Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

sowie

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

Vorgang: 2016-05-15-D-228 Emtricitabin /Tenofoviralafenamid

Datum: Mai 2016

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

Emtricitabin/Tenofoviralafenamid
zur Behandlung von Infektionen mit dem Humanen Immundefizienz-Virus Typ 1 (HIV-1) bei Erwachsenen und Jugendlichen > 12 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/nicht-medikamentösen Behandlungen	Beschlüsse gemäß § 35a SGBV zu: Dolutegravir/Abacavir/Lamivudin (vom 19.03.2015) Cobicistat (vom 18.09.2014) Dolutegravir (vom 07.08.2014) Rilpivirin/Emtricitabin/Tenofovirdisoproxil (neues Anwendungsgebiet) (vom 19.06.2014) Elvitegravir/Cobicistat/Emtricitabin/Tenofovirdisoproxil (vom 05.12.2013) Rilpivirin (vom 05.07.2012) Rilpivirin/Emtricitabin/Tenofovirdisoproxil (vom 05.07.2012)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*
[…] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	Nicht angezeigt

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Emtricitabin/ Tenovovir-alafenaamid Descovy®	„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“.
Proteasehemmer (PI)	
Saquinavir **(SQV)** J05AE01 Invirase®	Invirase ist zur Behandlung HIV-1-infizierter erwachsener Patienten angezeigt. Invirase ist nur in Kombination mit Ritonavir und anderen antiretroviralen Arzneimitteln anzuwenden.
Indinavir **(IDV)** J05AE02 Crixivan®	Crixivan ist in Kombination mit antiretroviralen Nukleosidanaloga für die Behandlung HIV-1-infizierter Erwachsene angezeigt.
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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.
Tipranavir **(TPV)** J05AE09 Aptivus®	APTIVUS in Kombination mit niedrig dosiertem Ritonavir ist angezeigt zur antiretroviralen Kombinationsbehandlung der HIV-1-Infektion bei mehrfach vorbehandelten Erwachsenen und Jugendlichen ab 12 Jahren mit Viren, die gegen mehrere Protease-Hemmer resistent sind. APTIVUS sollte nur als Teil einer antiretroviralen Kombinationsbehandlung bei Patienten angewendet werden, für die es keine anderen therapeutischen Optionen gibt. Diese Indikation basiert auf den Ergebnissen zweier Phase-III-Studien bei mehrfach vorbehandelten erwachsenen Patienten (im Mittel mit 12 vorausgegangenen antiretroviralen Wirkstoffen) mit einer Virusresistenz gegen Protease-Hemmer, sowie auf einer Phase-II-Studie zur Pharmakokinetik, Sicherheit und Wirksamkeit von APTIVUS bei überwiegend vorbehandelten jugendlichen Patienten im Alter von 12 bis 18 Jahren. Bei der Entscheidung über einen Behandlungsbeginn mit APTIVUS in Kombination mit niedrig dosiertem Ritonavir sollten sowohl die Vorbehandlung des jeweiligen Patienten als auch die mit den verschiedenen Wirkstoffen assoziierten Mutationsmuster sorgfältig abgewogen werden. Genotypische oder phänotypische Tests (soweit verfügbar) und die Vorbehandlung sollten die Entscheidung für eine Anwendung von APTIVUS leiten. Bei der Entscheidung sollten auch Mutationsmuster berücksichtigt werden, die das virologische Ansprechen auf APTIVUS in Kombination mit niedrig dosiertem Ritonavir ungünstig beeinflussen könnten.
Darunavir **(DRV)** J05AE10 Prezista®	PEZISTA 400 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 zusammen mit Cobicistat eingenommen ist indiziert in Kombination mit anderen antiretroviralen Arzneimitteln zur Therapie von Infektionen mit dem humanen Immundefizienzvirus (HIV-1) bei erwachsenen Patienten. PREZISTA 400 mg Tabletten können zur Erreichung der geeigneten Dosis zur Therapie der HIV-1-Infektion bei Erwachsenen und bei pädiatrischen Patienten ab 12 Jahre und mindestens 40 kg Körpergewicht angewendet werden, die: • antiretroviral nicht vorbehandelt (ART-naïv) sind.

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	• ART-vorbehandelt sind und keine Darunavir-Resistenz-assoziierte Mutationen (DRV-RAMs) und < 100.000 HIV-1-RNA-Kopien/ml im Plasma und eine CD4+-Zellzahl von ≥ 100 × 106 Zellen/l besitzen. 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. PREZISTA 150 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 **(ZDV/AZT)** J05AF01 Retrovir®	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 (ddl) **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	Lamivudin ist als Teil einer antiretroviralen Kombinationstherapie zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV) bei Erwachsenen und Kindern angezeigt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	
Abacavir (**ABC)** J05AF06 Ziagen®	Ziagen ist angezeigt in der antiretroviralen Kombinationstherapie zur Behandlung von Infektionen mit dem humanen Immundefizienz-Virus (HIV) bei Erwachsenen, Jugendlichen und Kindern. Der Wirksamkeitsnachweis von Ziagen 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. Ebenso wird vor Wiederaufnahme der Behandlung mit Abacavir eine Untersuchung für Patienten mit unbekanntem HLA-B*5701-Status empfohlen, die vorher Abacavir vertragen hatten. 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.
Tenofovir disoproxil **(TDF)** J05AF07 Viread®	Viread 245 mg Filmtabletten werden in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung HIV-1-infizierter Erwachsener angewendet. Bei Erwachsenen basiert der Beleg des klinischen Nutzens von Viread zur Behandlung einer HIV-1-Infektion auf Ergebnissen einer Studie bei nicht vorbehandelten Patienten, einschließlich Patienten mit einer hohen Viruslast (>100.000 Kopien/ml), und Studien bei antiretroviral vorbehandelten Patienten mit frühem virologischem Versagen (<10.000 Kopien/ml, bei den meisten Patienten <5.000 Kopien/ml). Viread wurde von den vorbehandelten Patienten dabei zusätzlich zu einer stabilen antiretroviralen Kombinationstherapie (hauptsächlich Dreifach-Kombination) eingenommen. Viread 245 mg Filmtabletten werden auch zur Behandlung HIV-1-infizierter Jugendlicher im Alter von 12 bis <18 Jahren 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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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).
Rilpivirin **(RPV)** J05AG05 Edurant®	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. Wie auch bei anderen antiretroviralen Arzneimitteln, soll die Anwendung von EDURANT anhand der Ergebnisse des genotypischen Resistenztests ausgerichtet werden. (siehe Abschnitte 4.4 und 5.1).
Antivirale Mittel zur Behandlung von HIV Infektionen, Kombinationen	
Elvitegravir/Cobicistat/Emtricitabin/Tenofoviral-afenamid	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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
(EVG/COBI/FTC/ TAF) J05AR18 Genvoya®	Mutationen aufweisen (siehe Abschnitte 4.2 und 5.1).
Lamivudin und Zidovudin **(3TC/AZT)** 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 **(ABC/3TC**) J05AR02 Kivexa®	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 .
Emtricitabin und Tenofovirdisoproxil (**FTC/TDF)** J05AR03 Truvada®	Truvada ist eine Fixkombination aus Emtricitabin und Tenofovirdisoproxilfumarat. Es wird in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung HIV-1-infizierter Erwachsener im Alter von 18 Jahren und darüber angewendet. Der Beleg des Nutzens der antiretroviralen Kombinationstherapie von Emtricitabin und Tenofovirdisoproxilfumarat basiert ausschließlich auf Studien mit nicht vorbehandelten Patienten.
Abacavir und Lamivudin und Zidovudin **(ABC/3CT/AZT)** J05AR04 Trizivir®	Trizivir ist angezeigt zur Behandlung von Infektionen mit dem humanen Immundefizienz- Virus (HIV) bei Erwachsenen. Diese fixe Kombination ersetzt die drei Arzneistoffe Abacavir, Lamivudin und Zidovudin, die in gleicher Dosis einzeln angewendet werden. Es wird empfohlen, während der ersten 6 bis 8 Wochen der Behandlung Abacavir, Lamivudin und Zidovudin einzeln anzuwenden. Die Wahl dieser fixen Kombination sollte primär nicht nur auf Überlegungen zur möglichen Adhärenz, sondern hauptsächlich auf Überlegungen zur Wirksamkeit und zum Risiko dieser drei Nukleosidanaloga beruhen. Der Nachweis des Nutzens von Trizivir basiert vor allem auf den Ergebnissen von Studien, die bei antiretroviral nicht vorbehandelten oder mäßig vorbehandelten Patienten durchgeführt wurden, bei denen die Krankheit noch nicht weit fortgeschritten war. Bei Patienten mit einer hohen Viruslast (>100.000 Kopien/ml) ist die Wahl der Behandlung besonders sorgfältig abzuwägen. Insgesamt könnte die virologische Suppression mit diesem Dreifach-Nukleosid-Regime derjenigen unterlegen sein, die mit anderen Kombinationstherapien erreicht wird. Hier sind insbesondere solche Therapien gemeint, die geboosterte Protease-Inhibitoren oder nicht-nukleosidische Reverse-Transkriptase-Inhibitoren enthalten. Daher sollte die Anwendung von Trizivir nur in

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	besonderen Fällen in Erwägung gezogen werden (z. B. bei Tuberkulose-Koinfektion). 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. Ebenso wird vor Wiederaufnahme der Behandlung mit Abacavir eine Untersuchung für Patienten mit unbekanntem HLA-B*5701-Status empfohlen, die vorher Abacavir vertragen hatten (siehe Abschnitt „Vorgehen bei erneuter Einnahme von Trizivir nach vorherigem Abbruch der Behandlung“). 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.
Efavirenz und Emtricitabin und Tenofovir disoproxil **(EFV/FTC/TDF)** J05AR06 Atripla®	Atripla ist eine fixe Dosiskombination aus Efavirenz, Emtricitabin und Tenofovirdisoproxilfumarat. Atripla wird zur Behandlung von Erwachsenen im Alter von 18 Jahren und darüber mit HIV-1-Infektion (Infektion mit dem Humanen Immundefizienzvirus 1) angewendet, die unter ihrer derzeitigen antiretroviralen Kombinationstherapie seit mehr als drei Monaten virussupprimiert sind mit Plasmakonzentrationen der HIV-1-RNA < 50 Kopien/ml. Bei den Patienten darf es unter einer früheren antiretroviralen Therapie nicht zu einem virologischen Versagen gekommen sein. Es muss bekannt sein, dass vor Beginn der initialen antiretroviralen Therapie keine Virusstämme mit Mutationen vorhanden waren, die zu signifikanten Resistenzen gegen einen der drei Wirkstoffe von Atripla führen. Der Beleg des Nutzens von Atripla ist in erster Linie durch 48-Wochen-Daten aus einer klinischen Studie belegt, in der Patienten mit stabiler Virussuppression unter einer antiretroviralen Kombinationstherapie auf Atripla umgestellt wurden. Zur Anwendung von Atripla bei nicht vorbehandelten und bei intensiv vorbehandelten Patienten liegen derzeit keine Daten aus klinischen Studien vor. Es liegen keine Daten zur Kombination von Atripla und anderen antiretroviralen Wirkstoffen vor.
Emtricitabin und Rilpivirin und Tenofovir disoproxil **(FTC/RPV/TDF)** J05AR08 Eviplera®	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. Die Anwendung von Eviplera sollte wie bei anderen antiretroviralen Arzneimitteln von einem genotypischen Resistenztest begleitet werden und/oder historische Resistenzdaten sollten berücksichtigt werden.
Cobicistat und Elvitegravir und Emtricitabin und Tenofovirdisoproxil **(COBI/EVG/FTC/TDF)**	Stribild wird zur Behandlung der Infektion mit dem Humanen Immundefizienzvirus 1 (HIV-1) bei Erwachsenen im Alter von 18 Jahren und darüber angewendet, 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 sind.

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J05AR09 Stribild®	
Lopinavir und Ritonavir **(LPV/RTV)** 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.
Darunavir und Cobicistat **(DRV/COBI)** J05AR14 Rezolsta®[1]	Rezolsta ist in Kombination mit anderen antiretroviralen Arzneimitteln zur Therapie einer Infektion mit dem humanen Immundefizienzvirus-1 (HIV-1) bei Erwachsenen ab 18 Jahre zugelassen. Die Entscheidung über eine Anwendung von Rezolsta sollte auf Basis der Daten einer Genotypisierung getroffen werden (siehe Abschnitte 4.2, 4.3, 4.4 und 5.1).
Atazanavir und Cobicistat **(ATV/COBI)** J05AR15 Evotaz®[1]	Evotaz ist in Kombination mit anderen antiretroviralen Arzneimitteln zur Behandlung von HIV-1-infizierten Erwachsenen indiziert. Die HI-Viren, dieser Patienten dürfen keine bekanntermaßen, mit Resistenz gegen Atazanavir verbundenen Mutationen aufweisen (siehe Abschnitte 4.4 und 5.1).
Dolutegravir und Abacavir und Lamivudin **(DTG/ ABC/3TC)** J05AR13 Triumeq®	Triumeq ist angezeigt zur Behandlung von Infektionen mit dem Humanen Immundefzienz-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.
Andere antivirale Mittel	
Enfuvirtid **(ENV)** 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

[1] Zugelassen, aber derzeit nicht verfügbar in Deutschland

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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.
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.
Maraviroc **(MVC)** J05AX09 Celsentri®	CELSENTRI ist angezeigt in Kombination mit anderen antiretroviralen Arzneimitteln zur Therapie vorbehandelter Erwachsener, bei denen ausschließlich CCR5-trope HI-Viren Typ-1 (HIV-1) nachgewiesen wurden. Diese Indikation beruht auf den Verträglichkeits- und Wirksamkeitsdaten von zwei doppelblinden, plazebokontrollierten Studien bei vorbehandelten Patienten.
Dolutegravir **(DTG)** J05AX12 Tivicay®	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.
Cobicistat **(COBI)** V03AX03 Tybost®	Tybost wird als pharmakokinetischer 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.

Quellen: AMIS-Datenbank, Fachinformationen

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 Typ 1 (HIV-1)* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 02.05.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 829 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 36 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Infektionen mit dem Humanen Immundefizienzvirus Typ 1 (HIV-1) bei Erwachsenen und Jugendlichen (ab 12 Jahren und einem Körpergewicht von mindestens 35 kg)

Berücksichtigte Wirkstoffe/Therapien:

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen:

3TC	Lamivudin
ABC	Abacavir
ART	Anti-Retroviral Therapy
ARV	antiretroviral
ATV/r	Atazanavir/ritonavir-boosted
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
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
TDF	Tenofovirdisoproxil(fumarat)
VL	Viral load
WHO	World Health Organization
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ZDV	Zidovudin

IQWiG Berichte/G-BA Beschlüsse

<table>
<tr>
<td>IQWiG, 2016 [23].

Rilpivirin (neues Anwendungsgebiet) - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag: A15-55

neu</td>
<td>Fragestellung
Bewertung des Zusatznutzens von Rilpivirin im Vgl. zu Efavirenz in Kombination mit Abacavir und Lamivudin als zweckmäßiger Vergleichstherapie für die Behandlung von Infektionen mit dem humanen Immundefizienzvirus Typ 1 (HIV-1) bei antiretroviral nicht vorbehandelten Kindern und Jugendlichen zwischen ≥ 12 und < 18 Jahren mit einer Viruslast von ≤ 100 000 HIV-1RNA-Kopien/ml

Ergebnis/Fazit
Ausmaß und Wahrscheinlichkeit des Zusatz-nutzens von Rilpivirin: Zusatznutzen nicht belegt</td>
</tr>
<tr>
<td>IQWiG, [21] 2016.

Elvitegravir/Cobicistat/ Emtricitabin/ Tenofoviralafenamid – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag: A15-61

neu</td>
<td>Fragestellung
Bewertung des Zusatznutzens von EVG/COBI/FTC/TAF im Vergleich zur zweckmäßigen Vergleichstherapie bei Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg), die mit dem humanen Immundefizienzvirus 1 (HIV-1) infiziert sind.

Population und zweckmäßige Vergleichstherapie
Tabelle 2: Zweckmäßige Vergleichstherapie zur Nutzenbewertung von EVG/COBI/FTC/TAF
<table>
<tr><th>Frage-stellung</th><th>Anwendungsgebiet</th><th>Zweckmäßige Vergleichstherapie des G-BA[a]</th></tr>
<tr><td>1</td><td>Therapienaive Erwachsene</td><td>Efavirenz in Kombination mit 2 Nukleosid- / Nukleotid-analoga (Tenofovirdisoproxil plus Emtricitabin oder Abacavir plus Lamivudin)</td></tr>
<tr><td>2</td><td>Therapienaive Jugendliche[b]</td><td>Efavirenz in Kombination mit Abacavir und Lamivudin</td></tr>
<tr><td>3</td><td>Vorbehandelte Erwachsene</td><td rowspan="2">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.</td></tr>
<tr><td>4</td><td>Vorbehandelte Jugendliche[b]</td></tr>
<tr><td colspan="3">a: Dargestellt ist jeweils die vom G-BA festgelegte zweckmäßige Vergleichstherapie. In den Fällen, in denen der pU aufgrund der Festlegung der zweckmäßigen Vergleichstherapie durch den G-BA aus mehreren Alternativen eine Vergleichstherapie auswählen kann, ist die entsprechende Auswahl des pU fett markiert.
b: ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg
COBI: Cobicistat; EVG: Elvitegravir; FTC: Emtricitabin; G-BA: Gemeinsamer Bundesausschuss; pU: pharmazeutischer Unternehmer; TAF: Tenofoviralafenamid</td></tr>
</table>
Ergebnis/Fazit
<u>Therapienaive Erwachsene:</u>
Anhaltspunkt für einen geringeren Nutzen

<u>Therapienaive Jugendliche ab 12 Jahre mit einem KG von mind. 35kg:</u>
Zusatznutzen nicht belegt

<u>Vorbehandelte Erwachsene (ohne Umstellungsindikation):</u>
o Männer: Zusatznutzen nicht belegt
o Frauen:Anhaltspunkt für geringen Zusatznutzen

<u>Vorbehandelte Erwachsene (mit Unstellungsindikation)</u>
Zusatznutzen nicht belegt

<u>Vorbehandelte Jugendliche ab 12 Jahre mit einem KG von mind. 35kg:</u>
Zusatznutzen nicht belegt</td>
</tr>
</table>

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 [19]	**Fazit:** 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 [12]. 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 [25]	**Fazit:** 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]. Zusammenfassende Dokumentation über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Dolutegravir, 7. August 2014 Vgl. IQWIG, 2014 [18]	**Fazit:** 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 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	**Fazit:** 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 [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/ Tenofovir-disoproxil, 05. Dezember 2013 Vgl. IQWiG, 2013[20]	**Fazit:** 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 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 [13]. 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 [24] und IQWiG 2012 [17].	**Fazit:** 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 [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 – Rilpivirin, 05. Juli 2012 Vgl. IQWiG 2012 [22] .	**Fazit:** 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

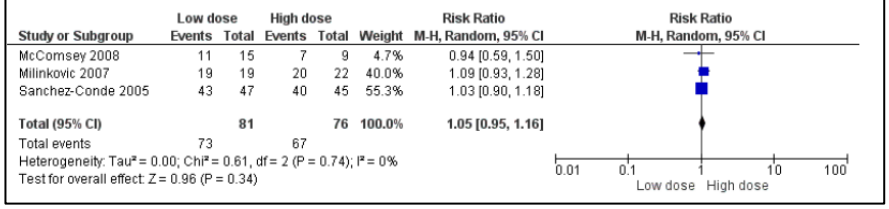
Magula N, Dedicoat M, 2015 [29]. Low dose versus high dose stavudine for treating people with HIV infection (Review)	1. Fragestellung ⇒ Evaluate the evidence supporting the effects of stavudine at dosages that are lower than standard dosage and the applicability of available data in resource-limited 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:

- The trials of McComsey 2008 & Sanchez-Conde 2005 using a cut-off of 50 copies/mL
- 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. ⇒ Virologic Failure (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 %). ⇒ Discontinuation for Adverse Events (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. ⇒ Change in lipids and in CD4 cells 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) not longer recommended by International Guidelines.
Shey MS et al., 2013 [33]. Co-formulated abacavir-lamivudine-zidovudine for initial treatment of	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

HIV infection and AIDS	**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 Virological failure (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

Li Sl et al., 2014 [28]. Effectiveness and Safety of Rilpivirine, a Non-Nucleoside Reverse Transcriptase Inhibitor, in Treatment-Naive Adults Infected 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 Infected 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 [16]. Comparative	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

effectiveness of tenofovir in treatment-naive HIV-infected patients: systematic review and meta-analysis neu	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%

	○ HDL-cholesterol -2.97 mg/dl (-4.41 to -1.53); I^2=39% ○ total cholesterol -18.42 mg/dl (-22.80 to -14.04); I^2=54% ○ triglycerides -29.77 mg/dl (-38.61 to -20.92) ;I^2=0% ○ Similar effects in trials comparing TDF/FTC-based regimens with ABC/3TC-based regimens. • Estimated glomerular filtration rate (8 trials) ○ 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) ○ 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%);) ○ 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 [27]. Efavirenz-Based Regimens in Antiretroviral-Naive HIV-Infected Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials Neu	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 [32]. Outcomes for Efavirenz versus	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

Nevirapine-Containing Regimens for Treatment of HIV-1 Infection: A Systematic Review and Meta-Analysis neu	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. o TDF/3TC or TDF/FTC was used less frequently, in only 7 studies. o 7 studies did not report on NRTI backbones. • Risk of bias: o RCTs: all open label, only 2 of 10 reported on allocation concealment, 5 of 10 reported loss to follow up • Quality of evidence:

	o evidence from RCTs was considered to be high quality for critical outcomes: no evidence of serious risk of bias, inconsistency, imprecision or indirectness o evidences from observational studies: 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 [26]. 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., 2013 [30]. Clinical Use of HIV Integrase Inhibitors: A Systematic Review and Meta-Analysis	1. Fragestellung 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

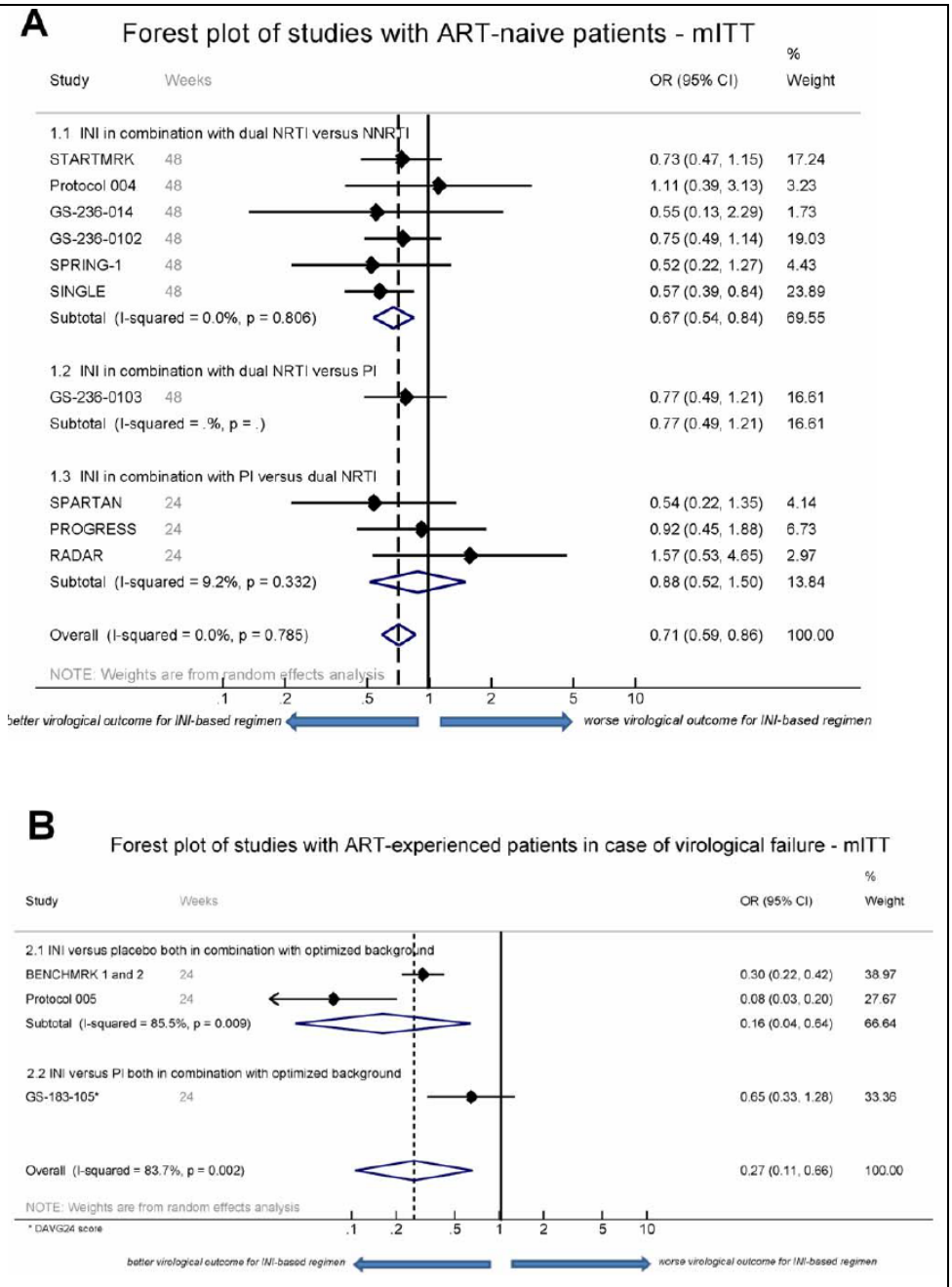
INI-containing treatment arm is underlined.
ART = antiretroviral treatment; INI = integrase inhibitor; CTR = control arm; VL<50 = viral load or HIV RNA <50 copies/ml; RAL = raltegravir; EFV = efavirenz; EVG = elvitegravir; COBI = cobicistat; DTG = dolutegravir; ATV = atazanavir; DRV = darunavir; TDF/FTC = 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

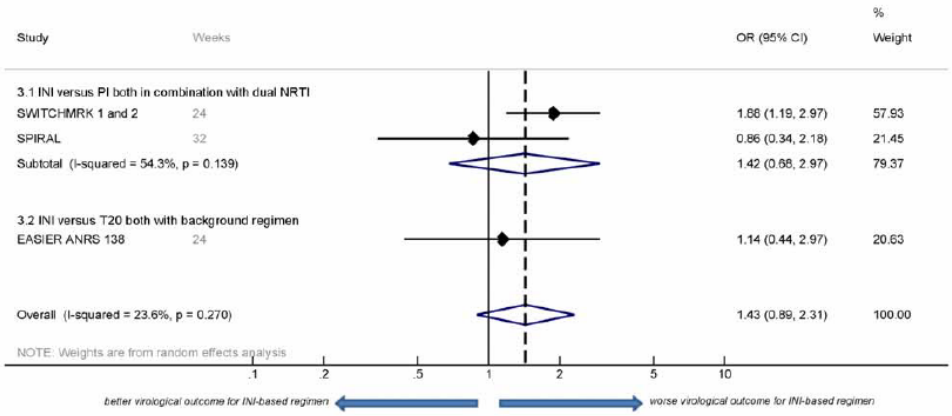
Results of MA for virological outcome (number of patients achieving HIV RNA below 50 copies/ml)

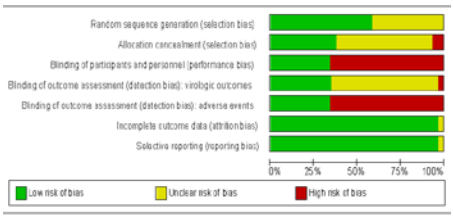
→Figure

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  **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: o no stat sign. differences between ABC and tenofovir (RR 1.26; 95% CI 0.99–1.61), o 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 [34]. A systematic review of a single-class maintenance strategy with nucleoside/nucleotide reverse transcriptase	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)

inhibitors in HIV/AIDS	**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	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).

atazanavir compared with ritonavir-boosted protease inhibitor maintenance therapy in HIV-infected adults with established virological suppression after induction neu	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 Trial / Sequence generation / Allocation concealment / Blinding* / Incomplete outcome data addressed / Free of selective reporting / Free of other bias Ghosn *et al.* 2010 [3] / Yes / Yes / Yes / Yes / Yes / Yes Gatell *et al.* 2007 [20] / Yes / Yes / Yes / Yes / Yes / Yes Wohl *et al.* 2012 [18] / Unclear / Unclear / Yes / Yes / Unclear / Unclear Squires *et al.* 2010 [14] / Yes / Yes / Yes / Yes / Yes / Unclear Soriano *et al.* 2008 [19] / Unclear / No / Yes / Yes / Yes / Unclear '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
Adverse Events	
Ford N et al., 2015	1. Fragestellung

[7]. Comparative Safety and Neuropsychiatric Adverse Events Associated With Efavirenz Use in First-Line Antiretroviral Therapy: A Systematic Review and Meta-Analysis of Randomized Trials Neu	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
	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 <u>Severe laboratory AE</u> • 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. <u>Severe neuropsychiatric AE</u> • 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
Cruciani M et al., 2011 [5]. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data	1. Fragestellung To combine all the evidence from RCTs by means of meta-analysis to estimate the effect of combined antiretroviral therapy (cART) containing abacavir on myocardial infarction and overall major cardiovascular events (CVEs).
	2. Methodik **Population:** HIV infected patients (treatment naïve or experienced) **Intervention:** abacavir (ABC), including double (ABC + lamivudine) and triple (ABC + lamivudine+zidovudine) fixed-dose coformulation as well as both once and twice-daily dosing

Komparator: other cART regimens

Endpunkte: assessed after at least 24 weeks of treatment

- Primary
  - myocardial infarction (MI)
  - overall major cardiovascular endpoint
  - death (all cause),
  - AE (overall),
  - AE requiring discontinuation of therapy.
- Secondary: rates of patients with viral load below the predefined cutoff

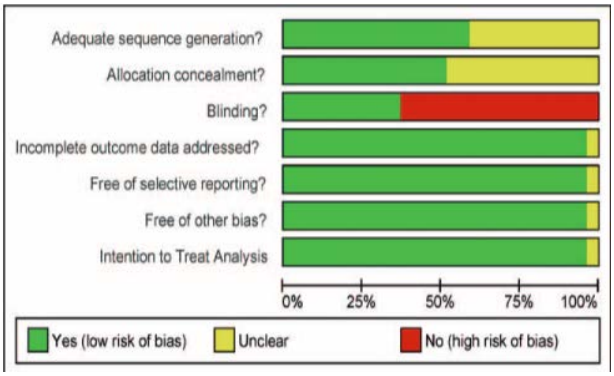
Suchzeitraum: from inception-December 2010 in CENTRAL, EMBASE, MEDLINE, Cochrane Database of Systematic Reviews, Meta Register of Controlled Trials

Anzahl eingeschlossene Studien/Patienten (Gesamt): 28 RCTs

Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool

Heterogeneity: explored clinical heterogeneity (e.g. study setting, characteristics of participants) and assessed statistical heterogeneity using Tau^2, Cochran's Q and estimated this using the I^2 statistic

3. Ergebnisdarstellung
   - 28 RCT (published and unpublished data), follow up mean 63 weeks (min 28w, max 104w)
   - Risk of Bias judgements about each methodological quality item presented as percentage across all included studies:



Results:

- MI (18 trials) RR 0.73, 95% CI 0.39–1.35; p=0.31
- CVE (20 trials) RR 0.95, 95% CI 0.62–1.44; p=0.80
- overall mortality (21 trials) RR 1.20, 95% CI 0.63–2.27; p=0.58)
- adverse events requiring discontinuation of treatment RR 0.82, 95% CI 0.67–1.00; p=0.05).

- There was a very high level of heterogeneity (e.g.I^2>75%) for the outcome overall AE→no quantitative analysis of data.
- The proportions of patients with viral load below the cut-off of detectability did not differ significantly between ABC recipients and controls

4. Anmerkungen/Fazit der Autoren

This meta-analysis of RCTs does not support the hypothesis that ABC

	containing cART regimens carry a greater risk of MI or major cardiovascular events relative to comparator cART.

Leitlinien

<table>
<tr><td>BHIVA 2015 [2].

British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015.

aktualisiert</td><td>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).</td></tr>
<tr><td></td><td>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 1January 2011 and July 2015
LoE/GoR: BHIVA has adopted the modified GRADE system for its guideline development.

<table>
<tr><td colspan="2">Strength of recommendation</td></tr>
<tr><td>Grade 1</td><td>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’)</td></tr>
<tr><td>Grade 2</td><td>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’)</td></tr>
<tr><td colspan="2">Quality of Evidence</td></tr>
<tr><td>Grade A</td><td>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.</td></tr>
<tr><td>Grade B</td><td>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.</td></tr>
<tr><td>Grade C</td><td>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.</td></tr>
<tr><td>Grade D</td><td>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.</td></tr>
</table>

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

1. Treatment-naive patients</td></tr>
</table>

Summary recommendation

We recommend therapy-naïve patients start ART containing two NRTIs plus one of the following: PI/r, NNRTI or INI (1A).

Which nucleoside reverse transcriptase inhibitor backbone?

We recommend therapy-naïve patients start combination ART containing TDF and FTC as the NRTI backbone (1A).

We suggest ABC and 3TC is an acceptable alternative NRTI backbone in therapy-naïve patients. In those with baseline VL <100 000 copies/mL it should be used with caution if there are clinical reasons to prefer over TDF and FTC (2A).

The caution regarding baseline VL does not apply if ABC/3TC is used with dolutegravir (2A).

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

Rationale

- evidence not changed since the last iteration of the guidelines in 2012
- 3 RCTs compared TDF/FTC with ABC/3TC as the NRTI backbone in combination with different third agents: atazanavir/r or efavirenz, efavirenz and lopinavir/r.
  - Assessment of virological efficacy as a critical outcome complicated by different definitions across the 3 studies.
  - no difference in rates of virological suppression at 48 weeks or 96 weeks (quality of evidence: low- very low) but the analysis excluded the largest of the three trials (ACTG 5202)
  - risk of virological failure at 48 weeks favoured TDF/FTC (RR 0.76, 95% CI 0.53–1.07), although the effect not statistically significant and heterogeneity in the analysis was relatively high.
  - virological failure at 96 weeks showed a significant difference favouring TDF/FTC (RR 0.73, 95% CI 0.59–0.92, 1 study; quality of evidence: high).
  - ACTG 5202
    - results complicated by early withdrawal of those individuals receiving ABC/3TC with baseline VL >100000 copies/mL at recommendation of the Data and Safety Monitoring Board owing to significantly inferior performance.
    - No difference in virological efficacy between TDF/FTC and ABC/3TC in those with baseline viral load <100,000 copies/mL
    - 96-week analysis, after discontinuation of those subjects in the higher viral load stratum, may therefore underestimate the difference between the two backbones.
  - other critical and important outcomes: no difference between TDF/FTC and ABC/3TC.
  - no data were available to assess quality of life outcomes.
  - Grade 3/4 AE (all) and grade 3/4 alanine transaminase/aspartate transaminase elevation: trends that favoured TDF/FTC
  - rate of drug resistance was not different between the NRTI backbones, but number developing drug resistance was higher numerically in those receiving ABC/3TC, given the higher rate of virological failure.
  - Bone mineral density outcomes significantly favoured ABC/3TC.
  - Observational studies reported associations between ABC and cardiovascular disease; TDF may cause renal disease

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).

Rationale for efavirenz as an alternative

- dolutegravir demonstrated superiority to efavirenz in SINGLE, as has rilpivirine in subgroup analyses, and raltegravir with longer---term follow- up of STARTMRK; difference between efavirenz and comparators is driven by a higher rate of discontinuation for AE on efavirenz---based regimens, mainly due to its potential for significant central nervous system toxicity.
- a meta-analysis of ACTG studies demonstrated a higher risk of suicidality in those randomised to efavirenz-containing regimens (Mollan et al. Ann Intern Med 2014; 161: 1–10.)
- Individuals with significant past or current mental health issues may be excluded from clinical

trial populations so the ACTG analysis could potentially underestimate the impact of efavirenz in higher-risk patients

- observational cohort study did not demonstrate an association between efavirenz use and suicidality(retrospective analysis: Smith et al. J Int AIDS Soc 2014; 17:19512.)
- although not considered an important outcome for the purpose of these guidelines, efavirenz is associated with an adverse impact on lipids compared to newer agents.
- Since there are several effective and well-tolerated alternative third agent options available: efavirenz downgraded from preferred to alternative option for initial therapy.
- majority of individuals who start efavirenz-based therapy tolerate it reasonably well, so it remains a reasonable alternative. For patients stable on efavirenz- based ART, we recommend a review of tolerability, including sleep and mood, at all visits.

Novel antiretroviral therapy strategies

We recommend against the use of PI monotherapy as initial therapy for treatment-naïve patients(1C).

Rationale

- 1 RCT comparing lopinavir/r *vs*. lopinavir/r plus zidovudine and lamivudine:
  - PI monotherapy as initial ART was associated with lower rates of virological suppression at 48 weeks and with the emergence of PI mutations
  - no significant differences in tolerability

We suggest the use of darunavir/r---based dual ART regimen with raltegravir in treatment-naïve patients with CD4 count >200 cells/μL and viral load <100,000 copies/mL where there is need to avoid ABC or and TDF (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).

Rationale

- similar virological efficacy of combination of NNRTI with a PI/r compared with triple-combination regimens in 1study
  - no significant differences in time to either virological or regimen failure with a combination of lopinavir/r and efavirenz compared with either two NRTIs and efavirenz or two NRTIs and lopinavir/r although the NRTI-sparing arm underperformed in individuals with high baseline viral load (greater than 100,000 copies/mL).
  - increased rate of drug resistance in the NRTI-sparing arm, with the emergence of more NNRTI-associated resistance mutations than the comparator arms.
  - increased rate of grade 3/4 toxicities, predominantly low-density lipoprotein cholesterol and triglyceride elevations.
- 2RCTs evaluated a dual-therapy regimen containing 1NRTI with a PI/r compared to standard therapy of a PI/r and 2 NNRTIs.
  - The GARDEL study: non- inferiority of the dual regimen of lopinavir/r plus lamivudine compared to lopinavir/r, lamivudine or emtricitabine plus a third NRTI in virological efficacy at 48 weeks irrespective of baseline viral load; *post hoc* analysis: no difference in virological efficacy with respect to the choice of dual NRTI backbone and pre-treatment CD4 cell count (<200 cells/μL)
  - A study comparing tenofovir and lopinavir/r to 2 NRTIs and lopinavir/r failed to demonstrate non-inferiority of the dual-therapy compared with a standard triple-therapy combination; numbers were small and response rates numerically similar at 51% and 53%, respectively
- efficacy of dual therapy with CCR5-receptor antagonist maraviroc in combination with a PI/r assessed in a number of studies but only one was powered to demonstrate non-inferiority:
  - This study comparing maraviroc/darunavir/ritonavir to TDF /FTC/darunavir/r showed lower virological efficacy of the dual therapy arm at 48 weeks.
- efficacy of the raltegravir plus a PI/r has been compared with standard triple therapy in several studies:
  - Demonstration of non-inferiority of raltegravir compared to TDF /FTC when combined with darunavir/r at 96 weeks.
  - dual-therapy was associated with higher rates of virological failure and with treatment-emergent integrase resistance (5/28 patients) in those with baseline CD4 cell count <200 cells/μL or viral load >100,000 copies/mL.
  - a single-arm study investigating raltegravir in combination with darunavir/r, showed increased risk of virological failure with emergent integrase resistance with baseline viral load >100,000 copies/mL compared with those with a baseline viral load <100,000 copies/mL
  - PROGRESS study demonstrated similar virological efficacy of raltegravir plus lopinavir/r compared to TDF /FTC and lopinavir/r (small study)
- use of raltegravir with unboosted atazanavir associated with development of integrase resistance in 4/6 of those who met the criteria for resistance testing

Table 5.1. Summary recommendations for choice of ART

	Preferred	Alternative
NRTI backbone	Tenofovir and emtricitabine	Abacavir and lamivudine[a,b]
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/emtricitabine/elvitegravir/c fixed-dose combination should not be initiated in individuals with creatinine clearance <70 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.

2. Treatment- experienced patients

Managing virological failure

Individuals with no or limited drug resistance

We recommend for individuals experiencing virological failure on first-line ART with WT virus at baseline and without emergent resistance mutations at failure, switch to a PI/r-based combination ART regimen is the preferred option (1C).

We recommend individuals experiencing virological failure on first-line ART with WT virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure, switch to a new PI/r-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 plus two-NRTI- based regimens, with limited major protease mutations, switch to a new active PI/r with the addition of at least one, preferably two, active agents of which one has a novel mechanism of action (1C).

Rationale

- remaining on the same regimen may be a reasonable approach but with close monitoring and adherence support.
- individual should be monitored carefully and repeat VL performed after approximately 4 weeks. If there is inadequate virological response, resistance testing should be performed to detect any additional archived resistance.
- limited data regarding the efficacy of switching to another PI/r, NNRTI, INI or maraviroc-based regimen and again the decision should individualised.
- switching to an INI, maraviroc or an NNRTI for a person with historical or existing reverse transcriptase mutations is not recommended because of an increased risk of virological failure and further emergence of resistance
- By contrast, because of the high genetic barrier of PI/r, sequencing to a regimen that includes a new PI/r is unlikely to lead to further emergent resistance and is recommended. Where PI/r mutations exist, darunavir/r is the preferred agent (unless resistance is likely) and inclusion of an INI, etravirine or maraviroc (if R5 tropic virus) as one of the additional drugs should be considered. Where darunavir/r is not suitable, depending on susceptibility, alternative PIs such

as tipranavir/r and lopinavir/r may be considered.

We recommend against switching a PI/r 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).

Rationale

First-line treatment failure with no resistance

- Failure is usually attributable to poor treatment adherence with drug levels that are both insufficient to maintain VL suppression and inadequate to select out viral mutations associated with drug resistance detectable on standard tests.
- absence of detectable resistance mutations does not exclude presence of mutations in minor virus populations, especially with the NNRTIs
- increased likelihood of subsequent failure if the same first-line drugs, or drugs in the same class, are prescribed
- testing for minority resistance is a specialist test and expert interpretation by a virologist is essential. There is no indication for routine minority-species testing for individuals with wild--type virus and failed therapy
- In deciding which option, knowledge as to the likely cause of virological failure especially the details of poor adherence are important. In an NNRTI/2NRTI regimen, when all three agents have been stopped, the chances of NNRTI resistance are 12–16% depending on whether there is a simultaneous or staggered interruption

First-line treatment failure with NNRTI resistance

- The finding of associated NRTI resistance is more frequent in those on a thymidine analogue (TA) backbone than on a non-TA one.
- Although potential options for second-line therapy after failure on an NNRTI-containing regimen include an integrase inhibitor (raltegravir, elvitegravir or dolutegravir), etravirine or maraviroc as the third agent, evidence supports the use of a PI/r.
- A switch to any PI/r-based regimen should lead to virological suppression and is unlikely to lead to further emergent resistance and should be considered whenever possible.
- Where NRTI resistance has been documented or likely, the addition of new active NRTIs or another ARV(s) should be considered in combination with a boosted PI.
- The exception to this is when M184V is present alone, when recycling of NRTIs may be feasible.
- Combining raltegravir with a boosted-PI has been found to be as efficacious as a boosted PI/r regimen with at least two new or recycled NRTIs
- There are no direct comparisons of boosted PIs in second-line treatment after first-line failure on an NNRT-based regimen and choice should be individualised.
- Sequencing from an efavirenz- or nevirapine- based regimen to etravirine is not recommended unless switching to a new combination including a boosted PI.
- Switching to an INI (raltegravir, elvitegravir or dolutegravir) or maraviroc with two active NRTIs is an option but is also not recommended if there are historical or existing reverse transcriptase mutations/previous NRTI virological failure

First-line treatment failure on a ritonavi-boosted PI-based two NRTI regimen with or without PI resistance

- remaining on the same regimen may be a reasonable approach but with close monitoring and adherence support.
- individual should be monitored carefully and repeat VL performed after approximately 4 weeks. If there is inadequate virological response, resistance testing should be performed to detect any additional archived resistance.
- limited data regarding the efficacy of switching to another PI/r, NNRTI, INI or maraviroc-based regimen and again the decision should individualised.
- switching to an INI, maraviroc or an NNRTI for a person with historical or existing reverse transcriptase mutations is not recommended because of an increased risk of virological failure and further emergence of resistance
- because of the high genetic barrier of PI/r, sequencing to a regimen that includes a new PI/r is unlikely to lead to further emergent resistance and is recommended.
- Where PI/r mutations exist, darunavir/r is the preferred agent (unless resistance is likely) and inclusion of an INI, etravirine or maraviroc (if R5 tropic virus) as one of the additional drugs should be considered. Where darunavir/r is not suitable, depending on susceptibility, alternative PIs such as tipranavir/r and lopinavir/r may be considered.

First-line treatment failure with integrase inhibitor-based resistance

- In studies of naïve subjects developing virological failure on raltegravir or elvitegravir regimens, up to one- half have been found to harbour viruses with primary integrase mutations and 25% NRTI mutations at 48 weeks: approximately half have wild-type virus
- no resistance has been seen in studies in treatment-naïve individuals with dolutegravir/2NRTI-based regimens
- data supporting a switch to PI/r, NNRTI or maraviroc but sequencing to a new regimen that includes a PI/r is unlikely to lead to further emergent resistance and is recommended.
- Similarly, although data from the VIKING---3 study in individuals with pree-existing integrase mutations after failure on raltegravir or elvitegravir in the context of three-class resistance and

with optimisation of the background regimen has shown over half achieve a VL <50 copies/mL

- no data to support sequencing to dolutegravir after first-line failure.
- Switching to an NNRTI or maraviroc with two active NRTIs is an option but is also not recommended in a person with historical or existing reverse transcriptase mutations or previous NRTI virological failure.
- Individuals experiencing virological failure on raltegravir or elvitegravir should switch to a new regimen as soon as possible to reduce the risk of accumulating resistance mutations that may affect susceptibility to dolutegravir where success of response has been linked to the profile and number of resistance mutations.

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/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 DRV/r and one agent with a novel mechanism (an INI, MVC or enfuvirtide) with ETV an option based on viral susceptibility (1C).

We recommend individuals with extensive drug resistance including reduced darunavir susceptibility receive DTG 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).

Rationale

- drugs currently used in triple-class failure:boosted PIs (predominantly twice-daily darunavir/r; but also on occasions tipranavir/r), INIs raltegravir and dolutegravir, CCR5 chemokine receptor antagonist maraviroc, NNRTI etravirine, fusion inhibitor enfuvirtide.
- available data for darunavir/r, tipranavir/r, raltegravir, elvitegravir, dolutegravir, etravirine and enfuvirtide show that they are most effective when used with other active drugs to which the virus is susceptible based on resistance testing and antiviral experience
- When used as the only effective agent, the likelihood of achieving virological suppression is significantly reduced and the development of emergent resistance to the drug greater, and a future opportunity for constructing an effective regimen is often lost.
- In a meta-analysis of 10 trials (excluding dolutegravir) of subjects with triple-class virological failure and virological resistance where the study drug was added to optimised background therapy and compared with placebo, associations were demonstrated with increased virological suppression (pooled OR 2.97) and larger CD4 cell count increases for the active agent
- In a further non-inferiority study, elvitegravir was found to be non-inferior to raltegravir when accompanied by a boosted PI and a third agent
- A non---inferiority trial comparing dolutegravir with raltegravir as the comparator examined those with triple- class experience but who were naive to integrase inhibitors and had at least two-class resistance and at least one fully active drug as optimised background therapy: once-daily dolutegravir was superior to raltegravir at 48 weeks in achieving a VL <50 copies/mL; no benefit in individuals who had not received darunavir/r or had no primary darunavir mutations.
- In two studies examining individuals previously naive to ART for whom an NNRTI/2NRTI regimen subsequently failed, a boosted PI/r regimen with at least two new or recycled NRTIs was no less efficacious than an NRTI-sparing regimen combining raltegravir with a boosted-PI. Even in the presence of limited or no predicted activity on the basis of genotypic assay, NRTIs retained substantial virological activity equivalent to that of raltegravir without evidence of increased toxicity and therefore may allow the introduction of drugs known to be active to be deferred. NRTI inclusion was demonstrated to achieve improved virological control over PI/r monotherapy out to 96 weeks; Once virological suppression has been achieved, the advantage of retaining NRTIs where partial or complete resistance is demonstrated is uncertain.

	• A small open RCT of 90 virologically suppressed individuals on safety of withdrawing NRTIs compared to a control arm of maintaining them in the context of partial NRTI activity and the presence of at least two fully active remaining drugs in the regimen: No significant difference in virological failure between the arms at 48 weeks • A study examined individuals who had triple---class failure and/or resistance when randomisation to the new regimen was based on treatment history, tropism testing and resistance profiles including a choice of NRTIs. Following randomisation, the subjects then received the chosen regimen with or without the NRTIs. The results demonstrated omitting NRTIs was non-inferior to their inclusion. Of note, subjects in this study received an average of three active drugs and therefore the lack of NRTI benefit is not altogether surprising. • Studies using lamivudine monotherapy for individuals developing therapy failure have shown that those harbouring M184V who continue on lamivudine maintain lower VLs, have smaller declines in CD4 cell counts, and rarely develop new reverse transcriptase mutations • presence of M184V mutation enhances in vitro susceptibility to tenofovir and this translates into a significant HIV RNA response in clinical trials of tenofovir intensification • Insufficient data to guide recommendations as to whether there are clinical benefits of trying to maintain M184V by continuing lamivudine/emtricitabine when switching to new combination ART; expert opinion: any decision should be individualised. • For those drugs with a novel mode of action (integrase and fusion inhibitors, and CCR5 antagonists), the absence of previous exposure indicates susceptibility, although maraviroc is only active against CCR5---tropic virus. For darunavir, tipranavir and etravirine, the number and type of mutations inform the degree to which these drugs are active • potential for drug–drug interactions important
WHO, 2013 [35,36]. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection	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 2010 **Grundlage der Leitlinie:** • syst. Literaturrecherche, • Konsensusprozess **Suchzeitraum:** bis 2012 **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 **1. Treatment-naive patients** **1a. Adults** <u>Preferred first-line regimens:</u> 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 options is recommended: • AZT + 3TC + EFV • AZT + 3TC + NVP • TDF + 3TC (or FTC) + NVP (strong recommendation, moderate-quality evidence). • Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence). • Special circumstances may include situations where preferred or alternative

regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons: Regimens containing ABC, d4Tb and boosted PIs

Rationale:

3TC vs FTC

- available evidence supports clinical equivalence of 3TC and FTC in terms of efficacy and safety.
- evidence with regards to drug resistance is inconclusive, with differences appearing to be small, and their clinical importance unclear.
- 3TC is available in more fixed-dose combination formulations than FTC.
- References:

Sanne et al. Two randomized, controlled, equivalence trials of emtricitabine (FTC) to lamivudine (3TC). XIV International AIDS Conference, Barcelona, 7–12 July 2002. Abstract 4432

Benson et al. A randomized study of emtricitabine and lamivudine in stably suppressed patients with HIV. AIDS. 2004;18:2269–76.

Mulenga A et al. Efficacy of tenofovir disoproxil fumarate/emtricitabine and tenofovir disoproxil both in combination with efavirenz in antiretroviral-naïve, HIV-1-infected Zambians. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Kuala Lumpur, Malaysia, 2013.

Ford N, Shubber Z, Hill A et al. Comparative efficacy of lamivudine and emtricitabine: a systematic review and metaanalysis of randomized trials. PLoS ONE. 2013;8:e79981

.EFV vs NVP

- exposure to EFV in early pregnancy has not resulted in increased occurrence of congenital anomalies or other significant toxicity.
- evidence suggests that EFV is clinically superior to NVP, since it provides better long-term viral suppression and has fewer adverse reactions and less risk of resistance, when combined with TDF + 3TC (or FTC)
- Cost of EFV decreased considerably, and it is now increasingly available as part of once-daily fixed-dose combinations.
- References:

Tang et al. A review of the virological efficacy of the 4 World Health Organization–recommended tenofovir-containing regimens for initial HIV therapy. Clin Infect Dis. 2012;54:862–75.

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Ouattara EN, Anglaret X, Wong AY et al. Projecting the clinical benefits and risks of using efavirenz-containing antiretroviral therapy regimens in women of childbearing age. AIDS. 2012;26:625–34.

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March of Dimes global report on birth defects: the hidden toll of dying and disabled children. White Plains, NY: March of Dimes Birth Defects Foundation; 2006 (http://www.marchofdimes.com/glue/files/BirthDefectsExecutiveSummary.pdf, accessed 17 February 2014).

Ford et al. Safety of efavirenz in the first-trimester of pregnancy: an updated systematic review and meta-analysis. AIDS. 2014;28(Suppl. 2):S1–9.

1b.Children 3 years of age and older (including adolescents):

- For children infected with HIV three years of age and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative (strong recommendation, low-quality evidence).

Special note: In determining the choice of NNRTI for first-line therapy, national programmes should consider the dosing characteristics of EFV (once-daily) and NVP (twice-daily) and how this aligns with the NRTI backbone. For example, NVP may be a better choice if the recommended regimen is a twice-daily option using a fixed-dose

combination.

- For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ARV regimen should align with that of adults and be one of the following, in preferential order:
    - TDF + 3TC (or FTC)
    - AZT + 3TC
    - ABC + 3TC

  (strong recommendation, low-quality evidence).

  Special note: TDF-containing fixed-dose combinations are currently only available in adult, unscored tablets for once-daily use. At or above 35 kg, the dose of TDF in adult dual and triple fixed-dose combinations and the dose of EFV in adult triple fixed-dose combinations are acceptable for use in adolescents. ABC or boosted PIs can be used in special circumstances.

Rationale

The US FDA and EMA approved using TDF for children older >2 years of age, providing an opportunity to offer the same regimen to both adults and children. Harmonizing treatment recommendations with adult regimens could improve children's access to ART. Other benefits of TDF include the ability to combine it with 3TC and EFV to create a potent once-daily regimen for children. In addition, the fact that HIV resistance to TDF – specifically K65R – can enhance the antiviral effect of AZT may make TDF a good choice for first-line therapy in terms of sequencing NRTIs from first- to second-line regimens. However, experience with TDF in young children is limited, and although TDF is known to reduce bone mineral density, it is not clear whether this is permanent and how it might affect future patterns of growth and fracture risk, as highlighted in the values and preferences survey among health workers. In addition, TDF formulations for younger children are not widely available and to date there are no TDF-containing paediatric fixed-dose combinations. ABC shares many of the benefits of TDF (once-daily dosage and a favourable resistance profile) but, in contrast to TDF, ABC has been more thoroughly studied in children and is generally well tolerated. ABC is also available in paediatric fixed-dose combination formulations but is significantly more costly. Further, among people with HLA-B*5701, it can cause potentially fatal hypersensitivity; although this is very rare among African children, it can affect up to 3–4% of Caucasian and Asian children.

A systematic review based on observational data indicates that EFV has a better short term toxicity profile and is associated with better virological response than NVP. Most children currently receiving ART are treated with regimens that contain NVP, whereas in adults, EFV is increasingly being selected as the preferred NNRTI. The primary reason for this discrepancy relates to the relative availability of NVP or EFV in fixed-dose combinations for children or adults. Children who are well controlled and stable on NVP containing regimens do not need to substitute EFV for NVP, but EFV would be a better choice for those initiating ART with other once-daily drugs.

Ref:
Tang et al. A review of the virological efficacy of the 4 World Health Organization–recommended tenofovir-containing regimens for initial HIV therapy. Clinical Infectious Diseases, 2012, 54:862–875.
Shubber et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. AIDS, 2013, 27:1403-1412.

Table 7.5 Summary of first-line ARV regimens for adults, adolescents, pregnant and breastfeeding women and children

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a] [b]
Adults (including pregnant and breastfeeding women and adults with TB and HBV coinfection)	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Adolescents (10 to 19 years) ≥35 kg		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP ABC + 3TC + EFV (or NVP)
Children 3 years to less than 10 years and adolescents <35 kg	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP
Children <3 years	ABC (or AZT) + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

[a] For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible. See Box 10.7 for guidance on phasing out d4T.

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

2. Treatment- experienced patients

WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

clinical failure: New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition)a after 6 months of effective treatment

Comment: The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure

immunological failure: CD4 count falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm3

Comment Without concomitant or recent infection to cause a transient decline in the CD4 cell count A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure

virological failure: Plasma viral load above 1000 copies/ ml based on two consecutive viral load measurements after 3 months, with adherence support .

Comment The optimal threshold for defining virological failure and the need for switching ART regimen has not been determined. An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed.

Recommendation: What ART regimen to switch to (second-line ART)

Table 7.18 Summary of preferred second-line ARV regimens for adults and adolescents

Target population	Preferred second-line regimen[a]	
Adults and adolescents (≥10 years)	If d4T or AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r
Pregnant women	Same regimens recommended for adults and adolescents	
HIV and TB coinfection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800 mg/200 mg twice daily) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily)
HIV and HBV coinfection	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)	

[a] ABC and ddI can be used as NRTI backup options but add complexity and cost without clinical advantages. DRV/r can be used as an alternative PI and SQV/r in special situations, but neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is in development.

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART.

2a. Second-line ART: recommendations for adults

- Second-line ART for adults should consist of 2NRTIs + 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).

Rationale

<u>PI options for second-line ART</u>

- no evidence to support changing the recommendation in the 2010 guidelines (6 clinical trials):
  low- to very-low-quality evidence (downgraded in the GRADE evaluation primarily for indirectness and imprecision) for using ATV/r or DRV/r (once-daily) over LPV/r (twice-daily) or vice versa as preferred boosted PI options:
    - ATV/r was considered to be comparable to LPV/r in 1 trial among ART-experienced individuals
    - In 1 trial among ART-naive individuals, ATV/r showed better virological response and better retention in care when compared with LPV/r
    - In 2 studies, people receiving DRV/rcontaining regimens also showed better virological response and retention in care than people receiving LPV/r, both in treatment-naive and experienced people

References:

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Banhegyi D et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. Current HIV Research, 2012, 10:171–181.

Molina JM et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. Journal of Acquired Immune Deficiency Syndromes, 2010, 53:323–332.

Josephson F et al. The relation between treatment outcome and efavirenz, atazanavir or lopinavir exposure in the NORTHIV trial of treatment-naive HIV-1 infected patients. European Journal of Clinical Pharmacology, 2010, 66:349–357.

Orkin C et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1- infected treatment-naive patients inthe ARTEMIS trial. HIV Medicine, 2012, doi: 10.1111/j.1468-1293.2012.01060.x.

- DRV/r has been used for second-line therapy in high-income settings.
- 2 key factors currently preclude DRV/r as a preferred option in these guidelines: high cost and it not being available as a heat-stable fixed-dose combination.
- Additional research is required to better understand sequencing strategies for PIs in second- and third-line therapy. The different drug toxicity profiles of ATV/r and LPV/r, the contraindication of ATV/r with rifampicin and the lack of WHO approval for the use of ATV/r in children younger than six years provide additional grounds for maintaining both PIs as equal options
- The Guidelines Development Group recommended that DRV/r should be maintained as a preferred third-line drug. Using it as an alternative option to LPV/r or ATV/r for second-line therapy can be considered, especially when competitively priced fixed-dose combinations are available

<u>NRTI backbone</u>

- The Guidelines Development Group maintained the rationale adopted in 2010, recommending drug sequencing consistent with ART-optimizing principles (in particular, availability as fixed dose combinations and tolerability) and resistance mutation risk, based on the NRTIs used in the first-line regimen.

2b. Second-line ART: recommendations for children (incl. adolescents)

- After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI. (Strong recommendation, moderate-quality evidence)
- After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken. (Conditional recommendation, very-low-quality evidence)
- After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI. (Conditional recommendation, 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)

Rationale

- After reviewing data for adults and children main recommendations established in the 2010 guidelines were maintained.

- RCT data among older children provide indirect evidence supporting the safe use of an NNRTI-based second-line regimen, but concerns remain about this approach for infants and young children.
- Based on the suboptimal performance of NVP-based regimens (and the limited data available to inform the use of EFV) in children younger <3 years and the potential rapid re-emergence of archived NNRTI-resistant HIV, second-line NNRTI-based regimens are expected to have limited durability in this age group
- Increasing evidence suggests that, in young children for whom LPV/r-based regimens have failed, selection of major mutations to PI is rare and accumulation of thymidine analogue mutations is very limited.
- Unboosted PIs (such as fosamprenavir (FPV), DRV and ATV) and other PIs (such as IDV/r, SQV/r, FPV/r and TPV/r) are associated with reduced virological suppression, high pill burden and/or a higher frequency of side effects and are therefore discouraged
- The sequencing of NRTI was determined based on optimizing principles for ARV drugs and the need to maximize antiviral activity despite the selection of resistance mutations.
- added value of ddI in second-line regimens is unclear;
- continuing 3TC despite the likely presence of 3TC resistance is the preferred option.
- HIV harbouring 3TC resistance with the M184V mutation may have reduced viral replication and may also induce some degree of resensitization to AZT or TDF, although this is based on in vitro data

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3. Third-line ART - New 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 integrase inhibitors and second-generation NNRTIs and PIs (conditional recommendation, low-quality evidence).
- Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen (conditional recommendation, very low-quality evidence).

Rationale

	• Data from RCTs available for DRV/r, etravirine (ETV) and raltegravir (RAL), most studies conducted in well-resourced or middle- to high-income countries: these data support efficacy of these agents in highly ART-experienced patients. • pooled subgroup analysis show superiority of DRV/r plus an optimized background regimen (OBR) chosen by genotyping and phenotyping compared to control group (boosted PI + OBR where the investigator selected the boosted PI) among highly treatment-experienced individuals • DRV/r non-inferior to LPV/r among treatment-experienced people after 96 weeks • Among individuals with limited treatment options, RAL + OBR provided better virological suppression than the OBR alone for at least 96 w. • ETV + OBR provided better virological suppression and improved immunological response than the optimized background regimen alone after 96 weeks • in people with multidrug resistant HIV who have few remaining treatment options, the combination of RAL, ETV and DRV/r was well tolerated and was associated with a rate of virological suppression similar to that expected among treatment-naive people • Evidence from post-marketing reports indicates higher rates of hypersensitivity to ETV than previously reported References Arasteh K et al. Efficacy and safety of darunavir/ritonavir in treatment-experienced HIV type-1 patients in the POWER 1, 2 and 3 trials at week 96. Antiviral Therapy, 2009, 14:859–864. Banhegyi D et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. Current HIV Research, 2012, 10:171–181. Gatell JM et al. Long-term efficacy and safety of the HIV integrase inhibitor raltegravir in patients with limited treatment options in a Phase II study. Journal of Acquired Immune Deficiency Syndromes, 2010, 53:456–463. Steigbigel RT et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatmentexperienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. Clinical Infectious Diseases, 2010, 50:605–612. Katlama C et al. Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials. Antiviral Therapy, 2010, 15:1045–1052. Imaz A et al. Efficacy and safety of nucleoside reverse transcriptase inhibitor-sparing salvage therapy for multidrug-resistant HIV-1 infection based on new-class and new-generation antiretrovirals. Journal of Antimicrobial Chemotherapy, 2011,66:358–362. Fagard C et al. Long-term efficacy and safety of raltegravir, etravirine, and darunavir/ritonavir in treatment-experienced patients: week 96 results from the ANRS 139 TRIO trial. Journal of Acquired Immune Deficiency Syndromes, 2012, 59:489– 493. Etravirine full prescribing information. Titusville, NJ, Janssen Products, 2008 (www.intelence.com/shared/product/intelence/prescribing-information.pdf, accessed 15 May 2013).
Günthard HF et al., 2014 [15]. 2014 recommendations of the International Antiviral Society-USA Panel Antiretroviral treatment of adult HIV infection	OBJECTIVE To provide updated treatment recommendations for adults with HIV, emphasizing when to start treatment; what treatment to start; the use of laboratory monitoring tools; and managing treatment failure, switches, and simplification.
	Methodik **Grundlage der Leitlinie:** • internationale Expertengruppe, • syst. Literaturrecherche, • Konsensusprozesse **Suchzeitraum:** 2012-2014 (Update des SR von Thompson MA, et al. 2012) **Weitere Kriterien für die Qualität einer Leitlinie:** Finanzierung durch die „IAS–USA - a not-for-profit, mission-based, nonmembership, educational organization“, CoI erfasst und 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

Recommended initial ART-Regimens[a]

Type of Regimen	Antiretroviral Drug Combination	Rating	Comments
Integrase strand transfer inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Dolutegravir[b] plus tenofovir/ emtricitabine	AIa	Dolutegravir is dosed once daily. Associated with modest increases in creatinine level due to inhibition of creatinine secretion
	Dolutegravir[b] plus abacavir[c]/ lamivudine	AIa	No evidence that abacavir/lamivudine performs less well at HIV-1 RNA levels >100 000 copies/mL when given with dolutegravir. A fixed-dose combination is in late-stage development.
	Elvitegravir[b]/ cobicistat/ tenofovir/ emtricitabine	AIa	Once-daily fixed-dose combination. Cobicistat is associated with modest increases in creatinine level due to inhibition of creatinine secretion; has similar drug interactions to ritonavir.
	Raltegravir[b] plus tenofovir/ emtricitabine	AIa	Raltegravir is taken twice daily.
Nonnucleoside reverse transcriptase inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Efavirenz[d] /tenofovir/ emtricitabine	AIa	Efavirenz central nervous symptoms may persist beyond 2-4 weeks but is no longer contraindicated for use in pregnant women.
	Efavirenz[d] plus abacavir[c] /lamivudine[e]	AIa	Efavirenz central nervous symptoms may persist beyond 2-4 weeks but is no longer contraindicated for use in pregnant women.
	Rilpivirine[f]/ tenofovir/ emtricitabine	AIa	Once-daily fixed-dose combination. Rilpivirine-based therapy is not recommended in patients with baseline HIV-1RNA levels >100 000 copies/mL.
Ritonavir-boosted protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Atazanavir[g,h] plus tenofovir/ emtricitabine	AIa	Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.
	Atazanavir[g,h] plus abacavirc/ lamivudine[e]	AIa	Atazanavir is associated with nephrolithiasis, cholelithiasis, and chronic kidney injury.
	Darunavir[g] plus tenofovir/ emtricitabine	AIa	During initial therapy, 800 mg of darunavir is given oncedaily with 100 mg of ritonavir given once daily.

[a] Regimen classes and drugs within these classes are listed in alphabetic order by the anchor (third) drug and not in order of preference. Ratings of the strength of the recommendations and quality of evidence are described in Table 1.

[b] Simultaneous administration with antacids or other medications with divalent cations (Ca^{2+}, Mg++, Al++, Fe++) should be avoided due to chelation of the integrase strand transfer inhibitor by the cation, thereby reducing absorption.

[c] Abacavir has been associated with increased cardiovascular risk, although data are conflicting; use with caution in patients with high cardiovascular risk. Should only be used in HLA-B*5701-negative patients.

[d] Should be taken on an empty stomach, and preferably at bedtime.

[e] The combination of abacavir and lamivudine was less efficacious with baseline HIV-1 RNA level above 100 000 copies/mL than the combination of tenofovir and emtricitabine when these agents were given with efavirenz or ritonavir-boosted atazanavir.

[f] Rilpivirine should not be given with proton pump inhibitors and should be taken consistently with a full meal.

[g] Should be taken with food.

[h] Co-administration with H2-blockers or proton pump inhibitors should be avoided if possible and, if not, specific doses and dose separation schedules are recommended as per prescribing information.

Alternatives to Recommended Initial Regimes:

Table 3. Alternatives to Recommended Initial Regimens[a]

Type of Regimen	Alternative Antiretroviral Drug Combinations	Rating	Comments
Integrase strand transfer inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Raltegravir[b] plus abacavir[c]/lamivudine	BIa	No evidence that abacavir/lamivudine performs less well at HIV-1 RNA levels >100 000 copies/mL when taken with raltegravir.
Nonnucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nucleoside reverse transcriptase inhibitors	Nevirapine plus 2 nucleoside reverse transcriptase inhibitors	BIa	Severe hepatotoxicity may occur in initial therapy when CD4 cell count is >250/μL in women and >400/μL in men. Severe rash is more common than with other NNRTIs.
	Rilpivirine[d] plus abacavir[c]/lamivudine	AIa	Rilpivirine-based therapy is not recommended in patients with baseline HIV-1 RNA levels >100 000 copies/mL.
Protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors	Atazanavir[e]/cobicistat[f] with 2 nucleoside reverse transcriptase inhibitors	BIa	Atazanavir plus cobicistat as a fixed-dose combination achieves atazanavir levels similar to those with ritonavir boosting. As separate agents, they were noninferior to ritonavir-boosted atazanavir, both in combination with tenofovir/emtricitabine.
	Darunavir[e]/cobicistat[f] with 2 nucleoside reverse transcriptase inhibitors	BIII	Darunavir plus cobicistat as a fixed-dose combination achieves darunavir levels similar to those with ritonavir boosting.
	Darunavir[e,g] plus abacavir[c]/lamivudine	BIb	Comparative clinical data from a subset of patients from a single, randomized study.
	Lopinavir[g] fixed-dose combination with 2 nucleoside reverse transcriptase inhibitors	BIa	Main advantage is fixed-dose combination. May have increased cardiovascular risk and be less tolerable than recommended options.
Nucleoside reverse transcriptase inhibitors limiting or sparing[h]	Darunavir[e,g] plus raltegravir	BIb	Raltegravir taken twice daily, ritonavir-boosted darunavir taken once daily. Less effective at CD4 cell counts of <200/μL and possibly HIV-1 RNA levels >100 000 copies/mL.
	Lopinavir[g] plus lamivudine	BIa	Single study; comparator nucleoside reverse transcriptase inhibitor included zidovudine (53.9%), tenofovir (36.6%), and abacavir (9.4%), each with lamivudine.
	Lopinavir[g] plus raltegravir	BIa	Both medications taken twice daily; single study with relatively small sample size and low baseline plasma HIV-1 RNA level.

[a] Regimen classes and drugs within these classes are listed in alphabetic order by the anchor (third) drug and not in order of preference. Ratings of the strength of the recommendations and quality of evidence are described in Table 1.

[b] Simultaneous administration with antacids or other medications with divalent cations (Ca^{2+}, Mg++, Al++, Fe++) should be avoided due to chelation of the integrase strand transfer inhibitor by the cation, thereby reducing absorption.

[c] Abacavir has been associated with increased cardiovascular risk, although data are conflicting; use with caution in patients with high cardiovascular risk. Should only be used in HLA-B*5701-negative patients.

[d] Rilpivirine should not be given with proton pump inhibitors and should be taken consistently with a full meal.

[e] Should be taken with food.

[f] US Food and Drug Administration approval of the fixed-dose combination is anticipated in 2014.

[g] Ritonavir-boosted regimen.

[h] Only in certain circumstances (see the NRTI-Sparing Therapy section in text for full explanation).

Recommendations for Changing the ART Regimen in Treatment-Experienced Patients

- Design of a new regimen should consider previous antiretroviral therapy exposure, previous resistance profile, drug interactions, and history of intolerance or toxic effects (AIIa).
- Depending on the resistance profile, viral tropism, and options available for patients with multidrug resistance, inclusion of a boosted protease inhibitor and agents from newer drug classes (eg, an integrase strand transfer inhibitor or maraviroc) should be considered (AIa).

	• Monotherapy with a boosted protease inhibitor is not recommended when other options are available (AIa). • Maintenance of virologic suppression is paramount when switching the regimen to improve tolerability, reduce toxicity, and improve convenience (AIa). Switching or regimen simplification in virologically suppressed individuals is generally safe if prior treatment and resistance profile are considered and full activity of the nucleoside reverse transcriptase inhibitors can be ensured for switches from a ritonavir-boosted protease inhibitor to drugs with low barriers to resistance (nonnucleoside reverse transcriptase inhibitors, unboosted protease inhibitors, or integrase strand transfer inhibitors) (AIa).

Ergänzende Dokumente

Neubert J et al., 2012 [31]. Leitlinie der Pädiatrische Arbeitsgemeinschaft AIDS (PAAD) e.V. zur antiretroviralen Therapie bei HIV-infizierten Kindern und Jugendlichen (2011)	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 Therapieemofehlungen 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

Detaillierte Darstellung der Recherchestrategie

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

#	Suchfrage
	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 Sort by: PublicationDate 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

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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/mm³ (3TC); 392 cells/mm³ (FTC)	None	d4T+NVP/EFV	d4T+NVP/EFV	48 weeks	Antiretroviral naive
Benson et al, 2004	43 sites in the USA	440 patients	42 years	14%	<50 copies/ml	527 cells/mm³	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/mm³ (3TC); 599 cells/mm³ (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/mm³ (3TC); 508 cells/mm³ (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/mm³ (3TC); 193 cells/mm³ (FTC)	None	ABC+LPV/r	TDF+LPV/r	96 weeks	Antiretroviral naive
				20% (FTC)							
Calza et al, 2009	Italy	89 patients	36 years (3TC)	29% (3TC)	<50 copies/ml	658 cells/mm³ (3TC); 611 cells/mm³ (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/mm³	None	ABC+ATV/r or EFV	TDF+ATV/r or EFV	96 weeks	Antiretroviral naive 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/mm³	None	ABC+DTG or RAL	TDF+DTG or RAL	96 weeks	Antiretroviral naive with VL>1000 copies/ml
Martinez et al, 2013	Spain	273 patients	47 years (3TC)	10% (3TC)	<50 copies/ml	515 cells/mm³ (3TC); 487 cells/mm³ (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/mm³	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/mm³	None	ABC+ATV/r	TDF+ATV/r	96 weeks	Antiretroviral naive
Mulenga	Zambia	332 patients	34 years	58%	110,000–130,000 copies/ml	143–169 cells/mm³	None	TDF+EFV	TDF+EFV	48 weeks	Antiretroviral naive

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, nonnucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

doi:10.1371/journal.pone.0079981.t001