8) 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

#	Suchfrage
	(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]))))
#11	Search #9 OR #10
#12	Search #9 OR #10 Filters: Publication date from 2011/04/01 to 2016/04/25

Leitlinien in Medline (PubMed) am 25.04.2016

#	Suchfrage
#1	Search ("hiv 1"[MeSH Major Topic]) OR "hiv infections"[MeSH Major Topic]
#2	Search (Human immunodeficiency virus[Title]) OR HIV[Title] OR HIV1[Title] OR HIVI[Title]
#3	Search #1 OR #2
#4	Search ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR ((guideline*[Title] OR recommendation*[Title]) NOT medline[sb])
#5	Search #3 AND #4
#6	Search #3 AND #4 Filters: Publication date from 2011/04/01 to 2016/04/25

Folgerecherche:

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 01.02.2017

#	Suchfrage
#1	**MeSH descriptor: [HIV-1] explode all trees**
#2	**MeSH descriptor: [Drug Therapy] explode all trees**
#3	**#1 and #2**
#4	**MeSH descriptor: [HIV Infections] explode all trees**
#5	**MeSH descriptor: [HIV Infections] explode all trees and with qualifier(s): [Drug therapy - DT, Therapy - TH]**
#6	**("HIV 1" or "hiv i" or "hiv1" or "hivi" or "human immunodeficiency virus 1" or "human immunodeficiency virus i" or "human immunodeficiency virus type 1" or "human immunodeficiency virus type i"):ti,ab,kw**
#7	**(treat* or therap* or monotherap* or polytherap* or pharmacotherap* or effect* or efficacy or management or drug*):ti,ab,kw**
#8	**#1 or #6**
#9	**#8 and #7**
#10	**#3 or #5 or #9 Publication Year from 2016 to 2017, in Cochrane Reviews (Reviews only)**
#11	**#1 or #4 or #6 Publication Year from 2016 to 2017, in Technology Assessments**

SR, Meta-Analysen, HTAs in Medline (PubMed) am 06.02.2017

#	Suchfrage
#1	Search ("hiv 1"[MeSH Major Topic]) AND "drug therapy"[MeSH Terms]
#2	Search "hiv infections/drug therapy"[MeSH Major Topic]
#3	Search (((((("hiv 1"[Title/Abstract]) OR "hiv i"[Title/Abstract]) OR "hiv1"[Title/Abstract] OR "hivi"[Title/Abstract] OR "human immunodeficiency virus 1"[Title/Abstract]) OR "human immunodeficiency virus i"[Title/Abstract]) OR "human immunodeficiency virus type 1"[Title/Abstract]) OR "human immunodeficiency virus type i"[Title/Abstract]

#	Suchfrage
#4	Search "hiv 1"[MeSH Major Topic]
#5	Search #3 OR #4
#6	Search ((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]
#7	Search #5 AND #6
#8	Search #1 OR #2 OR #7
#9	Search (#8) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#10	Search (#8) 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]))))
#11	Search #9 OR #10
#12	Search #9 OR #10 Filters: Publication date from 2016/04/25 to 2017/02/06

Leitlinien in Medline (PubMed)/ am 06.02.2017

#	Suchfrage
#1	Search ("hiv 1"[MeSH Major Topic]) OR "hiv infections"[MeSH Major Topic]
#2	Search (Human immunodeficiency virus[Title]) OR HIV[Title] OR HIV1[Title] OR HIVI[Title]
#3	Search #1 OR #2
#4	Search ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR ((guideline*[Title] OR recommendation*[Title]) NOT medline[sb])
#5	Search #3 AND #4
#6	Search #3 AND #4 Filters: Publication date from 2016/04/25 to 2017/02/06

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Anhang

Tabelle 1 (Study characteristics of Ford et al., 2013)

Study	Setting	Sample size (as randomized)	Age	% female	Baseline viral load	Baseline CD4	Treatment history	3TC regimen	FTC regimen	Duration of follow up	Enrollment criteria
Sanne et al, 2002	South Africa	468 patients	33	59%	85% <100,000 copies/ml	386 cells/mm^3 (3TC); 392 cells/mm^3 (FTC)	None	d4T+NVP/EFV	d4T+NVP/EFV	48 weeks	Antiretroviral naïve
Benson et al, 2004	43 sites in the USA	440 patients	42 years	14%	<50 copies/ml	527 cells/mm^3	Patients virologically suppressed on 3TC first line	d4T or AZT + PI or NNRTI	d4T or AZT + PI or NNRTI	48 weeks	Virologically suppressed for >12 weeks
Martin et al, 2009	Australia	360 patients	45 years	<3%	<50 copies/ml	627 cells/mm^3 (3TC); 599 cells/mm^3 (FTC)	2 NRTI + PI/r or NNRTI	ABC+PI/r or NNRTI	TDF+PI/r or NNRTI	96 weeks	Virologically suppressed for >12 weeks
Martinez et al, 2009	18 sites in Spain	335 patients	43 years	22%	<200 copies/ml	520 cells/mm^3 (3TC); 508 cells/mm^3 (FTC)	2 NRTI (inc 3TC) plus PI/r or NNRTI	ABC+PI/r or NNRTI	TDF+PI/r or NNRTI	48 weeks	Virologically suppressed for >24 weeks
Smith et al, 2009	USA and Puerto Rico	694 patients	38 years	16% (3TC)	70,795 copies/ml (43% ≥100,000)	214 cells/mm^3 (3TC); 193 cells/mm^3 (FTC)	None	ABC+LPV/r	TDF+LPV/r	96 weeks	Antiretroviral naïve
				20% (FTC)							
Calza et al, 2009	Italy	89 patients	36 years (3TC)	29% (3TC)	<50 copies/ml	658 cells/mm^3 (3TC); 611 cells/mm^3 (FTC);	PI-based antiretroviral regimen including one thymidine analogue	ATV/r+ABC	ATV/r+TDF	48 weeks	Virologically suppressed with hyperlipidemia for > 24 weeks
			37 years (FTC)	32% (FTC)							
Sax et al, 2011	59 sites in USA and Puerto Rico	1060 patients (low viral load group)	37 years	19%	25,000 copies/ml	266 cells/mm^3	None	ABC+ATV/r or EFV	TDF+ATV/r or EFV	96 weeks	Antiretroviral naïve and VL<100,000 copies/ml
Raffi et al, 2013	100 sites in the USA, Canada, Europe, and Australia.	827 patients	36 years	15%	33,000 copies/ml	359–362 cells/mm^3	None	ABC+DTG or RAL	TDF+DTG or RAL	96 weeks	Antiretroviral naïve with VL>1000 copies/ml
Martinez et al, 2013	Spain	273 patients	47 years (3TC)	10% (3TC)	<50 copies/ml	515 cells/mm^3 (3TC); 487 cells/mm^3 (FTC)	2 NRTI + PI/r	ABC+PI/r or RAL	TDF+PI/r or RAL	48 weeks	Virologically suppressed for >24 weeks
			44 years (FTC)	27% (FTC)							
Campo et al, 2013	76 sites in the USA	312 patients	46 years	15%	91% <50 copies/ml	532 cells/mm^3	3TC/ABC + PI/r	ABC+PI/r	TDF+PI/r	48 weeks	Virologically suppressed for >12 weeks
Nishijima et al, 2013	Japan	109 patients	36 years	2%	19,055 copies/ml	257 cells/mm^3	None	ABC+ATV/r	TDF+ATV/r	96 weeks	Antiretroviral naïve
Mulenga	Zambia	332 patients	34 years	58%	110,000–130,000 copies/ml	143–169 cells/mm^3	None	TDF+EFV	TDF+EFV	48 weeks	Antiretroviral naïve

3TC, lamivudine; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; ABC, abacavir; d4T, stavudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

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