HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Oral and parenteral preexposure prophylaxis (PrEP) to prevent HIV in people at risk

A systematic review of clinical effectiveness and safety with assessment of organisational, economic, patient/social, ethical and legal elements

Final report

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List of abbreviations

AIDS .....acquired immunodeficiency syndrome
ART.....antiretroviral therapy/treatment
ARV.....antiretroviral drug
CAB-LA .....long-acting injectable cabotegravir
DBS .....dried blood spot (specimen)
ECDC.....European Centre for Disease Prevention and Control
EEA .....European Economic Area
EMA .....European Medicines Agency
EU .....European Union
FDA.....US Food and Drug Administration
FTC .....emtricitabine
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
HIV.....human immunodeficiency virus
HR.....hazard ratio
IDU .....injecting drug use
INSTI.....integrase strand transfer inhibitor
ISR.....injection site reaction
MSM.....men who have sex with men
NNRTI.....non-nucleoside reverse-transcriptase inhibitor
NRTI.....nucleoside reverse-transcriptase inhibitor
PICO .....population, intervention, comparator, outcome
PLWH.....People living with HIV
PWID .....People who inject drugs
PrEP .....pre-exposure prophylaxis
py.....person-years
RCT.....randomized controlled trial
RR .....rate ratio
SR .....systematic review
STI.....sexually transmitted infection
TAF .....tenofovir alafenamide
TDF.....tenofovir disoproxil fumarate
WHO .....World Health Organization

Glossary

This glossary uses the definitions provided by the WHO guideline [1].

Pre-exposure prophylaxis (PrEP): the use of antiretroviral (ARV) drugs by people who do not have HIV to prevent the acquisition of HIV before exposure.

Men who have sex with men (MSM): refers to all men who engage in sexual relations with other men. The words "men" and "sex" are interpreted differently in diverse cultures and societies and by the individuals involved. Therefore, the term encompasses the large variety of settings and contexts in which male-to-male sex takes place, regardless of multiple motivations for engaging in sex, self-determined sexual and gender identities, and various identifications with any particular community or social group.

People in prisons and other closed settings: Here, the term "prisons and other closed settings" refers to all places of detention within a country, and the terms "prisoners" and "detainees" refer to all those detained in criminal justice and prison facilities, including adult and juvenile males, females, trans and gender diverse individuals, during the investigation of a crime, while awaiting trial, after conviction, before sentencing and after sentencing.

People who inject drugs (PWID): refers to people who inject psychoactive substances for non-medical purposes. These drugs include, but are not limited to, opioids, amphetamine-type stimulants, cocaine and hypno-sedatives, including new psychoactive substances. The injection may be through intravenous, intramuscular, subcutaneous or other injectable routes. People who self-inject medicines for medical purposes – referred to as "therapeutic injection" – are not included in this definition.

Sex workers: include female, male, trans and gender diverse adults (18 years of age and above) who receive money or goods in exchange for sexual services, either regularly or occasionally. Sex work is consensual sex between adults, can take many forms, and varies between and within countries and communities. Sex work also varies in the degree to which it is more or less "formal" or organised. As defined in the Convention on the Rights of the Child (CRC), children and adolescents under the age of 18 who exchange sex for money, goods or favours are "sexually exploited" and not defined as sex workers.

Substantial risk (of HIV infection): HIV acquisition risk varies considerably within populations and geographical locations. Population-level HIV incidence is an important determinant of individual-level risk of HIV acquisition. However, when considering who could benefit from PrEP, it is important to consider the characteristics and behaviours of individuals and their partners that could lead to HIV exposure. Even in locations with a low overall HIV incidence, there may be individuals at substantial risk who could benefit from PrEP services. Individuals requesting PrEP should be given priority when offering PrEP since requesting PrEP indicates that there is likely to be a risk of acquiring HIV.

Trans and gender diverse people: an umbrella term for those whose gender identity, roles and expression do not conform to the norms and expectations traditionally associated with the sex assigned to them at birth; it includes people who are transsexual, transgender, or otherwise gender nonconforming or gender incongruent. Trans and gender diverse people may self-identify as transgender, female, male, transwoman or transman, transsexual or one of many other gender nonconforming identities. They may express their genders in various masculine, feminine and/or androgynous ways. The high vulnerability and specific health needs of trans and gender diverse people necessitate a distinct and independent status in the global HIV response.

Chemsex: when individuals engage in sexual activity while taking primarily stimulant drugs, typically involving multiple participants and over a prolonged period.

Executive Summary

Introduction

A further and substantial reduction in HIV incidence is still needed across European Union (EU) countries if Europe is to meet the Sustainable Development Goals by 2030. A new approach is the implementation of pre-exposure prophylaxis (PrEP). PrEP is an antiretroviral therapy-based HIV prevention strategy to prevent HIV infection in people who have not been infected with the virus but are at high risk of infection. Three pharmaceuticals (two oral and one injectable long-acting) received marketing authorisation in the United States (US) and one oral in the EU for PrEP, including generic equivalents. In addition to a once daily oral PrEP schedule, an event-driven PrEP dosing schedule (as off-label use) is used in real word setting. Several European countries have implemented PrEP in their national health systems. At present, PrEP is available in Austria, but only with a private prescription at a reduced price in a few selected pharmacies. Costs are not reimbursed by the public sector. There is no standardised process regarding monitoring, regular check-ups and follow-up prescriptions.

HIV incidence needs to be further reduced in Europe

new approach: pre-exposure prophylaxis (PrEP) to prevent HIV infection in people at high risk

3 pharmaceuticals (2 oral and 1 injectable)

in Austria currently not reimbursed

This review aims to provide an update evidence synthesis based on a systematic literature search regarding the effectiveness and safety of approved oral and parenteral antiretroviral PrEP in the US (by the Food and Drug Administration, FDA) and/or EU (by the European Medicines Agency, EMA), to prevent HIV infection in populations at risk. The review also addresses potential organisational, economic, patient/social, ethical and legal aspects to support evidence-based decision-making on PrEP in Austria.

update evidence synthesis regarding effectiveness and safety, as well as organisational, economic, patient/social, ethical and legal domains

Methods

Based on two existing systematic reviews (SR), one related to oral PrEP (2019), And the second related to injectable PrEP (2022), an updated systematic literature search was conducted in three databases for clinical effectiveness and safety on oral and injectable PrEP. SRs and randomised controlled trials (RCTs) published between 07/2020 and 11/2022 were included. Data extraction and quality assessment of the identified studies were performed by two researchers. The new evidence was described narratively. The strength of the evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Three clinical trial registries were searched for ongoing RCTs.

updated systematic literature search based on 2 already existing systematic reviews

data extraction, quality assessment, GRADE

search for ongoing studies in registries

The selection of assessment elements for potential organisational, economic, patient/social, ethical and legal aspects was based on the EUnetHTA Core Model® Version 3.0. Literature search for these domains was undertaken through a non-systematic literature search, and no quality assessment tool was used. To contextualise and better understand the issue from the user's perspective, a call for patient input was sent to relevant patient organisations in Austria in January 2023 to provide answers to questions related to the impact of HIV, experience with currently available interventions for HIV prevention and expectations of/requirements for PrEP, from the perspectives of people at risk of HIV and HIV patients and/or caregivers.

assessment of other domains based on EUnetHTA Core Model®

questionnaire for Austrian patient organisations

Results

Clinical effectiveness and safety

4 new RCTs identified

In addition to the already published SRs, we identified four new RCTs through the update literature search. High-quality evidence from a total of 17 RCTs demonstrated that oral PrEP (tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)) is highly effective at preventing HIV infection in men who have sex with men (MSM) and serodiscordant couples. PrEP effectiveness is rising with increased adherence. One trial with high adherence found PrEP to be effective in preventing HIV infections in heterosexuals but was not effective in trials with low adherence. One study found that oral PrEP was effective in people who inject drugs. On-demand oral PrEP regimen was highly effective at preventing HIV infection in MSM. Daily tenofovir alafenamide (TAF, approved by FDA, but not EMA) has proven non-inferior efficacy to daily TDF for HIV prevention in MSM. Oral PrEP was found to be safe, and there was no difference in adverse event rates comparing single-agent tenofovir with tenofovir/FTC in combination. Some studies noted a transient elevation of creatinine which resolved after the study drug was discontinued. TAF has better renal and bone safety compared to TDF but is associated with small increases in weight.

oral PrEP (TDF/FTC) effective at HIV prevention in MSM and serodiscordant couples; less evidence for other groups, e.g., heterosexuals, people who inject drugs

on-demand use also effective in MSM

TAF non-inferior to TDF in MSM

injectable PrEP also safe and effective in MSM, transgender women who have sex with men, and women

High-quality evidence from two large RCTs demonstrated that injectable long-acting cabotegravir (not yet EMA approved) is safe and highly effective at preventing HIV infection in MSM, transgender women who have sex with men, and women. Most reported injection site reactions were mild, and event rates decreased over the course of the study. There were no studies identified related to effectiveness and safety in sex workers, people who inject drugs or other groups at risk.

drug resistance mutations can (rarely) occur

no changes in sexual behaviour or STI rates in clinical trials

While uncommon, viral drug resistance mutations may occur during oral and injectable PrEP. In clinical studies, PrEP did not alter sexual behaviour or lead to a rise in sexually transmitted infection (STI) diagnoses. Quality of life was not assessed in any of the included trials. No differences were found in pregnancy or perinatal outcomes associated with oral or injectable PrEP exposure.

Other key aspects related to PrEP and its implementation

oral PrEP (TDF/FTC) cost-effective or cost-saving in several developed countries

TAF/FTC not cost-effective; mixed results for injectable PrEP

Cost-effectiveness and modelling analyses support the cost-effectiveness or even cost-saving of oral PrEP containing TDF/FTC as a prevention strategy in several developed countries. Estimates of cost-effectiveness were dependent on the effectiveness and adherence of PrEP, the incidence of HIV, the cost of PrEP, the reduction in price due to generics and the lifetime cost of HIV. According to US data, branded TAF/FTC, compared to generic TDF/FTC, was not cost-effective, even in populations at the highest risk for TDF/FTC adverse events. Results of economic evaluations are mixed related to long-acting injectable cabotegravir PrEP compared to daily oral TDF/FTC.

PrEP as part of testing, prevention and treatment services, different settings & providers can be involved

PrEP programmes involve regular HIV testing, screening for other STIs, supporting adherence, advice on safer sex practices, counselling for individuals at substantial risk of infection and linking to treatment services for people with a positive HIV test before starting PrEP or seroconverting while using PrEP. PrEP should be offered as part of a comprehensive testing, prevention and treatment service. Different settings and healthcare providers can be involved in PrEP service delivery.

acceptance and interest to use PrEP of potential users

Potential users have acknowledged the drug's effectiveness and expressed a high willingness to use it, including injectables for PrEP, which have so far not been approved in Europe. Certain key populations, such as people who inject drugs, prisoners and undocumented migrants, still remain ineligible for PrEP. Pregnant and breastfeeding populations, as well as children and adolescents, are underrepresented in clinical trials of new PrEP pharmaceuticals. Many barriers on different levels (individual, healthcare provider, healthcare system) exist which need to be actively addressed in order to decrease inequalities. Austrian patient organisations report that stigma, including self-stigma, discrimination and social exclusion, are still present in the context of HIV/AIDS, and these factors also hugely affect PrEP uptake. Financial issues have been mentioned as an important barrier. This not only includes the cost of the drug itself but also travelling expenses (and time) if there is no PrEP prescribing service nearby.

many barriers need to be addressed, e.g.

stigma and discrimination, financial barriers

not reimbursing PrEP may increase health inequalities

Various guidelines based on high-quality evidence have clearly recommended to implement PrEP into national HIV prevention programmes. Not reimbursing PrEP restricts access to high-income and highly educated groups, thus substantially increasing health inequalities in often already vulnerable and disadvantaged groups.

Conclusion

reimbursement of oral drug (TDF/FTC) recommended, but several aspects to be considered for implementation

Based on the international findings on the benefit of the drug but also for equity and ethical reasons, we recommend reimbursement of daily oral PrEP (TDF/FTC) for Austria. However, the following aspects need to be considered in case of a reimbursement decision for PrEP: A thorough implementation concept is needed, addressing activities beyond prescribing the drug. PrEP needs to be offered as part of a comprehensive testing, prevention and treatment service, according to current guidelines, with clear responsibilities and pathways. The setting for PrEP service delivery should be easily accessible and accepted by different key populations. Current regional disparities need to be reduced. Appropriate training and further education of health care professionals are crucial, also targeting communication skills. Specific efforts are necessary to provide information and raise awareness among specific populations at risk, e.g., MSM with migration background or low income, women and heterosexual men at high risk for HIV infection (e.g., sex workers). A monitoring system has to be set up so that an evaluation of the programme can be conducted.

e.g., PrEP integration into other services, easily accessible settings, training and education, specific efforts to reach target groups, monitoring system

costs will incur beyond drug cost, while monetary benefits will occur later

Implementing PrEP according to evidence-based recommendations will incur costs beyond PrEP drug costs in the short term, while monetary benefits (e.g., reduced costs for treatment of HIV-infections) will occur later. Since responsibilities for reimbursing, implementing and monitoring are currently unclear in Austria, these responsibilities and related coordination activities need to be defined before reimbursement decisions are made.

injectable PrEP & oral TAF/FTC as potential additional options in case of marketing authorisation

Long-acting injectable cabotegravir may be offered in the future, in the case of marketing authorisation in the EU, as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches. The same is true for oral TAF/FTC, but probably just for those with serious renal or bone adverse events, due to the current high price of branded formulation, without available generic equivalents.

on-demand use of oral PrEP as off-label use

According to the recently published WHO guideline, so-called on-demand (intermittent) use of oral PrEP (off-label use) can be used to prevent the sexual acquisition of HIV by cisgender men and trans and gender-diverse people assigned male at birth who are not taking exogenous estradiol-based hormones. The German-Austrian HIV PrEP consensus guideline stated that such a regime may be considered for specific cases.

Zusammenfassung

Hintergrund

neuer Ansatz für Reduktion der HIV-Inzidenz: PrEP für Personen mit hohem Infektionsrisiko

Wenn Europa die Ziele für nachhaltige Entwicklung in Bezug auf HIV/AIDS bis 2030 erreichen will, muss die HIV-Inzidenz in den Ländern der Europäischen Union (EU) weiter deutlich gesenkt werden. Ein neuer Ansatz ist die Implementierung der Prä-Expositionsprophylaxe (PrEP). Die PrEP ist eine auf einer antiretroviralen Therapie basierende HIV-Präventionsstrategie zur Verhinderung einer HIV-Infektion bei Menschen, die nicht mit dem Virus infiziert sind, aber ein hohes Infektionsrisiko haben. In den USA sind bisher drei verschiedene Arzneimittel für die PrEP zugelassen, in der EU eines (sowie entsprechende Generika):

USA: 3 verschiedene Präparate (2 oral, 1 Injektion) zugelassen, EU: 1 orales Medikament + Generika

- Emtricitabin (FTC) 200 mg in Kombination mit Tenofovir-Disoproxilfumarat (TDF) 300 mg (TDF/FTC, Markenname Truvada®) oder generische Äquivalente von verschiedenen Herstellern), 1 Tablette täglich; in EU und USA zugelassen,
- Emtricitabin (FTC) 200 mg in Kombination mit Tenofovir-Alafenamid (TAF) 25 mg (TAF/FTC, Markenname Descovy®), 1 Tablette täglich; in USA zugelassen,
- Cabotegravir (CAB) 600 mg (Markenname Apretude®), intramuskuläre Injektion alle 2 Monate; in USA zugelassen, in EU derzeit EMA-Verfahren zur Zulassung laufend.

neben täglicher PrEP auch anlassbezogene Dosierung als „off-label use" möglich

Neben der einmal täglichen oralen PrEP wird in der Praxis ein anlassbezogenes PrEP-Dosierungsschema angewandt. Diese Anwendung ist außerhalb der Zulassung („off-label use"). Dabei werden 2-24 Stunden vor dem Geschlechtsverkehr zwei Tabletten eingenommen, gefolgt von einer Tablette 24 Stunden und eine weitere 48 Stunden nach den ersten beiden Tabletten (2+1+1 Schema).

PrEP in mehreren europäischen Ländern verfügbar

Ö: Generika auf Privatrezept in ausgew. Apotheken zu reduzierten Preisen erhältlich

Mehrere europäische Länder haben die PrEP in ihr nationales Gesundheitssystem aufgenommen und erstatten deren Kosten. Derzeit ist die PrEP in Österreich erhältlich, allerdings nur auf Privatrezept und zu einem reduzierten Preis in einigen ausgewählten Apotheken. Die Kosten werden vom öffentlichen Sektor nicht erstattet. Die Prozesse für Monitoring, regelmäßige Kontrolluntersuchungen und Folgerezepte orientieren sich an der deutsch-österreichischen Leitlinie; es gibt jedoch keine einheitlichen österreichischen Standards. Vor der Verschreibung der PrEP sind eine ausführliche Beratung und Anamnese sowie bestimmte Labortests erforderlich, z. B. Tests auf HIV, Hepatitis B, Gonorrhoe, Chlamydien, Syphilis, und eine Beurteilung der Nierenfunktion. Laut Informationen aus zwei Kohortenstudien gibt es derzeit in Österreich rund 3.000 PrEP-Nutzer*innen.

Ziel des Berichts: Evidenzsynthese zu Wirksamkeit und Sicherheit der PrEP

auch organisatorische, ökonomische, soziale, ethische, rechtliche Aspekte

Ziel dieser Übersichtsarbeit ist es, eine aktuelle Evidenzsynthese auf Basis einer systematischen Literaturrecherche zur Wirksamkeit und Sicherheit der in den USA (von der „Food and Drug Administration", FDA) und/oder der EU (von der „European Medicines Agency", EMA) zugelassenen oralen und parenteralen (injizierbaren) antiretroviralen PrEP zur Prävention von HIV-Infektionen in Risikogruppen zu erstellen. Der Bericht befasst sich auch mit potenziellen organisatorischen, ökonomischen, patient*innenbezogenen/sozialen, ethischen und rechtlichen Aspekten, um eine evidenzbasierte Entscheidungsfindung zur PrEP in Österreich zu unterstützen.

Methoden

aktualisierte systematische Literatursuche basierend auf 2 SRs

Datenextraktion, Bias-Risiko, GRADE

Suche in Studienregistern nach laufenden RCTs

Auf der Grundlage zweier bestehender systematischer Übersichtsarbeiten (systematic review, SR), von denen sich eine auf die orale PrEP (2019) und die zweite auf die injizierbare PrEP (2022) bezog, wurde eine aktualisierte systematische Literatursuche in drei Datenbanken zur klinischen Wirksamkeit und Sicherheit der oralen und injizierbaren PrEP durchgeführt. Eingeschlossen wurden SRs und randomisierte kontrollierte Studien (randomised controlled trial, RCT), die zwischen Juli 2020 und November 2022 veröffentlicht wurden. Die Datenextraktion und Qualitätsbewertung der identifizierten Studien wurde von zwei Wissenschafterinnen durchgeführt. Die neue Evidenz wurde narrativ beschrieben. Die Stärke der Evidenz wurde anhand von GRADE (Grading of Recommendations, Assessment, Development and Evaluation) bewertet. Es wurden weiters drei Register für klinische Studien nach laufenden RCTs durchsucht.

Auswahl weiterer Aspekte anhand EUnetHTA Core Model®, nicht-systematische Suche

Fragebogen an österr. Patient*innen-organisationen

Die Auswahl der Bewertungselemente für potenzielle organisatorische, ökonomische, patient*innenbezogene/soziale, ethische und rechtliche Aspekte erfolgte auf der Grundlage des EUnetHTA Core Model® Version 3.0. Die Literaturrecherche für diese Bereiche erfolgte durch eine nicht-systematische Literatursuche, und es wurde kein Qualitätsbewertungsinstrument verwendet. Zur Kontextualisierung und zum besseren Verständnis des Themas aus der Sicht der Nutzer*innen wurde im Januar 2023 ein Fragebogen an relevante Patient*innenorganisationen in Österreich versandt, um Antworten auf Fragen im Zusammenhang mit den Auswirkungen von HIV, den Erfahrungen mit derzeit verfügbaren HIV-Präventionsmaßnahmen und den Erwartungen/Anforderungen an die PrEP aus der Sicht von Menschen mit HIV-Risiko und HIV-Patient*innen und/oder Betreuer*innen zu erhalten.

Ergebnisse

Wirksamkeit und Sicherheit

4 neue RCTs durch Update-Suche

insgesamt 17 RCTs zu oraler PrEP → TDF/FTC wirksam in Bezug auf HIV-Prävention, v. a. bei MSM und serodiskordanten Paaren

anlassbezogene PrEP ebenfalls wirksam bei MSM

Zusätzlich zu den bereits veröffentlichten Studien wurden durch die aktualisierte Literatursuche vier neue RCTs identifiziert. Qualitativ hochwertige Evidenz aus insgesamt 17 RCTs (alle Studienpopulationen) zeigt, dass die orale PrEP (TDF/FTC) bei Männern, die Sex mit Männern haben (MSM), und serodiskordanten Paaren (d. h. ein/e Partner*in ist HIV-positiv, der/die andere HIV-negativ) eine hohe Wirksamkeit bei der Prävention von HIV-Infektionen aufweist. Bei MSM zeigt eine Meta-Analyse des bereits publizierten SR eine Rate Ratio (RR) von 0,25 (95 % CI 0,1-0,61), was auf eine 75-%ige Reduktion der HIV-Infektionsrate hinweist (hohe Vertrauenswürdigkeit der Evidenz nach GRADE). Betrachtet man nur jene Studien, bei denen eine hohe Adhärenz (d. h. Einhalten des Medikationsschemas) von ≥80 % erreicht wurde, beträgt die RR 0,14 (95 % CI 0,06-0,35), d. h. 86 % Reduktion der HIV Infektionsrate (hohe Vertrauenswürdigkeit der Evidenz). Bei serodiskordanten Paaren betrug die Reduktion der HIV-Infektionsrate ebenfalls 75 % (RR 0,25, 95 % CI 0,14-0,46, hohe Vertrauenswürdigkeit der Evidenz). In einer Studie mit hoher Adhärenz erwies sich die PrEP als wirksam bei der Prävention von HIV-Infektionen bei heterosexuellen Studienteilnehmer*innen (RR 0,39, 95 % CI 0,18-0,83; 61 % Reduktion der HIV-Infektionsrate, nur bei Männern signifikant), während sie in Studien mit geringer Adhärenz nicht wirksam war. Eine Studie ergab, dass die orale PrEP bei Menschen, die Drogen injizieren, wirksam ist (RR 0,51, 95 % CI 0,29-0,92; 49 % Reduktion der HIV-Infektionsrate). Die anlassbezogene orale PrEP war bei der Prävention von HIV-Infektionen bei MSM ebenfalls wirksam.

TAF/FTC nicht weniger wirksam als TDF bei MSM

Täglich verabreichtes TAF/FTC (von der FDA, aber nicht von der EMA zugelassen) hat sich in der HIV-Prävention bei MSM als nicht weniger wirksam erwiesen als tägliches TDF (HIV incidence rate ratio, IRR 0,54; 95 % CI 0,23-1,26; moderate Vertrauenswürdigkeit der Evidenz). Die orale PrEP erwies sich als sicher, und es gab keinen Unterschied bei den Nebenwirkungsraten im Vergleich zwischen Tenofovir als Einzelwirkstoff und Tenofovir/FTC in Kombination. In einigen Studien wurde ein vorübergehender Anstieg des Nierenfunktionsparameters Kreatinin festgestellt, der sich nach Absetzen des Studienmedikaments wieder zurückbildete. TAF weist im Vergleich zu TDF bessere Sicherheits-Outcomes bei Nieren- und Knochenparametern auf, ist jedoch mit einer leichten Gewichtszunahme verbunden.

2 RCTs: injizierbare PrEP (CAB) sicher & wirksam in Bezug auf HIV-Prävention bei MSM, trans Frauen, die Sex mit Männern haben, & cis Frauen

Zwei große RCTs haben gezeigt, dass langwirksames Cabotegravir (noch nicht von der EMA zugelassen), das mittels Injektion alle zwei Monate verabreicht wird, sicher und wirksam bei der Prävention von HIV-Infektionen bei MSM und trans Frauen, die Sex mit Männern haben (Hazard Ratio, HR 0,34; 95 % CI 0,18-0,62; $p<0,001$, zugunsten der CAB-Gruppe), und Frauen (HR 0,12; 95 % CI 0,05-0,31; $p<0,0001$, zugunsten der CAB-Gruppe) ist (hohe Vertrauenswürdigkeit der Evidenz nach GRADE). Die meisten gemeldeten Reaktionen an der Injektionsstelle waren leicht, und die Häufigkeit der Ereignisse nahm im Laufe der Studie ab. Es wurden keine Studien zur Wirksamkeit und Sicherheit bei Sexarbeiter*innen, Menschen, die Drogen injizieren, oder anderen Risikogruppen identifiziert.

Resistenzmutationen können (selten) auftreten

keine Veränderung des Sexualverhaltens oder der STI-Rate in klin. Studien

Obwohl selten, können bei der oralen und injizierbaren PrEP Arzneimittelresistenzmutationen auftreten. In klinischen Studien veränderte die PrEP weder das Sexualverhalten noch führte sie zu einem Anstieg der Diagnosen von sexuell übertragbaren Infektionen (STI). Die Lebensqualität wurde in keiner der eingeschlossenen Studien untersucht. Es wurden bisher keine Unterschiede bei den Schwangerschafts- oder Geburts-Outcomes gefunden, die mit der oralen oder injizierbaren PrEP-Exposition zusammenhängen; weitere Daten aus Surveillance-Programmen oder Registern sind erforderlich, um die Sicherheit der PrEP in der Schwangerschaft und Stillzeit zu beurteilen.

Weitere wichtige Aspekte im Zusammenhang mit der PrEP und ihrer Umsetzung

PrEP als Teil eines umfassenden Test-, Präventions- und Behandlungsdienstes

PrEP-Programme umfassen regelmäßige HIV-Tests, Screening auf andere STIs, Unterstützung der Adhärenz, Informationen zu Safer-Sex-Praktiken, Beratung für Personen mit erheblichem Infektionsrisiko und Anbindung an Behandlungsdienste für Personen mit positivem HIV-Test vor Beginn der PrEP oder bei Serokonversion während der Anwendung der PrEP. Es wird empfohlen, die PrEP als Teil eines umfassenden Test-, Präventions- und Behandlungsdienstes anzubieten. Verschiedene Einrichtungen und Gesundheitsdienstleister*innen können an der Erbringung von PrEP-Dienstleistungen beteiligt sein.

Monitoring-System zur Erhebung und Auswertung von Basis-Daten

Ein Monitoring-System wird in den internationalen Dokumenten empfohlen, damit gewisse Basisdaten erhoben und ausgewertet werden können, z. B. zu Personen, die PrEP nehmen, zum Absetzen der PrEP, zu Durchbruchsinfektionen, STI-Raten und Arzneimittelresistenzen. Bei der Entwicklung eines Implementierungskonzepts kann auch auf Erfahrungen und Berichten aus anderen Ländern (z. B. Deutschland) zurückgegriffen werden.

Identifizierung von Kostenkategorien, zusätzlich zu den Kosten für das Medikament

Kurzfristig fallen daher zusätzlich zu den Medikamentenkosten eine Reihe weiterer Kosten für Beratung, Risikoassessment, Testung auf HIV und andere STIs, Erhebung diverser Laborparameter vor und während der PrEP-Einnahme, sowie weitere Kosten im Zusammenhang mit der Implementierung des PrEP-Programms (z. B. Aus- und Fortbildung, Entwicklung von Versorgungspfaden, Errichtung eines Monitoring-Systems, spezifische Interventionen zur Erreichung der Zielgruppen) an.

orale PrEP (TDF/FTC) kosteneffektiv oder sogar kostensparend in mehreren Ländern

TAF/FTC nicht kosteneffektiv, für injizierbare PrEP uneinheitliche Ergebnisse

Mittelfristig zeigen die internationalen Kosteneffektivitäts- und Budgetfolgenanalysen aus mehreren Ländern des globalen Nordens, dass PrEP mit TDF/FTC kosteneffektiv oder sogar kosteneinsparend sein kann. Die Schätzungen der Kosteneffektivität waren abhängig von der Wirksamkeit und der Adhärenz der PrEP, der HIV-Inzidenz, den Kosten der PrEP, der Preissenkung durch Generika und den Lebenszeitkosten von HIV. Daten aus den USA zufolge war TAF/FTC als Markenpräparat im Vergleich zu TDF/FTC-Generika nicht kosteneffektiv, auch nicht in Bevölkerungsgruppen mit dem höchsten Risiko für TDF/FTC-Nebenwirkungen. Die Ergebnisse der ökonomischen Evaluationen in Bezug auf die injizierbare PrEP (Cabotegravir) im Vergleich zu täglich oralem TDF/FTC sind uneinheitlich. Die Ergebnisse von ökonomischen Evaluationen aus anderen Ländern können nicht direkt auf Österreich übertragen werden, aber aufgrund der einheitlichen Resultate zur Kosteneffektivität in anderen Ländern ist die Wahrscheinlichkeit hoch, dass die Ergebnisse für Österreich ähnlich wären.

Akzeptanz und Interesse der potentiellen Nutzer*innen

aktives Adressieren der zahlreichen Barrieren, z. B.

Stigmatisierung, Diskriminierung, finanzielle Barrieren

Potenzielle Nutzer*innen haben die Wirksamkeit des Medikaments anerkannt und eine hohe Bereitschaft bekundet, es zu verwenden. Dies gilt auch für die injizierbare PrEP (bisher in Europa nicht zugelassen), deren Vorteil v. a. im Wegfallen der täglich notwendigen Medikamenteneinnahme gesehen wird. Bestimmte Populationen, wie Menschen, die Drogen injizieren, Häftlinge und undokumentierte Migrant*innen, haben nach wie vor keinen Zugang zur PrEP. Schwangere und stillende Bevölkerungsgruppen sowie Kinder und Jugendliche sind in klinischen Studien zu neuen PrEP-Präparaten unterrepräsentiert. Es gibt viele Barrieren auf verschiedenen Ebenen (Individuum, Gesundheitsdienstleister, Gesundheitssystem), die aktiv adressiert werden müssen, um Ungleichheiten zu verringern. Österreichische Patient*innenorganisationen berichten, dass Stigmatisierung, einschließlich Selbststigmatisierung, Diskriminierung und soziale Ausgrenzung im Zusammenhang mit HIV/AIDS nach wie vor präsent sind und dass diese Faktoren auch die Nutzung der PrEP stark beeinflussen. Finanzielle Aspekte wurden als ein wichtiges Hindernis genannt. Dazu gehören nicht nur die Kosten für das Medikament selbst, sondern auch die Kosten für die notwendigen Tests sowie die Reisekosten (und der Zeitaufwand), wenn es in der Nähe des Wohnorts keine Möglichkeit zur Verschreibung der PrEP gibt.

Nicht-Erstattung der PrEP verstärkt potentiell gesundheitliche Ungleichheit

In verschiedenen Leitlinien, die sich auf hochwertige Evidenz stützen, wird klar empfohlen, die PrEP in nationale HIV-Präventionsprogramme aufzunehmen. Die Nicht-Erstattung der PrEP begrenzt den Zugang auf Gruppen mit hohem Einkommen und hohem Bildungsstand, wodurch die gesundheitlichen Ungleichheiten in häufig ohnehin schon gefährdeten und benachteiligten Gruppen erheblich verstärkt werden.

Conclusio

Erstattung des Medikaments empfohlen, aber mehrere Aspekte müssen bei Implementierung berücksichtigt werden

Basierend auf den internationalen Ergebnissen zum Nutzen des Medikaments, aber auch aus Gerechtigkeits- und ethischen Gründen, wird die Erstattung der täglichen oralen PrEP mit TDF/FTC für Österreich empfohlen. Bei einer Entscheidung über die Erstattung der PrEP sind jedoch folgende Aspekte zu berücksichtigen: Es bedarf eines umfassenden Implementierungskonzepts, das über die Verschreibung des Medikaments hinausgeht. Die PrEP ist als Teil eines umfassenden Test-, Präventions- und Behandlungsangebots gemäß den aktuellen Leitlinien zu betrachten. Das Setting für die Bereitstellung der PrEP sollte leicht zugänglich sein und von den verschiedenen Bevölkerungsgruppen akzeptiert werden. Die derzeitigen regionalen Ungleichheiten müssen abgebaut werden. Eine angemessene Aus- und Weiterbildung des Gesundheitspersonals ist von entscheidender Bedeutung, auch im Hinblick auf die Kommunikationsfähigkeiten. Besondere Maßnahmen sind erforderlich, um bestimmte Risikogruppen zu informieren und zu sensibilisieren, z. B. MSM mit Migrationshintergrund oder geringem Einkommen, Frauen und heterosexuelle Männer mit hohem HIV-Infektionsrisiko (z. B. Sexarbeiter*innen). Ein Monitoring-System ist nötig, damit eine Evaluierung des Programms durchgeführt werden kann.

z. B. Integration der PrEP in andere Dienste, Niederschwelligkeit, Aus- und Fortbildung, spezifische Maßnahmen zur Erreichung der Zielgruppen, Monitoring-System

kurzfristig Kosten, später monetärer Nutzen

Die Umsetzung der PrEP entsprechend den evidenzbasierten Empfehlungen wird kurzfristig Kosten verursachen, die über die Kosten der PrEP-Medikamente hinausgehen, während der monetäre Nutzen (z. B. geringere Kosten für die Behandlung von HIV-Infektionen) erst später eintreten wird. Da die Zuständigkeiten für die Kostenerstattung, die Durchführung und das Monitoring in Österreich derzeit unklar sind, sollten Zuständigkeiten und die damit verbundenen Koordinationstätigkeiten definiert werden, bevor Entscheidungen über die Kostenerstattung getroffen werden.

Klärung von Zuständigkeiten

injizierbare PrEP und orales TAF/FTC als mögliche zusätzliche Optionen im Falle einer Zulassung

Langwirksames injizierbares Cabotegravir könnte im Falle einer Marktzulassung in der EU in Zukunft als zusätzliche Präventionsmöglichkeit für Menschen mit hohem HIV-Infektionsrisiko im Rahmen von kombinierten Präventionskonzepten angeboten werden. Dasselbe gilt für die orale Einnahme von TAF/FTC, allerdings ist aufgrund des derzeit hohen Preises der Markenpräparate und der fehlenden Generika zunächst eine Einschränkung auf Personen mit schweren Nieren- oder Knochenerkrankungen empfehlenswert.

anlassbezogene PrEP als „off-label use“

Laut der kürzlich veröffentlichten WHO-Leitlinie kann die so genannte „on-demand“ (anlassbezogene) Anwendung der oralen PrEP (als „Off-Label-Use“) zur Verhinderung einer sexuellen Ansteckung mit HIV durch cisgender-Männer und trans- und gender-diverse Menschen, die bei der Geburt als männlich eingestuft wurden und keine exogenen Hormone auf Östradiolbasis einnehmen, eingesetzt werden. In der deutsch-österreichischen HIV-PrEP-Konsensus-Leitlinie wird ausgeführt, dass ein solches Vorgehen in bestimmten Fällen in Betracht gezogen werden kann.

1 Background

1.1 Epidemiology and current status of pre-exposure prophylaxis (PrEP) in Austria

Österreich 2020: ca. 7.725-8.350 Personen leben mit HIV; ca. 400-500 Neuinfektionen pro Jahr (Schätzung)

Übertragung: heterosex. Kontakt (35 %), *men who have sex with men* (MSM; 45 %), Drogen (14 %)

As HIV infection is not subject to compulsory registration in Austria, data on HIV/AIDS are mainly derived from the Austrian HIV cohort study or the number of HIV-positive persons reported annually to the national reference laboratory for HIV/AIDS [2]. According to the report of the Austrian HIV cohort study, it is estimated that between 7,725 to 8,350 people were living with HIV in Austria at the end of 2020 [3]. This corresponds to about 0.1% of the population, with 400-500 new HIV infections being diagnosed per year [2]. The report of the Austrian HIV cohort study states that 6,516 HIV infections were newly diagnosed in Austria between 2001 and 2021. The infections occurred in 35.0% through heterosexual transmission, in 44.5% through MSM (Men who have sex with men), and in 14.3% through IDU (Injecting Drug Use) [3].

90-90-90 Ziele teilweise erfüllt

hohe Testraten, aber viele Spätdiagnosen

According to an ECDC report, Austria has met the first two targets of the 90-90-90 strategy (90% of people living with HIV diagnosed, 90% of those diagnosed on anti-retroviral therapy [ART], 90% of those on treatment virally suppressed), but not the third target (90% of people on ART are virally suppressed) [4]. Although Austria has one of the highest rates of HIV tests in Europe (75 tests per year per 1,000 people), more than 40% of patients are diagnosed late[1] [3].

Präexpositionsprophylaxe (PrEP): Generika in Ö mit Privatrezept für ca. 60€/Monat erhältlich, keine öffentliche Refundierung

At present, pre-exposure prophylaxis (PrEP) is available in Austria, but only with a private prescription at a reduced price[2] in a few selected pharmacies (approx. 60 euros/month). Costs are not reimbursed by the public sector. The processes regarding the monitoring, regular check-ups and follow-up prescriptions are based on the German-Austrian guideline, but are discussed individually and may differ between PrEP providers. Before PrEP is prescribed, detailed counselling and anamnesis are necessary, as well as certain laboratory tests, such as tests for HIV and hepatitis B, check-up for sexually transmitted infections (STI; gonorrhoea, chlamydia and syphilis) and the assessment of renal parameters [2, 5].

Zahlen zu PrEP-Nutzer*innen in Ö aus 2 Kohortenstudien: insgesamt rund 3.000 Personen

There are no detailed official statistics on the number of current PrEP users in Austria. However, there are two cohort studies involving people living with HIV but also people using PrEP: the Austrian HIV cohort study reports data from 941 men and 16 women who were taking PrEP on the reference date 1st of March in the year 2022 [6][3]. Another cohort study is being conducted by the 'Austrian Society of Resident Doctors for the Care of HIV-Infected Persons' ("Österreichische Gesellschaft niedergelassener Ärzte zur Betreuung HIV-

[1] 'Late' diagnosis is defined as: CD4 cell count below 350 at time of HIV diagnosis and/or AIDS within 3 months of HIV diagnosis [3].

[2] The reduced price was achieved through negotiations between the Marienapotheke in Vienna and generics manufacturers, following the example of a German pharmacy, see: https://www.marienapo.eu/hiv/hiv-news/2017/prep-in-oesterreich-sandoz-in-kooperation-mit-marien-apotheke/, accessed 01/03/2023.

[3] There is no information on whether these people use daily or on-demand PrEP.

Infizierter", ÖGNA) that involves a total of 2,072 PrEP users in Austria in 2022 of which 1,139 take PrEP daily and 933 'on demand' [7][4].

Liste von PrEP-verschreibenden Ärzt*innen (Ambulanzen, niedergelassene Ärzt*innen unterschiedlicher Fachrichtungen)

The Austrian AIDS Society provides a list of PrEP-prescribing doctors in Austria who have good expertise on the topic of HIV, other sexually transmitted infections and the use of PrEP according to international recognized standards. The list currently (March 2023) involves a total of 28 doctors and hospital clinics, half of which (15) are located in Vienna. The list involves ten outpatient units ('Ambulanz') in hospitals (with different specialisations, e.g., dermatology, infectious diseases, internal medicine) and one outpatient clinic (not attached to a hospital) specifically for people with substance use disorders, six doctors specialised in dermatology and sexually transmitted diseases ('Fachärzt*in für Haut- und Geschlechtskrankheiten'), five general practitioners, four internists and two pulmonologists[5]. Furthermore, the Austrian AIDS Society offers PrEP training for doctors with 3 modules on PrEP medicines and dosing schedules; HIV (epidemiology, symptoms of acute HIV infection, diagnostics), and STIs and immunisations [5].

1.2 Overview of the HIV/AIDS and HIV preventive measures including PrEP in Europe

EU: 90-90-90 Ziele nicht durchgängig erreicht

weitere Reduktion der HIV Inzidenz notwendig

Fokus auf Prävention, z. B. PrEP

According to the European Centre for Disease Prevention and Control (ECDC), the 90-90-90 target set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) has not been met consistently across countries from the European Union (EU)/European Economic Area (EEA) [8]. A further and substantial reduction in HIV incidence is needed if Europe is to meet the Sustainable Development Goals by 2030. Reaching these goals requires a sustained focus on HIV prevention, including new interventions and approaches, including the implementation of PrEP and clear minimum standards for standardised delivery and monitoring of PrEP across the EU/EEA. PrEP is an antiretroviral therapy-based HIV prevention strategy to prevent HIV infection in people who have not been infected with the virus but are at high risk of infection [9].

WHO Europäische Region: in 23 (von 55) Ländern wird PrEP öffentlich finanziert, in 15 Ländern Generika erhältlich, aber keine (vollständige) Kostenübernahme

In 2015, ECDC recommended that the EU/EEA countries should consider integrating PrEP into their existing HIV-prevention packages for those most at risk of HIV infection, starting with men who have sex with men, based on several high-quality clinical trials results [10]. In 2022, 23 (of 55) countries in the WHO European Region reported that PrEP was available from their national health service, either through insurance or paid by the public sector. Fifteen countries reported that generic PrEP was available in healthcare settings, although it is not fully reimbursed. In Austria, PrEP is available, but the costs are not reimbursed by the public sector [11].

[4] There is no further information on the methodology of this study nor on the characteristics of the PrEP users, e.g., sex.

[5] One specialist for sexually transmitted diseases and one pulmonologist are also general practitioners

global: PrEP-Implementierung unzureichend, bzw. häufig ungleicher Zugang

Implementation of PrEP globally has been inadequate; this is especially the case for inequalities in uptake, which can be observed even in countries with comprehensive PrEP access. If countries want to pursue PrEP as a prevention strategy, various barriers need to be overcome, both at country level (establishment of a 'PrEP-friendly' health system) and at individual level (such as low awareness, low willingness to use PrEP, and the gap between self-perceived and actual HIV risk) [12].

mehrere Dokumente des ECDC zur Unterstützung der Implementierung

ECDC has undertaken several actions to guide EU/EEA countries in their PrEP implementation efforts, such as the development of operational guidance "HIV Pre-Exposure Prophylaxis in the EU/EEA and the UK: implementation, standards and monitoring" [9] as well as ECDC Technical report "Monitoring HIV pre-exposure prophylaxis programmes in the EU/EEA" [13].

versch. Präparate: orale PrEP, vaginaler Ring, injizierbare PrEP

Today, not only oral PrEP (daily or event-driven PrEP) is available. The Dapivirine vaginal ring is intended for use outside the EU for cisgender[6] women at substantial risk of HIV. Long-acting injectable cabotegravir, as an additional new option, has the potential to increase uptake and effective use of PrEP, and HIV prevention overall, as it allows people to choose a method that they prefer [1, 14].

Kosteneffektivitätsstudien & Modellierungen

In developed countries, several already published cost-effectiveness and modelling analyses support the cost-effectiveness of oral PrEP as a prevention strategy, especially among MSM [15].

1.3 Recommendations from international and national guidelines

Empfehlungen der WHO-Leitlinien (2022)

In their latest guidelines published in 2022 [1], the World Health Organization (WHO) recommends the following for pre-exposure prophylaxis for HIV:

> **Oral PrEP (containing tenofovir disproxyl fumarate) should be offered** as an additional prevention choice for **people at substantial risk of HIV infection** as part of combination HIV prevention approaches (**strong recommendation, high certainty of evidence**) [16].
>
> The **dapivirine vaginal ring may be offered** as an additional prevention choice for **cisgender women at substantial risk of HIV infection** as part of combination prevention approaches (**conditional recommendation, moderate certainty of evidence**) [16].
>
> **Long-acting injectable cabotegravir may be offered** as an additional prevention choice for people at **substantial risk of HIV infection**, as part of combination prevention approaches (**conditional recommendation, moderate certainty of evidence**) [1].

[6] Cisgender is a term used to describe a person whose gender identity corresponds to their sex assigned at birth.

Empfehlungen der EACS-Leitlinie (2022)

The European AIDS Clinical Society (EACS) Guidelines 2022 [17] provides further recommendations related to PrEP:

Recommendations on Pre-exposure Prophylaxis (PrEP)
(some of the recommendations are listed):

PrEP should be used in adults at high-risk of acquiring HIV infection when condoms are not used consistently. Before PrEP is initiated, HBV serology status should be documented.

- Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals when condoms are not used consistently with casual partners or with partners with HIV who are not virally suppressed on treatment. A recent STI, use of post-exposure prophylaxis or chem-sex may be markers of increased risk for HIV.
- May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and have multiple sexual partners where some may have untreated or inadequately suppressed HIV infection.

PrEP regimen:

- TDF/FTC 300*/200mg 1 tablet once daily. In both men and women PrEP should be taken for 7 days before the first exposure and stopped 7 days after the last exposure.
- For men only, PrEP may be dosed 'on demand' (double dose of TDF/FTC 2-24 hours before each sexual intercourse, followed by two single doses of TDF/FTC, 24 and 48 hours after the first drug intake).

Empfehlungen der deutsch-österreichischen Leitlinie (2018, derzeit in Überarbeitung)

The German-Austrian guideline on HIV PrEP [18] was developed by the German AIDS Society, together with various other medical societies and experts (including the Austrian AIDS Society), and published in 2018. It is classified as "S2k consensus guideline", according to the classification of the Association of the Scientific Medical Societies in Germany (AWMF). The guideline is valid until May 2023 and is currently being revised[7]. In this German-Austrian HIV PrEP consensus guideline [18, 19], the following recommendations are given:

Indications for oral HIV pre-exposure prophylaxis (PrEP)

Recommendation on the use of systematic oral HIV PrEP

Oral HIV pre-exposure prophylaxis (PrEP) should be offered as a preventive measure for people at substantial risk of becoming infected with HIV. [Strong consensus]

Recommendation on the definition of substantial risk of HIV infection

There is a substantial risk of becoming infected with HIV in the absence of access to PrEP if HIV incidence is >3 per 100 person-years. This is particularly relevant for the following HIV-negative individuals:

- MSM or transgender people who indicate that they have had anal sex without a condom in the past 3-6 months and/or who will foreseeably do so in the months ahead or who have had a sexually transmitted infection (STI) in the previous 12 months
- Serodiscordant couples with one viremic HIV-positive partner who is not receiving antiretroviral treatment (ART), is on non-suppressive ART, or is in the early stages of ART (i.e. HIV-RNA levels that have not been < 200 RNA copies/mL for at least 6 months)

Furthermore, individual risk might be substantial, particularly for the following groups:

- People who have had condomless anal or vaginal sex with partners in whom an undiagnosed HIV infection is likely
- People who inject drugs without using sterile injection equipment [Strong consensus]

[7] The guideline is currently updated, see https://register.awmf.org/de/leitlinien/detail/055-008 (accessed 13/02/2023).

Recommendation on selection of PrEP agents

The oral combination drug tenofovir disoproxil fumarate*/emtricitabine (TDF/FTC) should be used for PrEP. [Strong consensus]
(= or any other chemical salts of tenofovir disoproxil)*

Recommendation on mode of intake

PrEP should be prescribed as a continuous, once-daily intake of TDF/FTC.

Intermittent intake of PrEP may be considered for specific cases, although this prescription is outside approval ("off-label use"). [Strong consensus]

Recommendation on prescribing PrEP

Only drugs approved in Europe should be prescribed for PrEP [Strong consensus]

Recommendation on PrEP in the context of other prevention measures

HIV PrEP should only be prescribed in combination with risk reduction counseling concerning HIV, sexually transmitted infections (STIs), and viral hepatitis. In this context, it should be emphasized that HIV PrEP reduces the risk of HIV transmission, but it does not reduce the risk of acquiring other STIs. [Strong consensus]

1.4 Features of oral and injectable PrEP pharmaceuticals

Three pharmaceuticals received marketing authorisation in the United States (US) and one in the EU for PrEP, including generic equivalents (Table 1-1).

3 Arzneimittel mit Zulassung in USA und/oder EU

Table 1-1: Pharmaceuticals with marketing authorisation for PrEP in US and EU

Generic name/ ATC code	Trade name	Generic equivalent	EMA	FDA	Indication
Emtricitabine 200mg + tenofovir disoproxil fumarate (equivalent to 300mg of tenofovir disoproxil fumarate or 136mg of tenofovir), oral tbl; Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR03	Truvada®	Yes	Yes	Yes	In combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk; one tablet, once daily
Emtricitabine 200mg + tenofovir alafenamide 25mg (equivalent to 28mg of tenofovir alafenamide fumarate), oral tbl; HIV nucleoside analogue reverse transcriptase inhibitors (NRTIs)	Descovy®	No	No	Yes	At-risk adults and adolescents weighing at least 35kg for HIV-1 pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sex, excluding those who have receptive vaginal sex; not indicated in individuals at risk of HIV-1 infection from receptive vaginal sex because the effectiveness in this population has not been evaluated; one tablet, once daily
Cabotegravir 600mg, extended-release injectable suspension; HIV-1 integrase strand transfer inhibitor (INSTI)	Apretude®	No	No	Yes	At-risk adults and adolescents weighing at least 35kg for PrEP to reduce the risk of sexually acquired HIV-1 infection; 600mg intramuscular injection every two months as continuation injection (after initiation injection period)

Abbreviations: EMA – European Medicines Agency, FDA – Food and Drug Administration

USA: 3 Arzneimittel von FDA zugelassen

- Emtricitabin+ Tenofovirdisoproxil (TDF/FTC) (Truvada® sowie diverse Generika);

- Emtricitabin+ Tenofoviralafenamid (TAF/FTC) (Descovy®);

- Cabotegravir Injektion (CAB) (Apretude®)

In the US, the US Food and Drug Administration (FDA) has approved three medications for use as PrEP: two consist of a combination of drugs in a single oral tablet taken daily. The third medication is a medicine given by injection every two months.

- Emtricitabine (FTC) 200mg in combination with tenofovir disoproxil fumarate (TDF) 300mg (TDF/FTC – brand name Truvada® or generic equivalent produced by several manufacturers),
- Emtricitabine (FTC) 200mg in combination with tenofovir alafenamide (TAF) 25mg (TAF/FTC – brand name Descovy®),
- Cabotegravir (CAB) 600mg injection (brand name Apretude®).

EU: nur TDF/FTC (1 Tablette täglich) bisher von EMA zugelassen

In the EU, only emtricitabine (FTC) 200mg in combination with tenofovir disoproxil fumarate (TDF) 245mg (equivalent to 300mg of tenofovir disoproxil fumarate or 136mg of tenofovir) – Truvada® is approved, as well as its generic equivalent. Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil is converted in vivo to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have inhibitory activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination. Truvada® is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents at high risk, as one tablet once daily [20]. The same is true for generic equivalents produced by several manufacturers.

TAF/FTC: derzeit keine Zulassung in EU durch Hersteller angestrebt

The FDA approved emtricitabine 200mg and tenofovir alafenamide 25mg (Descovy®) in at-risk adults and adolescents weighing at least 35kg for HIV-1 PrEP to reduce the risk of HIV-1 infection from sex, excluding those who have receptive vaginal sex. Descovy® is not indicated in individuals at risk of HIV-1 infection from receptive vaginal sex because the effectiveness in this population has not been evaluated [21]. Descovy is a two-drug combination of emtricitabine (FTC) and tenofovir alafenamide (TAF); both are HIV nucleoside analogue reverse transcriptase inhibitors (NRTIs). On October 20, 2021, Gilead announced it will not pursue marketing authorization for Descovy® for PrEP in the EU at this time [22].

CAB (intramuskuläre Injektion, alle 2 Monate), seit 2021 von FDA zugelassen, in EU derzeit EMA-Verfahren zur Zulassung laufend

Cabotegravir extended-release injectable suspension (Apretude®) for intramuscular use was approved in the USA by the FDA in 2021. It is an HIV-1 integrase strand transfer inhibitor (INSTI) indicated in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test prior to initiating Apretude® (with or without an oral lead-in with oral cabotegravir [23, 24]. On 28 October 2022, ViiV Healthcare announced that the EMA had validated the company's marketing authorisation application (MAA) seeking approval for cabotegravir long-acting injectable for PrEP to reduce the risk of sexually acquired HIV-1 [25].

Dapivirin-Vaginalring: für Verwendung außerhalb der EU zugelassen

In addition to FDA and EMA-approved medications, Dapivirine Vaginal Ring 25mg is intended for use outside the EU. The EMA gave a positive opinion for Dapivirine Vaginal Ring 25mg on 23 July 2020, as part of its cooperation with the WHO, whereby the Agency evaluates medicines that are not intended for use in the EU but are needed to prevent or treat diseases of major public health importance around the world. It is a vaginal ring used to reduce the risk of a woman getting infected with human immunodeficiency vi-

rus type 1 (HIV-1) through vaginal intercourse. It is for use with safer sex practices (such as the use of condoms) by women 18 years of age or above when taking PrEP medicines orally is not feasible [26].

orale PrEP: statt 1 Tablette/Tag auch anlassbezogene PrEP als ‚off-label use' in Anwendung (2+1+1)

In addition to a once daily oral PrEP schedule, literature data show that other dosing regimen-schedules (as off-label use) are also used in real word settings, like event-driven PrEP [16]. This consists of the use of a double dose of oral PrEP 2-24 hours before sexual intercourse, followed by a third dose 24 hours after the first two doses and a fourth dose 48 hours after the first two doses. This has been described as 2+1+1. If more sex acts take place in the following days, a single dose can be continued daily as long as the sexual risk continues, with a single daily dose taken for each of the two days after the last sexual intercourse [16, 27].

2 Objectives and scope

Aim of this review

The review aims to provide an update evidence synthesis based on a systematic literature search regarding the effectiveness and safety of FDA and/or European Medicine Agency (EMA) approved oral and parenteral antiretroviral PrEP to prevent HIV infection in populations at risk. The review also addresses potential organisational, economic, patient/social, ethical and legal aspects to support the evidence-based decision-making process on PrEP in Austria.

Evidenzsynthese zur oralen und parenteralen PrEP für die HIV-Prävention

Research questions

The following research questions (RQ) are addressed in this review:

2 Forschungsfragen:

- **Effectiveness and safety:** What are the effectiveness and safety of FDA and/or EMA approved oral and parenteral antiretroviral PrEP medicines to prevent HIV infection in populations at risk?

Wirksamkeit & Sicherheit

- **Organisational, economic, patient/social, ethical and legal aspects:** What are the potential organisational, economic, patient/social, ethical and legal aspects of antiretroviral PrEP therapy to prevent HIV infection in populations at risk?

organisatorische, ökonomische, soziale & rechtliche Aspekte

Assessment scope according to the PICO framework

Table 2-1: PICO framework

Population	**HIV-negative people at risk for HIV** Including: Men who have sex with men (MSM), Trans and gender-diverse people, Heterosexuals (men and women), HIV-negative partners of serodifferent couples, People who inject drugs (PWID), Pregnant and breastfeeding women, Prisoners and other closed settings, Sex workers, Adolescents
Intervention	**PrEP as any oral or parenteral-injectable pharmaceutical** (approved by FDA and/or EMA): **Oral*** ■ Emtricitabine (F) 200mg in combination with tenofovir disoproxil fumarate (TDF) 300mg (F/TDF – brand name Truvada® or generic equivalent) – Approved by FDA and EMA ■ Emtricitabine (F) 200mg in combination with tenofovir alafenamide (TAF) 25mg (F/TAF – brand name Descovy®) – Approved by FDA **Parenteral-injectable** ■ Cabotegravir (CAB) 600mg injection (brand name Apretude®) – Approved by FDA (currently in submission to EMA, Nov 2022)
Comparison	Any **active oral** (daily and event-driven (on-demand) or intermittent dosing) or **parenteral-injectable PrEP** pharmaceutical, **placebo** or **no PrEP**
Outcomes	**Effectiveness Domain:** *Main outcome*: ■ HIV infection incidence *Additional outcomes*: ■ QoL ■ Adherence to PrEP ■ Sexual and reproductive health outcomes (i.e., Changes in sexual behaviour after PrEP initiation; Incidence of sexually transmitted infections) ■ Drug resistance (Resistance to PrEP pharmaceuticals among seroconverters)

Outcomes *(continuation)*	**Safety Domain:** short-term and long-term AEs and SAEs ■ Number of patients with one or more Adverse events (AE) ■ Number of patients with one or more Serious adverse events (SAE) ■ Number of deaths attributable to SAE ■ Number of withdrawals due to AEs ■ Description of most frequent AEs ■ Description of most frequent SAEs **Other Domains: Organisational, Economic, Patient/social, Ethical, Legal** (*according to the EUnetHTA Core HTA Model® 3.0*) [28], i.e., **Organisational:** ■ Implementation considerations (Accessibility, Training, Quality assurance and monitoring system) **Economic:** ■ Economic implications of providing PrEP **Patient/social:** ■ Values and preferences regarding PrEP **Ethical:** ■ Equity and acceptability and factors that could prevent using it **Legal:** ■ Regulation for the acquisition and use of the PrEP
Study design	**Effectiveness and Safety Domains:** Systematic Reviews (SR) (stand-alone or related to clinical guidelines and Health Technology Assessments (HTA) and randomised controlled trials (RCT) **Other Domains:** Qualitative and quantitative studies, reports or opinions (according to the EUnetHTA Core HTA Model® 3.0 [28]), i.e., SRs, Clinical guidelines, RCTs, Real-world studies like prospective cohort, longitudinal studies and registries studies, qualitative studies
Restrictions	English and German language; SRs and RCTs for effectiveness and safety; Time period: July 2020 – Nov 2022 (**updated search**) for the systematic literature search

* *Different dosing regimen (schedule) of oral PrEP was also considered, as off-label use*

3 Methods

Effectiveness and Safety Domains

systematischer Review (SR) zu Wirksamkeit und Sicherheit basiert auf bereits publizierten SRs/HTA-Berichten

To avoid redundancies and duplication, this systematic review (SR) on effectiveness and safety reused data from the recently published SR [29], related to an already published HTA [30] as well as clinical guidelines [1, 14, 31] to collect information and data on HIV PrEP, as they are applicable to our PICO framework. The data was included according to the methodology suggested by Whitlock 2008 [32] and Robinson 2014 [33] on how to integrate existing SRs into new SRs. As described by Robinson et al. [33], four different approaches could be followed: 1) use the existing SR(s)' list of included studies as a quality check for our literature search and screening strategy ('Scan References'), 2) use the existing SR(s) to completely or partially provide the body of included studies for one or more research questions of our assessment ('Use Existing Search'), 3) use the data abstraction, risk of bias assessments, and/or analyses from existing SRs for one or more research questions of our assessment ('Use Data Abstraction/Syntheses') and 4) use the existing SR(s), including conclusions, to fully or partially answer one or more research questions of our SR ('Use Complete Review'). The fourth approach was used related to effectiveness and safety of oral PrEP, and the first and second approach related to effectiveness and safety of injectable PrEP. New data was added, according to the updated literature search described below.

unterschiedliche Methoden zur Integration bereits bestehender SRs in neuen SR

Other Domains: Organisational, economic, patient/social, ethical and legal aspects

andere Domänen basierend auf EUnetHTA Core Model®

The selection of assessment elements (done by both reviewers) for potential organisational, economic, patient/social, ethical and legal aspects was based on the EUnetHTA Core Model® Version 3.0 [28].

3.1 Literature search

Effectiveness and Safety Domains

Update der systematischen Literatursuche in mehreren Datenbanken

The literature search from the sources mentioned above was updated in November 2022, for the period from July 2020 to November 2022, in the following databases:

- MEDLINE via PubMed,
- EMBASE,
- The Cochrane Central Register of Controlled Trials,

to find new SRs and RCTs on effectiveness and safety related to HIV PrEP in different groups of people at risk for HIV [29, 31]. The detailed search strategies for each of the databases can be found in Appendix ("Search strategies").

Screening der Titel und Abstracts, Volltextauswahl durch 2 Autorinnen

Two reviewers (MH, IR) independently screened the titles and abstracts of the systematic literature search to identify potentially eligible studies. Full-text articles were obtained for all citations identified as potentially eligible. Both reviewers independently read these to establish the relevance of the articles according to the pre-specified criteria. References were included or ex-

cluded according to the Population-Intervention-Control-Outcome (PICO)-scheme (as described in the Scope) and presented according to the PRISMA Statement, Figure 4-1 [34].

Other Domains

nicht-systematische Suche für andere Domänen

Literature search for other domains – qualitative and quantitative studies, reports or opinions (according to the EUnetHTA Core HTA Model® 3.0 [28]) – was undertaken by one reviewer through a non-systematic literature search in the TRIP database and PubMed from January 2020 – November 2022. In addition, relevant sources from the systematic literature search were consulted.

zusätzlich Leitlinien-Suche

A separate Guideline (GL) search (TRIP-Database and hand search) was performed as well, in November 2022, from January 2020 – November 2022, for all domains. The same is true for HTA reports (through INAHTA search).

und Handsuche

Manual searches (from reference lists of relevant studies and websites from ECDC, FDA, EMA …) were also carried out by one reviewer for all domains.

Ongoing studies

Suche nach laufenden RCTs (Phase 3 & 4) in Studienregistern

The following clinical trial registries were searched for ongoing RCTs (with restriction to phase 3 and 4 interventional trials) in January 2023:

- ClinicalTrials.gov (https://clinicaltrials.gov/),
- ISRCTN (https://www.isrctn.com/) and
- European Clinical Trials Registry (https://www.clinicaltrialsregister.eu/).

The detailed search strategies can be found in Appendix (“Search strategies”).

3.2 Data extraction and management

Effectiveness and Safety Domains

Datenextraktion

Data extraction was performed by one reviewer (MH) on pre-defined extraction tables and double-checked regarding completeness and accuracy by a second reviewer (IR). Any differences in extraction results were discussed to achieve consensus; any disagreements were resolved by a third reviewer (IZ). Qualitative or quantitative synthesis from existing SRs/meta-analyses (MA) was used and presented in the Result section as available and appropriate for specific outcomes. As additional RCTs were found, new data was added as well. For these new data, a qualitative synthesis of the evidence was performed. The results were presented in plain text format.

Other Domains

(see Effectiveness and Safety Domains)

3.3 Risk of bias and certainty of evidence

Effectiveness and Safety Domains

Studien zur Wirksamkeit und Sicherheit:

Bewertung des Verzerrungspotentials mittels Cochrane Risk of Bias (RoB) 2 Tool

Risk of bias was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [35] or reused from already published SR/MA sources. Each study was assessed with the Cochrane Risk of bias 2 (RoB 2) tool for randomized controlled trials [36] by one reviewer (MH) and double-checked by a second reviewer (IR). The Cochrane RoB 2 tool is structured into five domains: 1) risk of bias arising from the randomization process, 2) risk of bias due to deviations from intended interventions, 3) risk of bias due to missing outcome data, 4) risk of bias in measurement of the outcome, 5) risk of bias in selection of the reported result. Within each domain, a series of 'signalling questions' elicit information relevant to risk of bias assessment. The response options to the signalling questions are: 'Yes', 'Probably yes', 'Probably no', 'No' and 'No information'. A risk of bias judgement arising from each domain is generated by an algorithm based on answers to the signalling questions. Judgement can be 'Low', 'Some concerns' or 'High' risk of bias. Overall risk of bias will be considered as 'low risk of bias' if all domains are at low risk, 'some concerns' if at least one domain is of some concern and no domain is of high risk of bias, and 'high risk of bias' if there is at least one domain at high risk or several domains with some concerns.

Verwendung von GRADE zur Bewertung der Vertrauenswürdigkeit der Evidenz

For rating the certainty of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)-method was applied [37], related to three outcomes: HIV infections, AEs and SAEs. This approach specifies four levels of quality: 'High', further research is very unlikely to change our confidence in the estimate of effect; 'Moderate', further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates; 'Low', further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; 'Very low', we are very uncertain about the estimate.

Other domains

andere Domänen: keine Bewertung der Studienqualität

For other domains, no quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analyses of information were performed from the various sources explored.

3.4 Patient involvement

Einbindung von Patient*innen bzw. potentiellen PrEP-Nutzer*innen

für Kontextualisierung und besseres Verständnis aus Patient*innen-Perspektive

As patient involvement is recognised as important at different levels of the HTA process, a call for patient input was sent to relevant patient organisations in Austria in January 2023. We asked patient organisations to provide answers to the questions from people at risk of HIV and HIV patient and/or caregiver perspectives and experiences. The questionnaire asks general questions related to the impact of HIV, experience with currently available interventions for HIV prevention, expectations of/requirements for PrEP, and additional information which the people at risk of HIV and HIV patient and/or caregiver believed would be helpful to the HTA researchers. The questions are based on the modified Health Technology Assessment International questionnaire template, https://htai.org/. The information was collected to contextualise and better understand the issue from the user's perspective.

Fragebogen an verschiedene Patient*innen-Vertretungen (v. a. AIDS-Hilfen)

The questionnaire was sent to the following patient organisations between the 11th and 13th of January, 2023:

- AIDS-Hilfe Wien
- AIDS-Hilfe Oberösterreich
- AIDS-Hilfe Salzburg
- AIDS-Hilfe Tirol
- AIDS-Hilfe Kärnten
- AIDS-Hilfe Vorarlberg
- AIDS-Hilfe Steiermark
- Beratungsstelle Courage
- Verein an.doc.stelle
- Verein PULSHIV

4 ausgefüllte Fragebögen retourniert

Completed questionnaires were returned by three patient organisations (AIDS-Hilfe Wien, AIDS-Hilfe Steiermark, AIDS-Hilfe Vorarlberg) and one PrEP provider (Teampraxis Breitenecker). The answers from the patient's/user's perspective that were provided by the patient organisations can be found as a tabular and written summary in the Results section below (see chapter 5.1).

4 Results: effectiveness and safety domains

4.1 Study selection

1738 records were identified through database searching, and one additional record was identified through other sources. 993 results were left after automatic deduplication. 37 full-text articles were assessed for eligibility and after the exclusion of 27 full-text articles, one SR (with 15 RCTs) was included related to the effectiveness and safety of oral PrEP, as well as two new RCTs (published in 3 articles): one that compared two different types of oral tenofovir-containing PrEP (tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC) and one RCT comparing daily vs on-demand oral PrEP. Two RCTs were included for the effectiveness and safety of injectable PrEP (published in 4 articles). One SR (with 5 RCTs) was included related to the safety of oral PrEP in pregnancy.

993 Referenzen nach Deduplizierung

37 Volltexte

davon 2 SRs und 4 neue RCTs relevant

The flow diagram depicting the selection process of RCTs can be found below (see Figure 4-1).

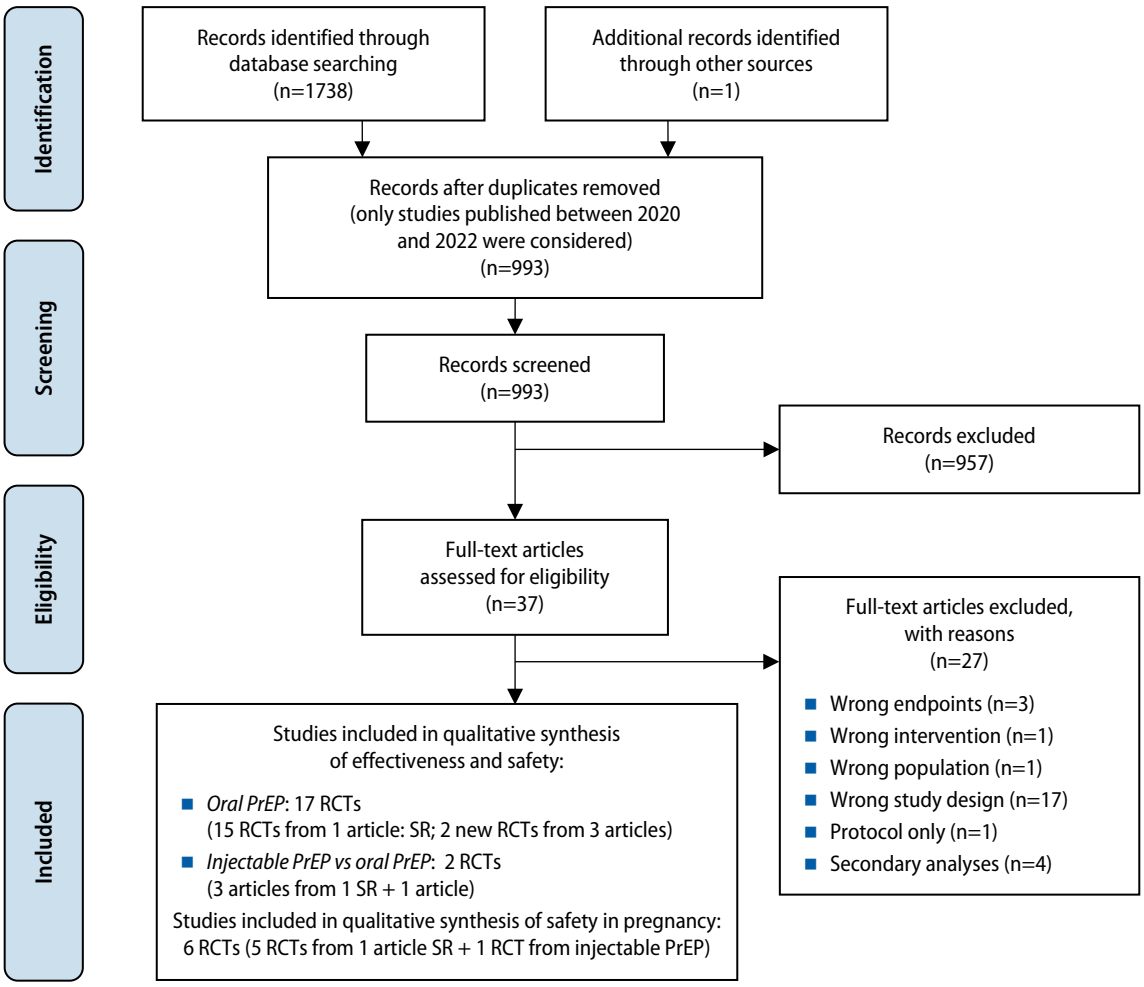

Figure 4-1: Flow chart of study selection (PRISMA Flow Diagram)

4.2 Oral PrEP

orale PrEP: 1 SR mit 15 RCTs und 2 neue RCTs eingeschlossen

The existing recently published SR on effectiveness and safety on oral PrEP (15 RCTs included) [29, 30] was used, and approach 4 was followed as suggested by Robinson et al. [33]: use the existing SR(s), including conclusions, to fully or partially answer one or more research questions of our SR ('Use Complete Review'). Additionally, data from two RCTs was added [38, 39], on which qualitative synthesis of the evidence was performed. In total, 17 RCTs were included on the effectiveness and safety of oral PrEP.

1 weiterer SR (mit 5 RCTs) zur Sicherheit von PrEP in der Schwangerschaft

One SR (with 5 RCTs published) related to the safety of oral PrEP in pregnancy was found, on which a summary of the results was presented descriptively [40]. Additionally, in the new HPTN 084 trial, comparing injectable PrEP vs oral PrEP [41], data on oral and injectable PrEP were found related to pregnancies and their outcomes.

SR/HTA-Bericht aus Irland: 15 RCTs zu TDF

unterschiedliche Dosierung (täglich bzw. anlassbezogen), Kontrollgruppe meist Placebo

In the SR already published within the Irish HTA document in 2019 [30] and later by O'Murchu et al. 2022 in a scientific article [29], 15 RCTs met the inclusion criteria and were included in the assessment of effectiveness and safety (Table 4-1). All studies in this systematic review relate to tenofovir disoproxil fumarate (TDF). Seven RCTs were placebo-controlled trials that evaluated daily oral PrEP [42-48]. Two studies randomised participants to receive either immediate or delayed PrEP [49, 50]. Three of the placebo-controlled trials investigated non-daily PrEP, including intermittent and on-demand (known as event-based) PrEP [51-53]. Two RCTs had an active comparator: one compared tenofovir with tenofovir/FTC [54], and one compared three different PrEP dosing schedules [55]. One study contained three arms: PrEP, placebo and 'no pill' [55, 56].

4 Populationen: MSM (6 RCTs), heterosexuelle Personen (5), serodiskordante Paare (3), Personen die Drogen injizieren (1)

insges. rund 25.000 Teilnehmer*innen mit 38.000 Patient*innen-Jahren Follow-up

Four patient populations were assessed. Six RCTs enrolled MSM [42, 49-52, 56]; five enrolled heterosexual participants [43, 45-47, 55]; three enrolled serodiscordant couples [48, 53, 54]; and one enrolled PWIDs [44]. Included studies involved 25 051 participants encompassing 38 289 person-years of follow-up data. Of the 15 062 participants that received the active drug in the intervention arms of trials, 55% received combination tenofovir/FTC, and 45% received single-agent tenofovir. Follow-up periods ranged from 17 weeks to 6.9 years. Four trials were conducted in high-income countries (USA, England, France and Canada); ten were conducted in low-income or middle-income countries (including nine trials in sub-Saharan Africa); and one was a multicentre trial conducted across four continents. All studies reported the results of a modified intention-to-treat analysis. All included individual RCTs were judged to have a low risk of bias by the Cochrane risk-of-bias tool (see Figure A-1 in the Appendix).

2 neue RCTs:

1 RCT: tägliche vs. anlassbezogene PrEP bei MSM

1 RCT: TDF/FTC vs. TAF/FTC bei MSM und trans Frauen

Additionally, two new RCTs (published in 3 articles) were identified through the updated literature search. One RCT compared oral daily and on-demand PrEP in MSM in Hong-Kong [38] (judged as high risk of bias by the Cochrane risk of bias 2 tool), and one RCT, the DISCOVER trial, compared two different types of oral tenofovir-containing PrEP, tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC (risk of bias judged as some concerns by the Cochrane risk of bias 2 tool) (see Appendix, Table A-3). In the DISCOVER trial, the majority, 99%, were high-risk cisgender men who have sex with men, and only 1% were transgender women who have sex with men [39, 57]. The main characteristics of the included studies are provided in Table 4-1 and in the Appendix (Table A-1).

Table 4-1: Studies included in SR of effectiveness and safety of oral PrEP: 15 RCTs from already published SR and 2 new RCTs from the updated literature search (Kwan 2021, DISCOVER trial)

Study	Location	Population	Intervention	Comparison	Number of participants	Follow-up	Adherence: high (≥80%) vs low (<80%)*
MSM							
Hosek 2013 (Project PrEPare)	USA	MSM, median age: 20 years	TDF/FTC	Daily PrEP versus placebo or 'no pill'	58	24 weeks; 27 person-years	Low: 62% by self-report
Grohskopf 2013 (CDC Safety Study)	USA	MSM, age range: 18-60 years	TDF	Immediate or delayed PrEP versus immediate or delayed placebo	400	2 years; 800 person-years	Low: 77% by pill count
Grant 2010 (iPrEx)	Brazil, Ecuador, South Africa, Peru, Thailand and USA	MSM (99%) and transgender women (1%), age range: 18-67 years	TDF/FTC	Daily PrEP versus placebo	2,499	3,324 person-years (median, 1.2 years; maximum: 2.8 years)	Low: 51% by plasma drug detection
McCormack 2016 (PROUD)	UK	MSM, median age: 35 years	TDF/FTC	Immediate PrEP versus delayed PrEP	544	504 person years. Maximum: 48 weeks	High: 88% (self-report and plasma drug detection†)
Molina 2015 (IPERGAY)	Canada and France	MSM, median age: 34.5 years	TDF/FTC	Intermittent ('on-demand'‡) PrEP versus placebo	400	431 person-years Maximum: 24 months. Median 9.3 months	High: 86% by plasma drug detection
Mutua 2012 (IAVI Kenya Study)	Kenya	MSM (93%) and female sex workers (7%), mean age: 26 years	TDF/FTC	Daily or intermittent PrEP versus daily or intermittent placebo	72	4 months; 24 person-years	High: 83% by MEMS
Kwan 2021	Hong Kong	MSM, median age: 30 years	TDF/FTC	Daily vs on-demand PrEP	119	32 weeks	High: measured as coverage of days with condomless anal intercourse (CLAI): self-report, 100% vs 93% days with CLAI covered by PrEP
Mayer 2020; Ogbuagu 2021 (DISCOVER)	*Europe* (Austria, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, and the UK) and *North America* (Canada and the USA)	MSM (99% cisgender men who have sex with men, 1% transgender women who have sex with men); median age: 34 years	Tenofovir alafenamide/ FTC	Daily PrEP Tenofovir alafenamide/ FTC versus TDF/FTC	5,399	48 weeks; 96 weeks	High: Median pill count adherence 98%; DBS analysis 84-96%
Serodiscordant heterosexual couples (when the HIV-positive partner is not on antiretroviral treatment)							
Kibengo 2013 (IAVI Uganda Study)	Uganda	Serodiscordant couples (negative partner: 50% male), mean age: 33 years	TDF/FTC	Daily or intermittent PrEP versus daily or intermittent placebo	72 couples	4 months; 24 person-years	High: 98% by MEMS
Baeten 2012 (Partners PrEP Study)	Kenya and Uganda	Serodiscordant couples (negative partner: 61%-64% male), age range: 18-45 years	TDF/FTC and TDF only	Daily PrEP versus placebo	4,747 couples	7,830 person-years. Median: 23 months, IQR 16-28, range 1-36 months	High: 82% by plasma drug detection

Study	Location	Population	Intervention	Comparison	Number of participants	Follow-up	Adherence: high (≥80%) vs low (<80%)*
Baeten 2016 (Partners PrEP Study Continuation)	Kenya and Uganda	Serodiscordant couples (negative partner: 62%-64% male), age range: 28-40 years	TDF/FTC and TDF only	TDF/FTC versus TDF	4,410 couples	8,791 person-years. For those assigned active PrEP at the initial randomisation: median 35.9 months; IQR 30-36 months. For those re-randomised from placebo: median 12 months; IQR 12-12 months	Low: 78.5% by plasma drug detection
Heterosexuals							
Bekker 2018 (ADAPT Cape Town)	South Africa	Women, median age: 26 years	TDF/FTC	Daily, time and event driven PrEP	191	29 weeks; 99 person-years	Low: 53%-75% by MEMS
Marrazzo 2015 (VOICE)	South Africa, Uganda and Zimbabwe	Women, median age: 24 years	5 arms: TDF/FTC, TDF only, 1% TDF vaginal gel, oral placebo and placebo vaginal gel	Daily PrEP versus placebo	4,969	5,509 person-years. Maximum: 36 months	Low: 29% by plasma drug detection
Peterson 2007	Nigeria, Cameroon and Ghana	Women, age range: 18-34 years	TDF	Daily PrEP versus placebo	936	428 person-years. Maximum: 12 months	Low: 69% by pill count
Thigpen 2012 (TENOFOVIR2)	Botswana	Heterosexual men (54.2%) and women (45.8%), age range: 18-39 years	TDF/FTC	Daily PrEP versus placebo	1,219	1,563 person-years. Median: 1.1 years; maximum: 3.7 years	High: 84.1% by pill count
Van Damme 2012 (FEM-PrEP)	Tanzania, South Africa and Kenya	Women, median age: 24.2 years	TDF/FTC	Daily PrEP versus placebo	2,120	1407 person-years. Maximum: 52 weeks	Low: 24% by plasma drug detection
PWIDs							
Choopanya 2013 (Bangkok Tenofovir Study)	Thailand	PWID (80% male), median age: 31 years	TDF	Daily PrEP versus placebo	2,413	9,665 person-years. Mean 4.0 years, SD 2.1; maximum: 6.9 years	Low: 67% by plasma drug detection

Sources: [29, 30, 38, 39, 57]

Abbreviations: CLAI – condomless anal intercourse; FTC – emtricitabine; MEMS – medication event monitoring system; MSM – men who have sex with men; PrEP – pre-exposure prophylaxis; PWID – people who inject drugs; PY – person-years; TDF – tenofovir disoproxil fumarate; TDF/FTC – tenofovir disoproxil fumarate and emtricitabine fixed-dose combination.

Explanations:

In all cases, tenofovir dose was 300mg and FTC dose was 200mg.

** Adherence in 15 RCTs in already published SR refers to the proportion of participants in trials that adhered to the study drug. In most studies, more than one method was used to measure adherence; taking a conservative approach, the trials used the lowest estimate of adherence. In trials that investigated daily and intermittent PrEP, adherence relates to daily PrEP. In studies that measured tenofovir and FTC separately, adherence refers to tenofovir detection. Adherence in 2 new RCTs refers to the proportion of participants in both arms that adhered to the study drug.*

† PROUD trial: adherence was determined by a combination of self-report and plasma drug detection. Sufficient study drug was prescribed for 88% of the total follow-up time, and the study drug was detected in 100% of participants who reported taking PrEP.

‡ On-demand dosing: participants were instructed to take two pills of TDF/FTC or placebo 2-24 hours before sex, followed by a third pill 24 hours later and a fourth pill 48 hours later.

4.2.1 Results from already published SR related to TDF (15 RCTs)

Effectiveness

The effectiveness of PrEP to prevent HIV acquisition was presented by study population and stratified by adherence, where appropriate.

Ergebnisse des SRs zu TDF, nach Studienpopulation

Outcome: HIV infection

MSM population

Six studies enrolled MSM [42, 49-52, 56]. A meta-analysis of all studies resulted in a rate ratio (RR) of 0.25 (95% CI 0.1 to 0.61), indicating a 75% reduction in the rate of HIV acquisition (high certainty of evidence). The estimated absolute rate difference (RD) was −0.03 (95% CI −0.01 to −0.05), indicating PrEP users had a 3% lower rate of HIV acquisition per person-year of follow-up.

MSM (6 RCTs): 75 % Reduktion der HIV-Infektionsrate (hohe Vertrauenswürdigkeit der Evidenz nach GRADE)

When stratified by adherence (≥80% vs <80%), heterogeneity was eliminated (I^2 reduced from 52% to 0%)[8]. PrEP was most effective in studies with high adherence (≥80%), where the rate of HIV acquisition was reduced by 86% (RR 0.14, 95% CI 0.06 to 0.35; RD −0.06, 95% CI −0.04 to −0.09; I^2=0%, n=3 studies) (high certainty of evidence) [50-52]. Of the three studies with high adherence, one study was small and reported non-significant findings due to few events (Mutua et al [52]). Of the remaining two studies, one study investigated daily PrEP use (McCormack et al, PROUD trial) [50], and the other investigated on-demand PrEP (Molina et al, IPERGAY trial) [51]. Both studies reported identical efficacy (PROUD: RR 0.14, 95% CI 0.04 to 0.47; IPERGAY: RR 0.14, 95% CI 0.03 to 0.6). When adherence was under 80%, acquisition rate was reduced by 45% (RR 0.55, 95% CI 0.37 to 0.81; RD −0.01, 95% CI −0.00 to −0.02; I^2=0%, n=3 studies) (high certainty of evidence) [42, 49, 56].

bei hoher Adhärenz (≥80 %): 86 % Reduktion der HIV-Infektionsrate (hohe Vertrauenswürdigkeit)

bei niedriger Adhärenz (<80 %): 45 % Reduktion der HIV-Infektionsrate (hohe Vertrauenswürdigkeit)

Serodiscordant heterosexual couples

In all three studies that enrolled serodiscordant heterosexual couples, the HIV-infected partner was not on antiretroviral therapy (studies were conducted in Kenya and Uganda; HIV-infected participants did not meet the criteria for antiretroviral therapy (ART) initiation at the time of enrolment) [48, 53, 54]. Two studies investigated the effect of daily oral PrEP compared with placebo [48, 53]. A total of 4,819 couples were enrolled, and the seronegative individual was male in the majority (>60%) of cases. One trial enrolled few participants (n=24 in the daily PrEP arm), and the duration of the trial was very short (4 months); the results of this study were excluded from the analysis as no seroconversions (the development of antibody to HIV) were reported in either arm of the trial [53]. The trial by Baeten et al [48] consisted of three arms: tenofovir/FTC (n=1,568 participants), tenofovir alone (n=1572 participants) and placebo (n=1,568 participants). Tenofovir/FTC resulted in a 75% HIV rate reduction (RR 0.25, 95% CI 0.14 to 0.46; RD −0.01, 95% CI −0.01 to −0.02) (high certainty of evidence), and tenofovir alone resulted in a 67% HIV rate reduction (RR 0.33, 95% CI 0.19 to 0.56; RD −0.01, 95% CI −0.01 to −0.02). A continuation of this trial (Baeten et al [54]) compared tenofovir/FTC with tenofovir alone: there was no significant difference between groups.

serodiskordante Paare (d. h. ein/e Partner*in HIV-positiv, der/die andere negativ) (3 RCTs):

TDF/FTC: 75 % Reduktion der HIV-Infektionsrate (hohe Vertrauenswürdigkeit)

nur TDF: 67 % Reduktion der HIV-Infektionsrate

[8] Statistical heterogeneity was examined using the I^2 statistics (I^2 values above 75% represented considerable heterogeneity)

Heterosexuals

heterosexuelle Teilnehmer*innen (5 RCTs), alle Studien aus Subsahara-Afrika (hohe HIV-Prävalenz)

4 RCTs (3 mit geringer Adhärenz): keine stat. signifikante Reduktion der HIV-Infektionsrate (geringe Vertrauenswürdigkeit der Evidenz); 1 RCT mit hoher Adhärenz: insgesamt 61 % Reduktion der HIV-Infektionsrate, jedoch nur bei Männern signifikant

Of the five studies enrolling heterosexual participants, four were placebo-controlled [43, 45-47] and one compared different drug schedules [55]. Four studies enrolled only women [43, 46, 47, 55], and one study enrolled both men and women [45]. All studies were conducted in a high-HIV prevalence context (countries in sub-Saharan Africa). A meta-analysis of the four placebo-controlled studies [43, 45-47] did not demonstrate a statistically significant reduction in HIV acquisition (RR 0.77, 95% CI 0.46 to 1.29; I^2=66%) (low certainty of evidence). Three of these four studies reported low adherence. In the only trial with high adherence (Thigpen et al [45]), a rate reduction of 61% was noted (RR 0.39, 95% CI 0.18 to 0.83; RD −0.02, 95% CI −0.01 to −0.04) (high certainty of evidence). This was the only trial to enrol both men and women, and when the results were analysed separately by sex, efficacy was noted only in men, with a rate reduction of 80% (RR 0.2, 95% CI 0.04 to 0.91). Females achieved a reduction of 51%, but without statistical significance. In a meta-analysis of three trials with low adherence, the result was non-significant (RR 1.03, 95% CI 0.75 to 1.43, I^2=21%) (moderate certainty of evidence).

A final study compared different PrEP regimens (daily PrEP, 'time-driven' PrEP and 'event-driven' PrEP) [55]. Fewer infections occurred in the daily PrEP arm; however, there were no significant differences in HIV acquisition comparing either event or time-driven PrEP with daily PrEP.

People who inject drugs

Personen, die Drogen injizieren (1 RCT): 49 % Reduktion der HIV-Infektionsrate (moderate Vertrauenswürdigkeit)

Only one study enrolled PWID [44]. Daily oral tenofovir compared to placebo was found to be effective (moderate certainty of evidence), with a 49% reduction in HIV acquisition (RR 0.51, 95% CI 0.29 to 0.92; RD −0.00, 95% CI −0.00 to −0.01). In this study, HIV transmission may have occurred sexually or parenterally.

Table 4-2 presents the summary of findings of the effectiveness to prevent HIV acquisition.

Relationship between efficacy and adherence

Meta-Regressionsanalyse zu Wirksamkeit und Adhärenz

10 %ige Abnahme der Adhärenz → Verringerung der Wirksamkeit um 13 %

A meta-regression analysis was performed to investigate the relationship between efficacy and adherence, accounting for trial size. Adherence was measured in a variety of methods across trials. Studies that did not confirm adherence through plasma drug detection rates were excluded from meta-regression analyses due to biases associated with other methods, such as self-report or pill count. Efficacy (as RRs) and adherence (by proportion with plasma drug detectable) were strongly associated ($p<0.001$). As the adherent proportion increases from 0.5 to 0.6, the RR decreases by 0.13. Therefore, on average, a 10% decrease in adherence decreases efficacy by 13%.

Table 4-2: Summary of findings table from already published SR: Oral PrEP, on effectiveness outcome: HIV infection

Summary of findings table: Effectiveness of PrEP						
Patient or population: **HIV prevention in participants at substantial risk** Intervention: **PrEP** Comparison: **no PrEP**						
	Anticipated absolute effects* (95% CI)		**Relative effect, expressed as RRs (95% CI)**	**Person-years of follow-up (studies)**	**Certainty of the evidence (GRADE)**	
Outcomes	**Rate with no PrEP**	**Rate with PrEP**				**Comments**
HIV infection: MSM (all clinical trials)	40 per 1000	10 per 1000 (4 to 24)	RR 0.25 (0.10 to 0.61)	5103 (6 RCTs)	⊕⊕⊕⊕ High†‡	PrEP is effective in preventing HIV acquisition in MSM with a rate reduction of 75%.
HIV infection: MSM, trials with high (≥80%) adherence	66 per 1000	9 per 1000 (4 to 23)	RR 0.14 (0.06 to 0.35)	960 (3 RCTs)	⊕⊕⊕⊕ High	PrEP is highly effective in preventing HIV acquisition in MSM in trials with high adherence (over 80%) with a rate reduction of 86%.
HIV infection: MSM, trials with low (<80%) adherence§	32 per 1000	18 per 1000 (12 to 26)	RR 0.55 (0.37 to 0.81)	4143 (3 RCTs)	⊕⊕⊕⊕ High	PrEP is effective in preventing HIV acquisition in MSM in trials with low adherence (under 80%) with a rate reduction of 45%.
HIV infection: serodiscordant couples,¶ all clinical trials: two studies with high (≥80%) adherence	20 per 1000	5 per 1000 (3 to 9)	RR 0.25 (0.14 to 0.46)	5237 (2 RCTs)	⊕⊕⊕⊕ High	PrEP is effective in preventing HIV acquisition in serodiscordant couples with a rate reduction of 75%.
HIV infection: heterosexual transmission, all clinical trials	41 per 1000	32 per 1000 (19 to 53)	RR 0.77 (0.46 to 1.29)	6821 (4 RCTs)	⊕⊕◯◯ Low†**	PrEP is not effective in preventing heterosexual HIV transmission (all trials).
HIV infection: heterosexual transmission, trials with high (≥80%) adherence	31 per 1000	12 per 1000 (6 to 26)	RR 0.39 (0.18 to 0.83)	1524 (1 RCT)	⊕⊕⊕⊕ High	PrEP is effective in preventing heterosexual HIV transmission in heterosexuals in one trial with high (over 80%) adherence. This trial enrolled men and women; note that efficacy was only reported for men.
HIV infection: heterosexual transmission, trials with low (<80%) adherence	45 per 1000	46 per 1000 (34 to 64)	RR 1.03 (0.75 to 1.43)	5297 (3 RCTs)	⊕⊕⊕◯ Moderate**	PrEP is not effective in preventing heterosexual HIV transmission in trials with low adherence. Note that all three trials enrolled heterosexual women.
HIV infection: PWID, all clinical trials: one study with low (<80%) adherence	7 per 1000	3 per 1000 (2 to 6)	RR 0.51 (0.29 to 0.92)	9666 (1 RCT)	⊕⊕⊕◯ Moderate††	PrEP is effective in preventing HIV transmission in PWID with a rate reduction of 49%.

Sources: [29, 30]

Abbreviations: GRADE – Grading of Recommendations Assessment, Development and Evaluation; MSM – men who have sex with men; PrEP – pre-exposure prophylaxis; PWID – people who inject drugs; RCT – randomised controlled trial; RR – rate ratio.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations:

** The rate in the intervention group (and its 95% CI) is based on the assumed rate in the comparison group and the relative effect of the intervention (and its 95% CI).*

† Downgraded one level for heterogeneity.

‡ Upgraded one level for large effect (RR <0.5).

§ Note that under alternative methods to account for zero events in one or both arms (beta-binomial), there is greater imprecision and the upper confidence bound crosses the line of no effect.

¶ In studies that enrolled serodiscordant couples, the HIV-positive individual was not on antiretroviral therapy. All studies relate to serodiscordant heterosexual couples.

*** Downgraded one level for imprecision.*

†† Downgraded one level for indirectness.

Outcome: Viral drug resistance mutations

Mutationen, die zu Arzneimittelresistenz führen: 44 Serokonversionen zu PrEP-Beginn, davon 9 Mutationen (8 in der PrEP-Gruppe, 1 in der Placebo-Gruppe)

Five placebo-controlled trials provided data on HIV mutations among patients who had acute HIV infection at enrolment (unknown to study investigators) [42, 44-46, 48]. In total, there were 44 seroconversions at enrolment, 25 who received the study drug and 19 who received placebo. There were nine mutations detected, eight among participants receiving the study drug and one in a patient receiving placebo. The RR for any drug mutation was 3.53 (95% CI 1.18 to 10.56, I^2=0%), which represents a rate difference (RD) of 0.57 (95% CI 0.21 to 0.94). Of the nine resistance mutations at enrolment, seven were for FTC. The RR for FTC mutation was 3.72 (95% CI 1.23 to 11.23, I^2=0%), which represents an RD of 0.6 (95% CI 0.23 to 0.97) in those receiving tenofovir/FTC [42, 45, 46, 48].

551 Serokonversionen nach PrEP-Beginn, davon 7 Mutationen

Among participants who seroconverted post-randomisation, the development of resistant mutations was uncommon. Of 551 seroconverters, only seven resistance mutations were detected: one tenofovir mutation was noted in a tenofovir-only arm (k65n, a rare tenofovir resistance mutation), and six FTC mutations were noted.

Outcome: Changes in sexual behaviour (Risk compensation)

Veränderungen im Sexualverhalten (Risikokompensation):

Changes in sexual behaviour, or risk compensation, were measured in a number of ways, including condom use, number of sexual partners, changes in STI rates and recreational drug use. Due to the differences in how sexual behaviour was reported across trials, including differing definitions and at different time points, a meta-analysis was not possible.

keine Gruppenunterschiede bzgl. Kondomverwendung und Anzahl der Sexualpartner*innen

Studies consistently showed no between-group difference in condom use or number of sexual partners. Studies showed either no overall change in condom use throughout the duration of the study (n=4 studies) or an increase in condom use (n=4 studies). Most studies showed no change in the number of sexual partners over time (n=6 studies); four studies showed a slight reduction in the number of sexual partners; and one showed an increase (investigators of this study noted the possibility of partner under-reporting at baseline) [52].

kein Unterschied bzgl. STI-Diagnosen

No study reported an increase in STIs or a between-group difference in STI diagnoses.

Reduktion des Risikoverhaltens bei PWID

In the only study to enrol intravenous drug users, a reduction in intravenous drug use, needle sharing and number of sexual partners over the course of the study was noted [44].

Safety

Sicherheit

Not all studies defined what constituted adverse events (including serious adverse events).

Outcome: AEs

unerwünschte Ereignisse (UE): keine signifikanten Gruppenunterschiede (hohe Vertrauenswürdigkeit)

Eleven studies reported data on any adverse events (high certainty of evidence), including ten that compared PrEP with placebo [42-48, 51-53] and two that compared tenofovir alone to tenofovir/FTC [46, 54]. A meta-analysis of placebo-controlled trials demonstrated no significant difference between groups (RR 1.01, 95% CI 0.99 to 1.03; I^2=42%).

Comparing tenofovir with tenofovir/FTC, one study noted a small increase in adverse events in the tenofovir/FTC group (RR 1.23, 95% CI 1.03 to 1.33) [46] and another failed to show any difference [54].

Several studies reported mild decreases in renal function among PrEP users that returned to normal following discontinuation of PrEP use, while a reduction in creatinine clearance (a measure of renal function) was not observed in others [44, 48]. Where renal function has been affected, PrEP was associated with mild, non-progressive and reversible reductions in creatinine clearance [42, 44, 48, 50, 51].

tw. leichte Verschlechterung der Nierenfunktion, mit Normalisierung nach Absetzen der PrEP

Some trials also found slight decreases in bone mineral density [45, 46].

tw. leichte Abnahme der Knochenmineraldichte

Outcome: SAEs

All 15 studies reported data in relation to the risk of serious adverse events (high certainty of evidence): 12 were placebo-controlled [42-49, 51-53, 56]; one compared PrEP with no PrEP [50]; two compared tenofovir/FTC with tenofovir [46, 54] and one compared different dosage schedules [55]. A meta-analysis of placebo-controlled trials did not find an increased risk (RR 0.91, 95% CI 0.74 to 1.13; I^2=67%). In the only trial that compared PrEP with no treatment, an increased rate of serious adverse events was noted in the treatment arm (RR 3.42, 95% CI 1.4 to 8.35) [50]. These adverse events were not considered study drug-related. Two studies compared tenofovir with tenofovir/FTC: one found no significant difference between groups [54], and another found an increased rate in the tenofovir/FTC group (RR 2.48, 95% CI 1.42 to 4.33) [46].

schwerwiegende UEs:

kein erhöhtes Risiko im Vergleich zu Placebo (hohe Vertrauenswürdigkeit)

Outcome: Death

No study found an increased mortality rate associated with PrEP use, and of the deaths that occurred, none were considered to be drug-related.

Mortalität: keine Gruppenunterschiede

Table 4-3 presents the summary of findings of the safety of oral PrEP.

Table 4-3: Summary of findings table from already published SR: Oral PrEP on safety outcomes

Summary of findings table: Safety of PrEP						
Patient or population**: HIV prevention in participants at substantial risk.** Intervention**: PrEP.** Comparison**: no PrEP**						
	Anticipated absolute effects* (95% CI)		**Relative effect (95% CI)**	**Person-years of follow-up (studies)**	**Certainty of the evidence (GRADE)**	
Outcomes	**Rate with no PrEP**	**Rate with PrEP**				**Comments**
Safety outcome: any adverse event	776 per 1000	784 per 1000 (768 to 799)	RR 1.01 (0.99 to 1.03)	17 358 (10 RCTs)	⊕⊕⊕⊕ High	Adverse events do not occur more commonly in patients taking PrEP compared with placebo. Adverse events were common in trials (78% of patients reporting 'any' event).
Safety outcome: serious adverse events	81 per 1000	73 per 1000 (60 to 91)	RR 0.91 (0.74 to 1.13)	17 778 (12 RCTs)	⊕⊕⊕⊕ High	Serious adverse events do not occur more commonly in patients taking PrEP compared with placebo. Serious adverse events occurred in 7% of patients in trials but most were not drug related.
Safety outcome: deaths	13 per 1000	10 per 1000 (8 to 15)	RR 0.83 (0.60 to 1.15)	12 720 (11 RCTs)	⊕⊕⊕◯ Moderate†	Deaths did not occur more commonly in people taking PrEP compared with placebo in trials. No deaths were related to PrEP.
Safety outcome: drug resistance mutations in patients with acute HIV at enrolment	53 per 1000	186 per 1000 (62 to 556)	RR 3.53 (1.18 to 10.56)	44 (5 RCTs)	⊕⊕⊕◯ Moderate†	Patients randomised to receive PrEP who had acute HIV at enrolment were at increased risk of developing resistance mutations to the study drug. Most conferred resistance to emtricitabine.

Sources: [29, 30]

Abbreviations: GRADE – Grading of Recommendations Assessment, Development and Evaluation; PrEP – pre-exposure prophylaxis; RCT – randomised controlled trial; RR – rate ratio.

Note that only a minority of studies tested for viral drug resistance mutations.

GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations:

** The rate in the intervention group (and its 95% CI) is based on the assumed rate in the comparison group and the relative effect of the intervention (and its 95% CI).*

† Imprecision was detected due to few observations.

4.2.2 Results from new RCTs

1 RCT: Vergleich von täglicher & Anlass-bezogener PrEP

1 RCT: Vergleich von 2 oralen PrEP-Medikamenten (TAF/FTC vs. TDF/FTC)

Results from one RCT that compared oral daily and on-demand PrEP in MSM [38] and from another RCT, the DISCOVER trial, that compared two different types of oral tenofovir-containing PrEP, tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC, are presented below. In the DISCOVER trial, the majority, 99% were high-risk cisgender MSM, and only 1% were transgender women who have sex with men [39, 57]. Main characteristics of these two RCTs abstracted from the scientific publication can be found in Table 4-1 and in Appendix (Table A-1).

MSM: Oral daily PrEP vs on-demand PrEP, oral tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) tablets

tägliche vs. anlassbezogene PrEP (TDF/FTC) in 119 MSM (crossover RCT)

To address the research gap related to regimen switch, which is not uncommon in real-life settings, Kwan et al. 2021 [38] compared MSM's prevention-effective adherence to daily and on-demand PrEP, by examining the coverage of days with condomless anal intercourse (CLAI), in 119 participants in Hong Kong, in a randomized, controlled, open-label, crossover trial. Participants in the daily-first arm were put on daily PrEP (oral tenofovir disoproxil fumarate 300mg/emtricitabine 200mg (TDF/FTC) tablets) for 16 weeks, then on-demand PrEP (oral tenofovir disoproxil fumarate 300mg/emtricitabine 200mg, TDF/FTC tablets) for another 16 weeks. Another arm received PrEP in a reversed regimen sequence.

Effectiveness

Outcome: Prevention-effective adherence to daily and on-demand PrEP through PrEP coverage of days with condomless anal intercourse (CLAI)

Adhärenz/PrEP-Abdeckung der Tage mit ungeschütztem Analverkehr: 100 % (IQR 83-100) bei täglicher Einnahme, 93 % (IQR 90-100) bei anlassbezogener Einnahme (sehr geringe Vertrauenswürdigkeit)

Median number of days with CLAI was 13 with an IQR of 4-28, 11 (IQR: 3-20) of which were covered by PrEP. Participants in the daily-first arm had a median of 10 (IQR: 4-33) days with CLAI (CLAI-days), 9 (IQR: 3-31) of which were covered by PrEP. Out of a median of 15 (IQR: 4-24) CLAI-days in the on-demand-first arm, 14 (IQR: 2-22) were covered. Differences in the numbers of CLAI-days (p=0.94), PrEP-covered CLAI days (p=0.97) and the proportions of days with PrEP-covered CLAI (p=0.93) were not statistically significant between the two arms. A median of 7 (IQR: 3-16) and 8 (IQR: 2-12) CLAI-days were covered by PrEP during the daily and on-demand periods, respectively (p=0.93). The median proportion of days with PrEP-covered CLAI was 100% (IQR: 83-100%) during the daily periods and 93% (IQR: 80-100%) during the on-demand periods (p=0.14) (Table 4-4, very low certainty of evidence).

kein statistisch signifikanter Unterschied zwischen den Gruppen

The median number of days with PrEP was 129 (IQR: 97-167), equivalent to about 73% (IQR: 59-85%) of the person-days. The median number and percentage of days on PrEP during the daily and on-demand periods were 93 (IQR: 64-106) days or 96% (88-100%) and 45 (IQR: 25-70) days or 54% (32-75%), respectively. The daily-first arm had a higher median number of days on PrEP during both periods compared with the on-demand-first arm. Participants on the daily regimen first had more days on PrEP during the on-demand period, while those taking the on-demand first had fewer days on daily PrEP.

Outcome: STI

47 % hatten mindestens eine STI-Infektion in der Follow-up Periode

In total, 47% (53/113) had at least one incident STI during the follow-up period, with an incidence rate of 87.46 per 100 person-years. Participants in the daily first arm had similar odds of having incident STI as those in another arm (p=0.072). In both groups, the incidence rate of all-site gonorrhoea was 45.95/100 py; the incidence rate of all-site chlamydia was 50.29/100 py; about 12% (13/113) tested positive for syphilis during their follow-up, with an incidence rate of 17.74/100 py.

Outcome: Intention to continue PrEP

96 % der Teilnehmer wollten nach Studienende weiterhin PrEP nehmen

Upon completion of or withdrawal from the study, almost all (96%, 105/109) indicated their intention to continue PrEP for HIV prevention. Sixteen (15%) participants accepted both daily and on-demand PrEP, while 44 (40%) and 43 (39%) showed preference only for daily and on-demand PrEP, respectively.

Outcome: Perceived risk of HIV infection

mehr Teilnehmer schätzten ihr Risiko geringer ein im Vergleich zu Studienbeginn

More participants had a lower perceived risk of HIV infection compared with the baseline (39% vs 17%). The 18 (17%) participants who considered themselves as having a high risk of HIV infection at the endpoint were more likely to have sex partners on PrEP at the baseline (p=0.012), report STI diagnosis at week 16 (p=0.026) and have an emotionally attached partner at week 24 (p=0.016).

Safety

Outcome: AEs

UE bei ca. 1/3 der Teilnehmer (meist Grad 1),

am häufigsten: Diarrhöe, Übelkeit, Kopfschmerzen, Schwindelgefühl

More than one-third (36%, n=43) reported different grades of adverse events: the most common were diarrhoea, headache, nausea and dizziness. Three quarters (77%, n=33) reported adverse events with daily regimen only, with all but one completing all follow-up visits. Nine out of 37 participants with adverse events during the daily regimen had persistent symptoms throughout the entire 16 weeks. Five of the 10 participants reporting adverse events during the on-demand period attributed their symptoms to the loading double-dose (Table 4-4, very low certainty of evidence). All but one reported grade 1 adverse events.

Dauer der UEs: 14 Tage

The participant who reported grade 2 nausea, depression and sleep disturbance was taking on-demand PrEP until week 16, during which he reported 94 days of PrEP use before withdrawal. Overall, the reported adverse events lasted for a median of 14 days (IQR: 4-63 days).

Kreatinin-Clearance: kein Gruppenunterschied

The change of creatinine clearance over time was –0.39ml/min (95% CI: –0.49 to –0.28, p<0.0001) per week from an intercept of 120.12 (95% CI: 115.48-124.75, p<0.0001), with no difference between the two arms. A higher proportion (74.11%) of variance was attributable to between-person variation, while only 25.89% was attributable to within-person variation.

Outcome: SAEs

keine schwerwiegenden UEs

None reported.

Table 4-4 presents the summary of findings of the effectiveness outcome Prevention-effective adherence to daily and on-demand PrEP through PrEP coverage of days with condomless anal intercourse (CLAI)and safety outcomes AEs and SAEs.

Table 4-4: Summary of findings table: 1 RCT – Oral PrEP: TDF/FTC daily vs on-demand, in MSM, on effectiveness and safety outcomes: Proportion of days with PrEP-covered CLAI, AE, SAE

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Effect size TDF/FTC daily vs on-demand	Number of participants (RCTs)	Certainty of evidence (GRADE)
Proportion of days with PrEP-covered CLAI	Serious [a]	Not serious	Serious [b]	Serious [c]	Serious [d]	Median proportion of days with PrEP-covered CLAI 100% (IQR: 83-100%) during the daily period vs 93% (IQR: 80-100%) during the on-demand period (p=0.14)	119 (1 RCT) [e]	⨁◯◯◯ Very low
AE	Serious [a]	Not serious	Serious [b]	Serious [c]	Serious [d]	33 (77%) with daily regimen vs 5/10 (50%) participants during the on-demand period	119 (1 RCT) [e]	⨁◯◯◯ Very low
SAE	Zero events in both groups	Zero events in both groups	Zero events in both groups	Zero events in both groups	Zero events in both groups	Zero events in both groups	119 (1 RCT) [e]	⨁◯◯◯ Very low

Abbreviations: AE – adverse events; CLAI, condomless anal intercourse; GRADE – grading of recommendations assessment development and evaluation; RCT – randomized controlled trial; SAE – serious adverse events IQR, interquartile range; PrEP, pre-exposure prophylaxis

GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect;
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect;
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations:

[a] *Risk of bias: Serious, downgraded -1;*
[b] *Indirectness: Serious as single centre design, a single study from a single country, therefore results in this population might not be generalizable to other settings, downgraded -1;*
[c] *Imprecision: Serious due to low number of participants, downgraded -1. Zero SAE in both groups, downgraded -1.*
[d] *Other: Short term follow-up, downgraded -1. e [38]*

MSM: Tenofovir alafenamide (TAF) plus FTC vs tenofovir disoproxil fumarate (TDF) plus FTC

2 Publikationen zu Non-Inferiority RCT (DISCOVER): TAF/FTC vs. TDF/FTC bei MSM und trans Frauen, die Sex mit Männern haben (nur 1 % der Teilnehmer*innen)

n=5.399, 96 Wochen Follow-up

As already mentioned above, two new publications (with results at 48 weeks and 96 weeks) were identified through the update literature search related to one non-inferiority RCT (DISCOVER trial, NCT02842086). This RCT compared two different types of oral tenofovir-containing PrEP, tenofovir alafenamide (TAF) plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC in high-risk MSM; only 1% were transgender women who have sex with men [39, 57]. 5,399 participants were randomised to emtricitabine (200mg) and tenofovir alafenamide (25mg) tablets daily (n=2,700) and to emtricitabine (200mg) and tenofovir disoproxil fumarate (300mg) tablets daily (n=2,699). Main characteristics of this RCT abstracted from the scientific publication can be found in Table 4-1 and Table A-1 (Appendix). One publication is related to outcomes at 48 weeks [39], and the other to outcomes at 96 weeks. Results on effectiveness and safety at 96 weeks are presented below [57].

Effectiveness

Outcome: HIV infection

Nicht-Unterlegenheit der TAF/FTC bei HIV-Prävention (moderate Vertrauenswürdigkeit)

8 Infektionen in TAF/FTC-Gruppe, 15 in TDF/FTC-Gruppe

The study found that the daily TAF group showed non-inferior efficacy to the daily TDF group for HIV prevention (moderate certainty of evidence). At 96 weeks of follow-up, there were eight HIV infections in participants who had received TAF/FTC (0.16 infections per 100 person-years [95% CI 0.07-0.31]) and 15 in participants who had received TDF/FTC (0.30 infections per 100 person-years [0.17-0.49]). TAF/FTC maintained its non-inferiority to TDF/FTC for HIV prevention (HIV incidence rate ratio, IRR 0.54 [95% CI 0.23-1.26]).

Outcome: Adherence

Adhärenz je nach Messmethode zwischen 78 und 98 %

78-82% of participants reported taking study medication more than 95% of the time across all study visits. Median pill count adherence at week 96 was 98% (IQR 93-100%) in both study groups. Objective adherence was measured by dried blood spots (DBS) analysis through the primary endpoint; at each visit, 84-96% of participants in both groups had tenofovir diphosphate concentrations consistent with taking at least four tablets per week.

Outcome: Drug resistance

Medikamentenresistenz: 4 von 20 Resistenz gegen FTC

Viral RNA could be amplified for genotypic testing in 20 (87%) of the 23 participants who were infected with HIV. Four (20%) of 20 had emtricitabine resistance detected (M184V or M184I), all of whom were in the TDF/FTC group and were suspected of having been infected before study enrolment. No participants had genotypic mutations detected that conferred resistance to tenofovir.

Outcome: Sexually transmitted infections (STI)

STIs: kein Gruppenunterschied bei Infektionsraten

Rates of STI were similar across groups (21 cases versus 20 cases per 100 person-years for rectal gonorrhoea, 27 cases per 100 person-years for rectal chlamydia in both groups, ten cases versus nine cases per 100 person-years for syphilis).

Safety

Outcome: AEs

Similar rates of adverse events were observed between study groups (94%) (moderate certainty of evidence). Most adverse events were grade 1 (mild) or 2 (moderate) in severity, and the most common were bacterial sexually transmitted infections. Study drug-related adverse events occurred in 564 (21%) participants in the TAF/FTC group and 654 (24%) in the TDF/FTC group. 9% of participants in each group (246 in the TAF/FTC group and 240 in the TDF/FTC group) had grade 3 or higher laboratory abnormalities.

kein Gruppenunterschied bei UEs (moderate Vertrauenswürdigkeit)

meist Grad 1 oder 2, bakterielle STI am häufigsten

Outcome: SAEs

The incidence of serious adverse events was also similar between groups (202 [7%] in the TAF/FTC group vs 186 [7%] in the TDF/FTC group) (moderate certainty of evidence); serious adverse events considered by the investigator to be related to study drug were rare (three [<1%] individuals in the TAF/FTC group and five [1%] in the TDF/FTC group).

kein Gruppenunterschied bei schwerwiegenden UEs; nur wenige in Zusammenhang mit Medikament

Outcome: Discontinuation due AEs

The incidence of adverse events leading to premature study drug discontinuation was low and similar between groups: 40 (1%) of 2,694 participants in the TAF/FTC group and 51 (2%) of 2,693 in the TDF/FTC group.

frühzeitige Beendigung wegen UEs bei 1 % bzw. 2 %

Outcome: Death

The same percentage of death occurred at week 96 in both groups: 3 (<1%) in the TAF/FTC group vs 2 (<1%) in the TDF/FTC group.

kein Gruppenunterschied bei Mortalität

Outcomes: Renal AEs, bone fracture and weight gain

At week 96, TAF/FTC continued to show superiority over TDF/FTC in all but one of the six prespecified bone mineral density and renal biomarkers (with the exception of study drug-emergent urine to protein creatinine ratio of more than 22.6mg/mmol). Study drug-related renal events occurred in 18 (1%) participants in the TAF/FTC group and 36 (1%) participants in the TDF/FTC group. Renal adverse events leading to discontinuation were rare; two occurred in the TAF/FTC group and six in the TDF/FTC group.

Überlegenheit der TAF/FTC in 5 von 6 vorab definierten Biomarkern bzgl. Nierenfunktion und Knochenmineraldichte

In each study group, 60 participants had fracture events; of these, one (2%) in the TAF/FTC group and two (3%) in the TDF/FTC group were nontraumatic (pathological).

in beiden Gruppen Knochenfrakturen, davon 2 % bzw. 3 % nicht-traumatisch

There was more weight gain among participants who had received TAF/FTC (median weight gain 1.7kg vs 0.5kg, p<0.0001). Over a median exposure of 120 weeks, no new safety signals were detected.

höhere Gewichtszunahme in der TAF/FTC-Gruppe

Table 4-5 presents the summary of findings of the effectiveness to prevent HIV acquisition and safety outcomes AEs and SAEs at 96 weeks.

Table 4-5: Summary of findings table: 1 RCT – Oral PrEP: Tenofovir alafenamide (TAF) plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC – DISCOVER trial, in MSM, on effectiveness and safety outcomes: HIV incidence, AE, SAE

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Effect size TAF/FTC vs TDF/FTC	Number of participants (RCTs)	Certainty of evidence (GRADE)
HIV incidence	not serious	not serious	serious [a]	not serious[b]	none	8/2,700 (0.3%) vs 15/2,699 (0.56%); 0.16 infections per 100 person-years [95% CI 0.07-0.31] vs 0.30 infections per 100 person years [0.17-0.49]	5,399 (1 RCT) [c]	⨁⨁⨁◯ Moderate
AE	not serious	not serious	serious [a]	not serious	none	2,523/2,694 (94%) vs 2,521/2,693 (94%)	5,387 (1 RCT) [c]	⨁⨁⨁◯ Moderate
SAE	not serious	not serious	serious [a]	not serious	none	202/2,694 (7%) vs 186/2,693 (7%)	5,387 (1 RCT) [c]	⨁⨁⨁◯ Moderate

Abbreviations: AE – adverse events; GRADE – grading of recommendations assessment development and evaluation; RCT – randomized controlled trial; SAE – serious adverse events

GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect;
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect;
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations:

[a] *The evidence is not directly related to many populations of interest (99% men who have sex with men, and 1% transgender women who have sex with men), other populations for whom exposure to HIV is of potential concern, such as youth aged <18 years, people who inject drugs, people who are pregnant or breastfeeding, transgender men, were not included in the trial, relatively low number of transgender women and people from minority ethnic or racial groups enrolled in the study limits the generalisability of study findings. Findings cannot be generalised to individuals whose risk of HIV is through receptive vaginal or frontal sex or by injection drug use, downgraded by 1 level;*

[b] *Only 8 cases of HIV infection were identified among participants receiving tenofovir alafenamid; the sample size of the this trial was sufficiently large, thus the evidence was not downgraded for imprecision; c [57]*

4.3 Injectable PrEP

Injectable cabotegravir vs daily oral tenofovir disoproxil fumarate/emtricitabine

systematischer Review der WHO als Basis

The existing recently published SR by the WHO on the effectiveness and safety of injectable PrEP [14] was used. Here, approaches 1 and 2 were followed [33]: 1) use the existing SR(s)' list of included studies as a quality check for our literature search and screening strategy ('Scan References'); 2) use the existing SR(s) to completely or partially provide the body of included studies for one or more research questions of our assessment ('Use Existing Search').

2 neue RCTs durch Update-Suche

The data from 2 RCTs is provided according to the updated literature search [41, 58]. A qualitative synthesis of the evidence was performed. The results are presented in plain text format.

Cabotegravir (CAB-LA) 600mg Injektion + Placebo vs. TDF/FTC + Placebo

HPTN 083 Studie: MSM & trans Frauen, die Sex mit Männern haben, n=4.570, ø 1,4 Jahre Follow-up

HPTN 084 Studie: cis Frauen, n=3.224, ø 1,24 Jahre Follow-up

Two phase 2b/3 RCTs were included (see Table 4-6): the HPTN 083 trial, NCT02720094, with at-risk cisgender MSM and transgender women who have sex with men (12.5%), and the HPTN 084 trial, NCT03164564, including women (female sex at birth). Both RCTs compared injectable CAB-LA 600mg i.m every eight weeks plus TDF–FTC placebo to daily oral PrEP (oral tenofovir disoproxil fumarate 300mg – emtricitabine 200mg, TDF/FTC) plus cabotegravir placebo. In the HPTN 083 trial, 4,570 participants were randomised: 2,283 CAB-LA vs 2,287 TDF/FTC, with follow-up of 153 weeks (median follow-up of 1.4 years, interquartile range IQR, 0.8 to 1.9) [58, 59]. In the HPTN 084 trial, 3,224 were randomised: 1,614 CAB-LA vs 1610 TDF/FTC, with follow-up of 24 months (median follow-up time 1.24 years, interquartile range IQR 0.92-1.56) [41, 60]. Results were published in four scientific articles [41, 58-60]. Two of them are related to a detailed description of drug-resistant mutations [59, 60]. Study characteristics of these two RCTs can be found in Appendix, Table A-2.

beide RCTs aufgrund guter Ergebnisse bei Interimsanalyse vorzeitig abgebrochen

Both trials stopped early for efficacy, one on review of the results of the first preplanned interim end-point analysis and one on review of the results of the second preplanned interim end-point analysis (the Data and Safety Monitoring Board concluded that the results met the prespecified criteria for stopping the trial on the basis of efficacy).

Table 4-6: Studies included in SR of effectiveness and safety of injectable cabotegravir vs tenofovir disoproxil fumarate/emtricitabine: 2 RCTs from the updated literature search

Study	Location	Population	Intervention	Comparison	Number of participants	Follow-up	Adherence: high (≥80%) vs low (<80%)*
MSM							
Landovitz 2021 HPTN 083 [58]	US, Latin America, Asia, Africa	MSM and transgender women who have sex with men, 12.5%; median age 26 years	Long-acting injectable cabotegravir (CAB-LA) 600mg i.m every 8 weeks	Daily oral tenofovir disoproxil fumarate 300mg – emtricitabine 200mg (TDF–FTC)	4,570	153 weeks (median follow-up of 1.4 years)	High: 91.5% in injectable CAB-LA vs Low: 74.2% in TDF–FTC group by plasma drug detection
Heterosexuals (Women)							
Delany-Moretlwe 2022 HPTN 084 [41]	sub-Saharan Africa	Women (Female sex at birth); median age 25 years	Long-acting injectable cabotegravir (CAB-LA) 600mg i.m every 8 weeks	Daily oral tenofovir disoproxil fumarate 300mg – emtricitabine 200mg (TDF–FTC)	3,224	24 months (median follow-up time 1.24 years	High: 93% in injectable CAB-LA vs Low: 41.9% in TDF–FTC group by plasma drug detection

* *Adherence refers to the proportion of participants in trials that adhered to the study drug.*

Effectiveness

Outcome: HIV infection

Both RCTs found that the use of CAB-LA resulted in a statistically significant reduction in HIV risk, compared to oral PrEP (high certainty of evidence): in the HPTN 083 trial, out of total 52 HIV infections, 13/3205 were in the cabotegravir group (incidence, 0.41 per 100 person-years) vs 39/3187 in the TDF/FTC group (incidence, 1.22 per 100 person-years), Hazard Ratio (HR) 0.34 (95% confidence interval [CI], 0.18 to 0.62; p<0.001). In the HPTN 084 trial, out of total 40 HIV infections, 4/1956 HIV infections were observed in the cabotegravir group (HIV incidence 0.20 per 100 person-years [95% CI 0.06-0.52]) vs 36/1942 in the TDF/FTC group (1.85 per 100 person-years [1.3-2.57], HR 0.12 [0.05-0.31]; p<0.0001).

statistisch signifikante Reduktion der HIV-Infektionsrate in CAB-LA Gruppe (hohe Vertrauenswürdigkeit)

HPTN 083: 13 Neuinfektionen CAB-LA vs. 39 TDF/FTC; HPTN 084: 4 vs. 36

Of HIV infections identified in the groups randomized to CAB-LA, five were breakthrough infections (infections that occurred during appropriately timed CAB-LA injections). In the groups randomized to TDF/FTC, only two infections occurred in cases in which the drug concentrations measured were consistent with good PrEP adherence and in one participant who had drug concentrations consistent with partial adherence (4-6 doses per week).

CAB-LA: 5 Infektionen trotz zeitlich korrekt durchgeführter Injektionen; TDF/FTC: 2 Infektionen bei guter Adhärenz, 1 bei teilweiser Adhärenz

Outcome: Adherence

Adherence to daily oral TDF/FTC was lower than for cabotegravir injections every eight weeks. There was high overall adherence to injections. In HPTN 084, 93%, and in HPTN 083, 92% of person-years in the study were considered to have been "covered" by injectable CAB-LA/placebo – defined as injections received within two weeks after the scheduled date.

Adhärenz für tägliche orale PrEP geringer als für Injektionen; 92-93 % der Personenjahre durch CAB-LA/Placebo-Injektionen abgedeckt

In the HPTN 083 trial, better adherence to TDF/FTC was observed than in the HPTN 084 trial. In a randomly selected cohort of 390 participants, 74% of samples had drug concentrations (measured in dried blood spots) consistent with at least four doses per week over the preceding 1-2 months or 86.0% who were above the lower limit of quantitation (0.31ng per millilitre). In the HPTN 084 trial, samples from a randomly selected cohort of 405 participants in the TDF/FTC arm showed poor or inconsistent adherence over time. Overall, 1,084 (55.9%) of 1,939 evaluated samples yielded quantifiable plasma tenofovir concentrations (≥0.31ng/mL), whereas 812 (41.9%) of 1939 had tenofovir concentrations consistent with daily use (≥40ng/mL).

Adhärenz für TDF/FT: je nach Messmethode und Schwellenwert 42-86 %

Outcome: Drug resistance

Integrase strand transfer inhibitors (INSTI) resistance mutations were detected in 5 cases in the CAB arm (all in HPTN 083) (4 with INSTI resistance only and 1 with INSTI and nonnucleoside reverse-transcriptase inhibitor – NNRTI resistance).

INSTI Resistenz in 5 Fällen in CAB-Gruppe

In the HPTN 084 trial, nucleoside reverse-transcriptase inhibitor (NRTI) resistance was detected in 1 of 36 incident cases (poor adherence to TDF/FTC); 9 had nonnucleoside reverse-transcriptase inhibitor (NNRTI) resistance. None of the cases had CAB resistance (INSTI-resistance mutations).

NRTI Resistenz in 1 Fall (mit geringer TDF/FTC-Adhärenz), NNRTI Resistenz in 9 Fällen

Outcomes: STI and change in sexual behaviour

in beiden RCTs kein Gruppenunterschied bei STIs

Neither RCTs reported differences in incident sexually transmitted infections (STIs) between study arms: overall incidence of gonorrhoea was 13.49 per 100 person-years in HPTN 083 trial and 7.7 per 100 person-years in HPTN 084 trial. The overall incidence of chlamydia was 21.36 per 100 person-years and 19.6 per 100 person-years, respectively.

sexuelles Verhalten nicht erhoben

No studies reported on outcomes relevant to sexual behaviour, including condom use or number of sexual partners.

Outcome: Increases in body weight

anfänglich höhere Gewichtszunahme in CAB-LA Gruppe, später kein signifikanter Unterschied mehr

In the HPTN 083 trial, increases in body weight were noted across study arms, with those in the CAB-LA arm gaining on average 1.23kg per year and those in the TDF/FTC arm gaining on average 0.37kg. Differences in weight change between the groups were observed primarily in the first 40 weeks of participation and were similar in the two groups later in the trial. In the HPTN 084 trial, investigators noted an initial, immediate weight gain among participants randomized to CAB-LA but no statistically significant difference in weight increase when comparing mean increases in body weight among those in the CAB-LA arm and those in the TDF/FTC arm.

Outcome: Pregnancy incidence

insgesamt 49 Schwangerschaften, kein Gruppenunterschied

In HPTN 084 trial, overall confirmed pregnancy incidence in the trial was low (1.3 per 100 person-years [95% CI 0.9-1.7]) and did not appear to differ meaningfully by study group. Out of 49 confirmed pregnancies, 29 were in the cabotegravir group (1.5 per 100 person-years [1.0-2.2]) and 20 were in the TDF/FTC group (1.0 per 100 person-years [0.6-1.6]).

Safety

Outcome: AEs

92 % mind. 1 UE (≥ Grad 2), kein Gruppenunterschied (hohe Vertrauenswürdigkeit)

Most participants (92%) experienced at least one adverse event of grade 2 or higher during the study, but no significant differences were identified in rates of any adverse events between those randomized to CAB-LA and those randomized to TDF/FTC (high certainty of evidence).

Outcome: SAEs

2-5,3 % schwerwiegende UE, kein Gruppenunterschied (hohe Vertrauenswürdigkeit)

In HPTN 083 and HPTN 084, 5.3% and 2% of participants, respectively, reported serious adverse events, with percentages similar in the CAB-LA and TDF/FTC groups (high certainty of evidence).

Outcomes: Death

insgesamt 14 Todesfälle, davon 1 in TDF/FTC Gruppe assoziiert mit Tabletten oder Injektion

In the HPTN 083 trial, 11 participants died (7 in the TDF/FTC group and 4 in the cabotegravir group; hazard ratio, 0.57, 95% CI, 0.17 to 1.96). One death in the TDF/FTC group that resulted from cardiovascular disease was considered to be related to oral tablets or injections.

In the HPTN 084 trial, three deaths occurred, all in the cabotegravir group (0.2%). None of these three deaths observed were attributed to the study product; these deaths were due to hypertensive heart disease (n=1), a cerebrovascular accident (n=1), and an unexplained headache that could not be further investigated (n=1).

Outcome: Injection site reactions (ISR)

UEs im Zusammenhang mit Reaktionen an der Injektionsstelle (ISR)

Adverse events related to injection site reactions (ISR) were reported across both studies.

deutlich häufiger in CAB-LA Gruppe

In HPTN 083, 81.4% of participants randomized to CAB-LA who received at least one injection reported at least one ISR. Of these, 2.4% (n=50) of participants permanently discontinued injections due to ISRs. Within the group randomized to TDF/FTC (and placebo injections), 31.3% experienced ISRs. Injection site reactions were mostly mild or moderate in severity and decreased in frequency over time. Of 10,666 injection-site reactions in the cabotegravir group, 6,486 (60.8%) were pain, and 2,530 (23.7%) were tenderness; the events began a median of 1 day (IQR, 0 to 2) after injection and lasted a median of 3 days (IQR, 2 to 6).

ISR meist mild bis moderat, im Verlauf der Studie abnehmend

2,4 % Beendigung wegen ISR in einer Studie (in anderer Studie niemand)

In HPTN 084, 577 (38.0%) of 1,519 participants in the cabotegravir group compared with 163 (10.8%) of 1,516 in the TDF/FTC group experienced injection site reactions. Most reported ISRs were mild, and event rates for ISRs decreased over the course of the study. In the cabotegravir group, injection site reactions were reported in 438 (28.8%) of 1,519 participants at the first injection; this decreased to 25 (1.9%) of 1,322 participants by the fourth injection. There were no reported discontinuations due to ISRs.

Table 4-7 presents the summary of findings of the effectiveness to prevent HIV acquisition and safety outcomes AEs and SAEs.

Table 4-7: Summary of findings table: 2 RCTs – Injectable PrEP vs oral PrEP, in MSM, transgender women who have sex with men and cisgender women, on effectiveness and safety outcomes: HIV incidence, AE, SAE

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Effect size in RCTs Injectable cabotegravir vs oral TDF/FTC	Number of participants (RCTs)	Certainty of evidence (GRADE)
HIV incidence	not serious	not serious	not serious[a]	not serious[b]	none	17/3,896 (0.4%) vs 75/3,894 (1.9%)	7,790 (2 RCTs) [c]	⨁⨁⨁⨁ High
AE	not serious	not serious	not serious	not serious	none	3593/3,894 (92.3%) vs 3602/3,892 (92.5%)	7,786 (2 RCTs) [c]	⨁⨁⨁⨁ High
SAE	not serious	not serious	not serious	not serious	none	153/3,894 (3.9%) vs 154/3,892 (4.0%)	7,786 (2 RCTs) [c]	⨁⨁⨁⨁ High

Abbreviations: AE – adverse events; GRADE – grading of recommendations assessment development and evaluation; RCT – randomized controlled trial; SAE – serious adverse events

GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect;
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect;
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations:

a The evidence is directly related to many populations of interest, including cisgender women, men who have sex with men, and transgender women who have sex with men, but some populations for whom exposure to HIV is of potential concern, such as youth aged <18 years, people who inject drugs, people who are pregnant or breastfeeding, and transgender men, were not included in the two trials;

b Only 17 cases of HIV infection were identified among participants receiving CAB; but the sample sizes of the two trials were sufficiently large, so the evidence was not downgraded for imprecision. One case in HPTN 083 and one case in HPTN 084 were initially classified as incident infections but later re-adjudicated as baseline infections. These cases have been included in the primary analyses reported in each trial, they are also reported here. The true number of incident infections seen among those in the CAB arms is 15;

c [41, 58]

4.4 Safety of oral and injectable PrEP in pregnancy and lactation

SR zur Sicherheit von oraler TDF-basierter PrEP bei schwangeren und stillenden Frauen

One systematic review that assesses tenofovir disoproxil fumarate (TDF)-based oral PrEP safety in pregnant and breastfeeding HIV-uninfected women [40] included 14 studies, five completed and nine ongoing/planned, that evaluate maternal and/or infant outcomes following PrEP exposure during pregnancy or breastfeeding.

5 Studien aus Afrika mit insges. 1.042 PrEP-exponierten Schwangerschaften

in 4 Studien keine Unterschiede in Bezug auf Schwangerschafts- & kindliche Outcomes

1 Studie: im 1. Monat geringeres Wachstum, aber kein Unterschied nach 1 Jahr

Five completed studies included women in Kenya, Uganda, Zimbabwe and South Africa, between 2014 and 2018 [61-65], with a total of 1042 PrEP-exposed pregnancies. Partners PrEP Study [61], FEM-PrEP [62], and VOICE [65] were sub-studies of PrEP randomized control trials among HIV-serodiscordant couples or young women in African settings. As the original PrEP efficacy trials excluded pregnant women from enrolment and conducted monthly pregnancy testing, with discontinuation of the study drug as soon as pregnancy was detected, these studies provided data based on early first-trimester exposure, when teratogenic exposures can cause pregnancy loss and structural abnormalities such as neural tube defects. Four of the five completed studies found no differences in pregnancy or infant outcomes in the PrEP-exposed compared to unexposed arms. Infants from 246 women who were pregnant during PrEP exposure were evaluated at six weeks postpartum. Only one study out of these five, found that PrEP-exposed infants had a lower z-score (centile growth) at 1 month; but there was no difference at 1 year [63].

HPTN 084 Studie zu CAB-LA vs. TDF/FTC: insges. 49 Schwangerschaften, keine angeborenen Fehlbildungen

Additionally, in the new HPTN 084 trial, comparing injectable PrEP vs oral PrEP [41], data on both oral and injectable PrEP were found related to pregnancies and their outcomes. Out of 49 confirmed pregnancies, 29 were in the cabotegravir group (1.5 per 100 person-years [1.0-2.2]), and 20 were in the TDF/FTC group (1.0 per 100 person-years [0.6-1.6]). Outcome data were available for 31 (63%) of 49 pregnancies at the time of data lock, with the remainder of pregnancies ongoing. Most pregnancies resulted in a live birth (13 of 18 in the cabotegravir group and 10 of 13 in the TDF/FTC group), with the remainder ending in pregnancy loss (spontaneous or induced). No congenital anomalies were observed.

4.5 Ongoing trials

derzeit neun laufende RCTs registriert, davon 5 zu in diesem SR berücksichtigten Medikamenten, und 4 RCTs zu 2 anderen Medikamenten

Currently, there are nine registered ongoing RCTs (phase 2/3, 3 or 4) in ClinicalTrials.gov, ISRCTN and European Clinical Trials Registry, evaluating oral and injectable pharmaceuticals for HIV PrEP. Five RCTs are evaluating pharmaceuticals currently assessed in our SR, and four RCTs are evaluating the effectiveness and safety of two other antivirals: lenacapavir (a multistage, selective inhibitor of HIV-1 capsid function) and islatravir (a long-acting first-in class nucleoside reverse transcriptase translocation inhibitor).

Details can be found in Table A-8 in Appendix.

5 Results: other domains

Apart from effectiveness and safety, we also gathered information regarding the following other relevant domains, as specified by the EUnetHTA Core Model® Version 3.0 [28]: organisational, cost/economic, patient/social, ethical and legal domains. Additionally, this chapter summarises the results from the patient involvement in Austria, which also provides information relevant to the before mentioned domains.

auch organisatorische, ökonomische, soziale, ethische & rechtliche Aspekte berücksichtigt

5.1 Patient involvement in Austria

Three patient organisations: AIDS-Hilfe Wien, AIDS-Hilfe Steiermark, AIDS-Hilfe Vorarlberg, and Teampraxis Breitenecker (on behalf of different groups as a provider of service to people with HIV Infection, PEP, PrEP users, transgender medicine, intravenous drug addiction including opioid substitution therapy (OST), chemsex, and others) contributed to the AIHTA call for patient input, sent in January 2023. The information was collected to contextualise and better understand the issue from the user's perspective.

4 Fragebögen wurden ausgefüllt retourniert: AIDS-Hilfen aus 3 Bundesländern, 1 Teampraxis

The summary of the answers received related to different questions on the impact of HIV; experience with currently available interventions for HIV prevention; expectations of/requirements for a new medicine for PrEP, and additional information which the people at risk of HIV and HIV patient and/or caregiver believed would be helpful to the HTA researchers. The main aspects are summarised below; details are provided in Appendix (0).

Fragebogen zu HIV-Impact, Erfahrungen mit HIV-Prävention, Erwartungen an PrEP, … (Details im Anhang)

Zusammenfassung wichtiger Aspekte:

Impact of HIV: Austrian users stressed the negative impact of HIV on daily living, quality of life, psychological and social wellbeing, as well as the burden on carers/unpaid caregivers.

Experiences with currently available interventions for HIV prevention: Still, there is a big lack of knowledge on prevention and on sexual health as such, as well as on PrEP. PrEP is not promoted enough.

mangelndes Wissen über Prävention und sexuelle Gesundheit

Current use of PrEP: In Austria, PrEP is mainly used in the group MSM; only very few women and heterosexual men are using PrEP. PrEP is especially popular in the age between 25 and 40, from people who can afford it and used during sex parties or holidays and other occasions.

PrEP derzeit v. a. von MSM genutzt, kaum von anderen Gruppen

Specific risk groups: There are groups of people who currently don't have good access to available interventions for HIV prevention, such as migrants, people who fear being discriminated because of their sexual orientation, the group of the classic HIV-late-presenter (heterosexual men around 50 from the less urban areas), and vulnerable MSM.

spezifische Risikogruppen: z. B. Migrant*innen, vulnerable MSM

Barriers to PrEP use: Different factors could prevent access to interventions for HIV prevention, like stigma, financial issues and language barriers. People who live under financial constraints cannot afford PrEP, so PrEP medication might be ordered through the internet, without any quality assurance and without medical supervision. There should not be any financial obstacles in preventing HIV. PrEP must be offered free of charge, and cost coverage should be provided by Austrian health insurance companies, like in many European countries.

Barrieren: Stigma, PrEP-Kosten, …

mehr Information für Risikogruppen und Gesundheitspersonal

Availability of PrEP: It is important to reach the vulnerable groups with campaigns in different languages. More information is needed for heterosexual women and men, but also for health care providers, i.e., general practitioners and gynaecologists. More physicians are needed who prescribe PrEP.

Verbesserung der Lebensqualität sowie des Sexual- und Soziallebens durch PrEP

Benefits of PrEP: Quality of life and sexual and social life are all improved for PrEP users. HIV medicines (emtricitabine+tenofovir) as PrEP are extremely effective in preventing HIV infection, whether taken daily or on demand. It has been shown to be cost-effective. It is very likely that higher uptake of PrEP will reduce future transmissions and diagnoses of HIV in Austria and would prevent stigma and self-stigma.

5.2 Organisational Domain

organisatorische Aspekte

Several international guidelines and guidance documents provide detailed recommendations on the implementation of PrEP, e.g. the following documents:

Dokumente der WHO, ECDC mit Informationen zur PrEP-Implementierung

- WHO, 2021: Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach [16]
- WHO, 2022: Guidelines on long-acting injectable Cabotegravir for HIV prevention [14]
- WHO, 2022: Differentiated and simplified pre-exposure prophylaxis for HIV prevention. Update to WHO implementation guidance [66]
- ECDC, 2021: HIV Pre-Exposure Prophylaxis in the EU/EEA and the UK: implementation, standards and monitoring. Operational Guidance [9].

WHO-Empfehlungen:

orale PrEP (TDF) als Angebot für Personen mit hohem Risiko für HIV-Infektion, d. h. Inzidenz >3 pro 100 Personenjahre

individuelles Risiko abhängig von individuellem Verhalten

seit 2022 auch WHO-Empfehlung für CAB-LA als weitere PrEP-Option

The WHO recommends that oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection, which was defined as HIV incidence greater than 3 per 100 person-years without PrEP. This incidence has been identified among MSM, transgender women and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection. However, the individual risk is largely depending on individual behaviour and the characteristics of the sexual partners and, therefore, varies considerably within populations. Thus, local context and heterogeneity in risk should be considered in PrEP programmes and when deciding who might benefit from PrEP. The guideline additionally states that individuals requesting PrEP should be given priority to be offered PrEP because that indicates that there is a risk of acquiring HIV [16]. The WHO guideline from 2022 on CAB-LA [14] recommends that CAB-LA may be offered as an additional prevention choice for people at substantial risk of HIV infection as part of prevention approaches. It should be delivered as an additional option alongside other PrEP options (i.e., oral PrEP), which has the potential to increase uptake and effective use of PrEP, as it allows potential PrEP users to choose their preferred method. The detailed guideline recommendations can be found in chapter 1.3.

HIV PrEP not only consists of providing a drug, but has several other aspects. A PrEP programme is defined as 'a coherent set of activities as part of routine services that aim to identify, reach, and provide PrEP to the target population (however defined)' [13]. The Operational Guidance from the ECDC [9] defined ten core principles of effective PrEP programmes. For each of the principles, a rationale as well as quality statements and minimum standards are given.

PrEP: nicht nur Bereitstellung eines Medikaments, sondern Programm nötig

10 Prinzipien für effektive PrEP-Programme (ECDC):

1. **Early and ongoing stakeholder engagement:** Representatives of all stakeholder groups involved in or affected by the initiation of a PrEP programme should be engaged at relevant points in programme planning, delivery and monitoring, including, e.g., policy-makers, civil society, representatives from key populations/(potential) PrEP users, healthcare providers, researchers.

Einbeziehung aller Stakeholder

2. **Implementation within a stigma-free environment:** PrEP programmes should be centred on a positive and respectful approach to sexuality and sexual relationships, individuals' personal and cultural experiences and behavioural choices. This should help reduce PrEP stigma, encourage HIV testing and prevention, and reduce HIV infection. Whole society PrEP education is needed to take care that PrEP roll-out does not reinforce HIV/PrEP stigma. Stigma and bias can result in providers not willing to prescribe PrEP and may prevent potential PrEP users from requesting PrEP. People who experience multiple stigmas may need more tailored interventions for PrEP access. It is recommended to create a PrEP-positive and informed environment, e.g., through non-targeted community education campaigns which present PrEP as a responsible choice that protects both partners.

gesellschaftliche PrEP-Aufklärung um Stigma zu reduzieren

3. **Population-wide access, based on need**: PrEP should be accessible and affordable to all people in need of HIV prevention, where clinically appropriate, as part of combination prevention services. Availability of PrEP in a variety of settings that are easy to access for the groups that were identified as being in greatest need of PrEP is recommended, which may include telemedicine-delivered PrEP.

leistbarer Zugang für alle, die PrEP brauchen

4. **PrEP embedded in combination STI and HIV prevention and sexual health programmes:** PrEP should be provided, wherever possible, alongside and in combination with other STI and HIV prevention and sexual health and well-being programmes tailored to the individual's wants and needs. Where these additional services cannot be provided, PrEP users should be made aware of relevant services. This frames PrEP as a positive health and well-being choice.

Einbettung in andere STI- und HIV-Präventionsangebote, sowie Programme zur sexuellen Gesundheit

5. **Proactive approach to raising PrEP awareness and demand creation:** People from groups that have been carefully identified as being in greatest need of HIV prevention should be made aware of PrEP, how to access it and how to use it safely and effectively. Raising community-wide interest in and knowledge of PrEP could facilitate adherence and uptake. Self-referral is associated with strong adherence; therefore, a focus on demand creation could support adherence and thus effectiveness of the programme at population level.

proaktiver Ansatz zur Sensibilisierung und Information zu PrEP

6. **Compliance with clinical and public health guidelines:** PrEP programmes should be delivered within a system that enables and supports provider awareness of and compliance with relevant clinical and public health guidelines (i.e. local, national, EACS, WHO guidelines). National and local guidance, clear protocols for each PrEP delivery setting and standard operating procedures are necessary and should be reviewed regularly as part of ongoing quality improvement.

(inter-)nationale, lokale Leitlinien, klare Protokolle

standardisierte Kriterien zur Beurteilung des Bedarfs

7. **Use of standardised eligibility criteria to assess need:** PrEP programmes should offer clinical and behavioural/risk assessment against standardised eligibility criteria to determine whether PrEP is a suitable option for an individual.

Anbindung an HIV-Behandlung und andere relevante Einrichtungen

8. **Linkage into care:** PrEP programmes should promptly refer individuals who are diagnosed with HIV (at any stage) to appropriate settings where they can receive HIV treatment and care as needed. In addition, where needed, individuals should be referred to appropriate settings where they can receive sexual health and well-being information and support, e.g., mental health, drug and alcohol misuse, pregnancy testing and care, STI treatment and prevention.

Unterstützung bei der PrEP-Anwendung, z. B. Adhärenz, Follow-up Termine

9. **Continuation of PrEP:** PrEP programmes should support PrEP users to use PrEP appropriately, as required for their individual needs. This is a critical component of safe and effective PrEP use. Support can be delivered through a combination of clinical and community-based interventions/services and should include support with adherence, risk compensation, follow-up appointments, and when/how to safely stop/restart PrEP. PrEP provision should be flexible and is expected to vary according to the local health system, and infrastructural and epidemiological factors.

Monitoring und Evaluierung, Sammlung einiger Basisdaten

10. **Monitoring and Evaluation:** PrEP programmes should strive to deliver services within a monitored system in which it is possible to measure basic data on, e.g. people on PrEP, stopping PrEP, breakthrough infections, new STI infections, and transmitted drug resistance, so that effectiveness of the programme can be measured. The report provides 'preparatory questions' that address the main data areas for PrEP monitoring (see chapter 5.2.4) [9].

Guidance der WHO zur Implementierung einer differenzierten PrEP-Bereitstellung

The WHO implementation guidance update from 2022 [66] provides guidance on differentiated PrEP service delivery, which is person- and community-centred and adapts services to the needs and preferences of potential PrEP users. The document describes a framework using four building blocks of differentiated PrEP service delivery:

- Where? (service location; e.g., primary health care facility, community setting, virtual setting),
- Who? (service provider; e.g., physician, nurse, pharmacist, peer),
- When? (service frequency; e.g., monthly, every three months), and
- What? (service package; including HIV testing, clinical monitoring, PrEP prescription and dispensing, and comprehensive services).

These building blocks can be different for PrEP initiation, continuation and re-initiation, and for different PrEP medicines (i.e., oral or injectable PrEP).

5.2.1 HIV PrEP as part of existing prevention services

PrEP-Kaskade mit 6 Schritten

PrEP service delivery follows a cascade that is analogous to the HIV treatment cascade and includes the following steps: 1. screening individuals for HIV risk to identify potential PrEP candidates; 2. determining eligibility and interest in PrEP; 3. initiating PrEP; 4. achieving adherence (that is, taking medicines as prescribed); 5. continuing to take PrEP over time (including clinical monitoring) if risk continues; 6. stopping PrEP [67].

PrEP implementation should not replace other effective and well-established HIV prevention measures (e.g., distribution of condoms and harm reduction for people who inject drugs) but should be offered as part of a comprehensive testing, prevention and treatment service. The implementation of PrEP involves more than just ensuring the supply of medicines. PrEP programmes also include regular HIV testing, screening for other STIs, supporting adherence, advice on safer sex practices, counselling for individuals at substantial risk of infection and linking to treatment services for people with a positive HIV test before starting PrEP or seroconverting while using PrEP [16, 29, 68].

PrEP als Teil eines umfassenden Test-, Präventions- und Behandlungsdienstes

PrEP Programm: nicht nur Medikament, auch Testen auf HIV/ andere STIs, Beratung etc.

Oral PrEP

Interventions that should be provided before or accompanying **oral PrEP** use include the following [16, 18, 19]:

Interventionen vor PrEP oder begleitend:

Counselling

Before PrEP is prescribed, a comprehensive briefing and counselling should be done, which should address at least the following topics:

- risk reduction based on the effectiveness of oral PrEP,
- STI transmission risk and vaccination prevention,
- test procedures (including the 'diagnostic gap' of HIV serology),
- other preventive measures (e.g., condoms, therapy as prevention, post-exposure prophylaxis),
- the importance of adherence,
- accompanying examinations,
- limitations of PrEP, including the possible development of resistance,
- potential side effects, interactions, and complications of PrEP,
- symptoms of acute and/or primary HIV infection [18, 19].

umfassende Beratung zu mehreren Themen

z. B. Risikoreduktion, notwendige Tests, andere Präventions-maßnahmen, Adhärenz, potentielle Nebenwirkungen etc.

HIV testing

Before starting PrEP, a negative HIV test (fourth-generation ELISA with p24 antigen/HIV antibody; not older than 14 days) is required. The HIV test should be repeated after one month of PrEP use to detect an infection that may have been present when PrEP was initiated. HIV testing should be conducted regularly, e.g., every three months, during PrEP use [16, 18, 19].

negativer HIV-Test nötig vor PrEP-Start, Wiederholung nach 4 Wochen, danach regelmäßig (z. B. alle 3 Monate)

Monitoring renal function

A reduced kidney function (creatinine clearance of <60mL/min) is a contraindication for using oral PrEP containing TDF. However, abnormal creatinine clearance among PrEP users younger than 30 years with no kidney-related comorbidities is rare, and creatinine screening may therefore be considered optional in this group. The WHO guideline suggests that all individuals aged 30 years and older and those younger than 30 years who have comorbidities are screened for serum creatinine once within 1-3 months after oral PrEP initiation to simplify the delivery and cost of PrEP. For individuals of any age with a history of comorbidities such as diabetes or hypertension, those aged 50 years or older and those who have had a previous creatinine clearance of <90ml/min, a further test after the baseline screening and every 6-12 months thereafter can be considered [16].

Monitoring der Nierenfunktion (Kreatinin-Clearance <60mL/Min. = Kontraindikation für PrEP)

Testschema je nach Alter und individuellem Risiko (Komorbiditäten)

Empfehlungen der deutsch-österreich. Leitlinie

The German-Austrian guideline recommends testing serum creatinine for examination of estimated glomerular filtration rate (eGFR) every 3-6 months if eGFR 60-90ml/min and/or age > 40 years and/or risk factors for renal conditions and every 6-12 months if eGFR > 90mL/min and < 40 years [18, 19].

Testing for other STIs

empfohlene Tests: Hepatitis B, Hepatitis C, Syphilis, Gonorrhö, Chlamydien

The WHO guideline recommends testing for hepatitis B surface antigen (HBsAg) once at PrEP initiation and considering Hepatitis C antibody testing at PrEP initiation and every 12 months thereafter, depending on the local epidemiological context. Hepatitis B or C infections are not a contraindication for oral PrEP use [16]. The German-Austrian guideline recommends repeating syphilis testing and medical history indicating symptoms of an STI every three months and testing for pharyngeal, anorectal and genital/urine gonorrhoea and chlamydia using nucleic acid amplification testing (NAAT) every 3-6 months [18, 19].

Adherence support

Unterstützung der Adhärenz

z. B. Beratung → Verbindung der Einnahme mit täglicher Gewohnheit, Wecker, App; auch Peer-Gruppen, soziale Medien

PrEP users should be informed that PrEP is highly effective when used as prescribed. For daily oral use, it may be helpful to provide brief client-centred counselling that daily medication should be linked with a daily habit, e.g., after waking up, before going to sleep or with a regular meal. Other recommendations to improve adherence of PrEP users are setting a daily alarm, using a special smartphone application for adherence, storing medication at several places, or using a week-dispenser [16, 69]. The WHO guideline also suggests that tailored interventions may be needed to improve adherence among particular groups, such as young people. The offer of support groups, including social media groups, may be helpful for sharing experiences and challenges among peers [16].

Injectable PrEP

injizierbare PrEP (CAB-LA)

HIV-Test, evt. Leberfunktionstest vor PrEP-Beginn

ebenfalls Kombination mit anderen effektiven Präventions-maßnahmen, z. B. STI-Tests, Bereitstellung von Kondomen

Regarding the implementation of **injectable PrEP** (long-acting cabotegravir, CAB-LA), HIV testing is also required before offering CAB-LA and should be conducted before each injection. Liver function testing can be considered before and during CAB-LA use because raised liver function levels have been reported in a small number of people in the CAB-LA trials (although similar levels were found among those receiving placebo injections). Advanced liver disease or acute viral hepatitis are contraindications for using CAB-LA. Testing for HBV and HCV is recommended, but clinical trial data and implementation experience with CAB-LA and HBV or HCV infections are very limited. For people with HBV, TDF-based oral PrEP is the preferred option, as this will both suppress HBV and prevent HIV. Kidney function testing and monitoring are not required for CAB-LA use. As with oral PrEP, CAB-LA should be combined with other effective and well-established prevention approaches and health services. This includes, e.g., the provision of condoms, testing and treatment of STIs and viral hepatitis, sexual and reproductive health services, mental health support, services that prevent and protect against gender-based violence, gender-affirming care and harm reduction services for people who use drugs (including for chemsex) [14].

Beratung wichtig: z. B. …

PrEP products should be used during periods of substantial HIV risk and can be stopped if a person is no longer at risk or decides to use an alternative PrEP product or HIV prevention measure. When a scheduled injection is missed or PrEP is discontinued, CAB concentrations decline slowly and become gradu-

ally less protective in this so-called pharmacokinetic tail. HIV infections may occur in this period, and there is a risk of drug resistance when HIV infection occurs soon after discontinuation. It is, therefore, very important to counsel CAB-LA users on the need to receive injections as scheduled (i.e., every two months) to ensure that CAB-LA is most effective. Further counselling topics include the risks for drug resistance, the occurrence of possible side effects and the importance of using other prevention options if CAB-LA is discontinued in periods where the client is still at risk of HIV acquisition. Tailored interventions to support adherence to the injection schedule are recommended. The possibility for peer-to-peer sharing of experiences and challenges in support groups, including social media groups, may be helpful [14].

… zur Unterstützung der Adhärenz (Injektionen alle 2 Monate), potentielle Nebenwirkungen, andere Präventionsoptionen bei Absetzen von CAB-LA und weiter bestehendem HIV-Infektionsrisiko etc.

5.2.2 Accessibility

Different types of healthcare and lay providers can be involved in PrEP services, e.g., nurses, pharmacists, and lay and peer providers. In most countries, clinicians prescribe PrEP [13], and other healthcare providers may take part in providing other aspects of PrEP services, e.g., HIV testing. Task-sharing with, e.g., nurses or peer and community health workers, could improve health system efficiency, may support service delivery models that are more acceptable to users and reduce barriers to PrEP uptake and adherence. Adequate training is necessary for all providers involved in PrEP service delivery [16, 66].

unterschiedliche Gesundheitsberufe beteiligt

PrEP-Verschreibung meist durch Ärzt*innen

The guideline from the National Institute for Health and Care Excellence (NICE) on 'Reducing sexually transmitted infections' (2022) [70] recommends that services that do not provide PrEP themselves should refer people who are interested and eligible for PrEP to a service prescribing PrEP and there should be clear referral pathways. Services that offer PrEP should be welcoming and accessible for all eligible population groups, which can be facilitated, e.g., by co-designing services with the key population group. NICE further recommends raising awareness among local groups with greater sexual health needs and focusing specifically on groups with less knowledge or lower uptake of PrEP. These include, e.g. trans people, cisgender women, young people, and people with migration or lower socioeconomic status backgrounds. It is also recommended to normalise PrEP use, reduce stigma and increase trust in services with the support of peers [70].

Zugänglichkeit von PrEP-Einrichtungen

Fokus auf Gruppen mit geringem PrEP-Wissen, z. B. Migrant*innen, trans Personen, junge Menschen

Normalisierung, Verringerung von Stigmatisierung

The WHO guideline also suggests strongly involving community-based organisations, especially those working with key populations, by providing information about PrEP availability and use and by linking with PrEP providers and other health, social and community services [16].

Einbeziehung von kommunalen Einrichtungen

According to the ECDC operational guidance on implementation, standards and monitoring [9], all PrEP delivery settings should have access to the following:

Zugang zu Ressourcen für PrEP-Einrichtungen:

- Physicians with expertise in the management of HIV infection, antiretroviral drugs, and STIs (to prescribe/oversee prescribing, provide expertise in clinical decision-making),
- Standardised clinical histories of potential PrEP users,
- Pharmacy service for storing, supervising and dispensing medication,
- Laboratory for HIV infection diagnosis, viral load measurement, and resistance studying,

z. B. Ärzt*innen mit entsprechender Expertise, Lagerung und Ausgabe der Medikamente, Labors, Kapazitäten für Beratung zu Adhärenz und sexuelle Gesundheit etc.

- Laboratory for evaluation of blood parameters and biochemistry,
- Capacity to evaluate referral pathways to STI diagnosis facilities,
- Capacity to provide counselling on adherence and sexual health.

mögliche Settings für PrEP-Angebote

Integration in bestehende Dienste, z. B. Sexual- oder Familienberatungsstellen, Organisationen für MSM oder trans Personen, Einrichtungen für Sexarbeiter*innen, Hausärzt*innen, Apotheken, gemeindenahe Einrichtungen

It should be ensured that PrEP is available in a setting that is accessible to the populations in greatest need of PrEP. Ideally, PrEP services should be integrated into settings which are already attended by the target population for other purposes, e.g., sexual health. Intersectional service delivery may improve access, e.g., PrEP could be offered in migrant support services or drug use support groups. Other settings that could consider integrating PrEP services include sexual health clinics, family planning services, services for MSM and transgender people, services for sex workers, family practitioners and pharmacies. Before the implementation of PrEP, countries should consider the national context, i.e. where HIV and STI testing and treatment are currently provided and where potential target populations for PrEP seek care. This could also be, for example, gynaecological care providers who might be a preferred setting for women. Certain aspects of a PrEP programme could possibly be shared with other areas of HIV prevention, testing and care to facilitate scale-up and reduce costs. It can also be helpful to consider if PrEP can be offered in a client-centred approach, e.g., within comprehensive sexual health packages in community settings. Other potentially relevant questions refer to the possibility of changing legislation so that a wider group of healthcare professionals (e.g., nurses) can prescribe PrEP or so that HIV self-testing is allowed [9].

Beispiele für differenzierte PrEP-Angebote, z. B. Apotheken, fixe oder mobile kommunale Einrichtungen, Telemedizin

Vorteile von entmedikalisierten und gemeindenahen Angeboten, aber regelmäßiger persönlicher Kontakt wichtig

The WHO implementation guidance [66] mentions a range of examples for differentiated oral PrEP service delivery models, e.g., in fixed and mobile community sites, pharmacies or telehealth models. Some of these models provide PrEP services for initiation and continuation outside healthcare facilities, and others involve the initiation of PrEP at a healthcare facility and continuation in community settings. PrEP delivery outside of clinic settings was commonly implemented during COVID-19 restrictions and has often been maintained due to clients' preferences for, e.g., fewer clinic visits or more privacy. Telehealth and online services can be especially useful for follow-up consultations of PrEP users who have no challenges to effective use, which allows for more time for clinic staff for clients initiating PrEP or those who have complex medical and psychosocial needs. It is also reported that differentiated services are supported by HIV self-testing and STI self-sampling. However, most providers emphasized that regular in-person engagement with PrEP users is important for examinations and discussions about sexual health. Nevertheless, they recognised the benefits of demedicalised and community-based PrEP delivery, and some providers were concerned that new PrEP products (i.e. CAB-LA) may lead to remedicalisation of PrEP services.

ECDC: meist genanntes Setting = Ambulanz für Infektionskrankheiten, weiters private Anbieter*innen, Internet

The ECDC progress report 2022 found that the most common setting for the provision of PrEP was infectious disease clinics (cited by 29 of 49 countries), followed by private providers and the internet (14 of 49 countries each). 11 of 49 countries reported that PrEP is provided in sexual health clinics and primary care, respectively [11]. There is growing expert opinion that follow-up visits of ongoing PrEP use (after the initial eligibility consultation) could be provided by non-HIV specialists and in non-medicalised settings, e.g. in primary care, gynaecological clinics and/or community-based settings, following appropriate local, national and international clinical guidance [9].

Primärversorgung oder kommunale Einrichtungen werden seltener genannt

However, these models of service delivery do not seem to be very common yet. A supplementary document related to the ECDC operational guidance [9] includes case studies from 17 European countries[9] regarding the implementation of PrEP programmes and defines five different PrEP service delivery models (clinic-based, community-based, HIV specialist, primary care, peer/population/online-based). All countries report the use of either HIV specialist model and/or clinic-based service delivery model. Community-based models exist (among other models such as HIV specialist or clinic-based) in only 4 of the 17 countries (Italy, Poland, Spain, Switzerland). Only one country (Switzerland) reports that PrEP is also provided in a primary care model (in addition to other models) [9].

5.2.3 Training and education

Aus- und Fortbildung für alle PrEP-Anbieter*innen

Several guidelines and guidance documents emphasise the need for adequate training and continuing education for all PrEP providers [9, 16, 70], which is described as a key component of facilitating PrEP programmes [9] and also aims to raise awareness among healthcare professionals [70]. Training and education should address, e.g.:

Inhalte: z. B. Wirksamkeit der PrEP, Auswahlkriterien, HIV-Risikoassessment, Beratung, andere Präventions-maßnahmen, Wissen zu sexuellen Minderheiten, Sexualverhalten etc.

- HIV and PrEP literacy,
- PrEP effectiveness,
- PrEP delivery according to clinical guidelines,
- PrEP eligibility assessments, prescribing and management,
- long-term health effects of using PrEP,
- counselling and HIV risk assessment,
- sexual behaviours and sexual orientation,
- sexual history taking and sexual minority competence,
- other HIV prevention interventions [9, 70].

Schulung der Kommunikationsfähigkeiten sehr wichtig, um individuelles Infektionsrisiko sowie mögliche Barrieren zu besprechen

Healthcare providers involved in PrEP services need adequate training and support to be able to have conversations to explore sexual and injecting risk behaviour with their patients and to help them estimate their individual risk of HIV infection and the potential benefit of PrEP use. It is important that service providers consider all health, social and emotional needs of PrEP users and interested people. They should be able to provide or refer to services as needed, e.g., services for mental health, intimate partner and gender-based violence, family planning, and STI testing and care. Respectful and inclusive services are needed that are appropriate for all key populations, including young people. A strong patient-carer relationship is helpful in enabling discussion of barriers and facilitators regarding adherence and self-care [16].

viele Barrieren im Zusammenhang mit Aus- und Fortbildung

A literature review from 2018 identified several barriers on different levels (patient, provider, healthcare system; see below) and matched them with interventions to overcome these barriers. On a provider level, most interventions are related to education and training on PrEP, but also regarding trans- and gender-affirming care [71].

[9] Belgium, Croatia, Czechia, England, Finland, France, Germany, Greece, Ireland, Italy, Malta, Netherlands, Poland, Scotland, Spain, Sweden, Switzerland

Informationskampagnen empfohlen, um Bewusstsein zu erhöhen und Wissen über PrEP in der Bevölkerung zu verbessern

The ECDC guidance additionally recommends to also focus on community education to raise awareness and increase knowledge of PrEP in the community which can facilitate adherence and uptake. Such a campaign should, e.g., describe PrEP and its use as well as provide advice regarding eligibility for PrEP and other HIV prevention methods. Multimedia approaches, community forums, and social media can be used. Information should be produced in the languages, formats and tones that are most accessible to the target populations [9].

Ausbildungsinhalte bezüglich CAB-LA:

Regarding the – not yet EMA approved – injectable PrEP (CAB-LA), provider training should include the following aspects:

u. a. korrekte Verabreichung, Besprechung von Präferenzen, Schulung in respektvoller & sensibler Gesprächsführung, Berücksichtigung aller gesundheitlichen, sozialen & emotionalen Bedürfnisse

- capacity building on discussing HIV prevention needs and preferences with clients,
- assessing the appropriateness of the different HIV prevention options available,
- correct administration of CAB-LA,
- support for safe and effective use,
- provision of or referral to other services,
- training to provide respectful, non-judgemental and inclusive services, to discuss sensitive behaviour and to build a strong patient-provider relationship,
- training on how to have respectful and sensitive discussions with clients on HIV prevention needs and preferences,
- awareness of emotional and physical trauma that people at substantial risk of HIV infection may have experienced,
- consideration of all health, social and emotional needs of people interested in and using PrEP and provision or referral to appropriate services [14].

5.2.4 Quality assurance and monitoring

Monitoring-System empfohlen um Basisdaten zu messen

It is recommended that PrEP programmes should deliver services in a monitored system that makes it possible to measure basic data on, e.g., people on PrEP, stopping PrEP, breakthrough infections, new STI infections, and drug resistance [9].

ECDC: Liste vorbereitender Fragen für Länder, zu folgenden Bereichen:

The ECDC guidance [9] includes a list of preparatory questions addressing the main areas for PrEP monitoring, which can be useful for countries to review their surveillance systems:

STI- und HIV-Monitoring

- STI and HIV surveillance in your country/region:
  - How many HIV tests are currently performed annually?
  - How many individuals have one or more HIV tests annually?
  - How many individuals have been newly diagnosed with HIV annually?
  - How many individuals have one or more STI tests annually?
  - How many individuals have been newly diagnosed with one or more STIs in your region?

PrEP-Bedarf und -Nachfrage

- Need and demand:
  - What is the demand for PrEP in your region by population group?
  - What is the need for PrEP in your region by population group?
  - How many individuals have ever used PrEP?

- Access and uptake: **PrEP-Zugang und -Akzeptanz**
  - In which settings is PrEP available? And to which populations?
  - How many individuals have attempted to access PrEP in a 12-month period?
  - How many individuals were eligible for PrEP in a 12-month period?
  - How many individuals were offered PrEP in a 12-month period?
  - Are reasons for not offering or not being eligible recorded in a standardised way?
  - In prescribing data, is it possible to distinguish ARTs for HIV prevention (PrEP) from ARTs prescribed for treatment purposes?
  - How many individuals accepted the offer of/were prescribed PrEP for HIV prevention purposes in a 12-month period?
- PrEP use: **PrEP-Nutzung**
  - How many people have been prescribed PrEP at least once in a 12-month period?
  - How many people have only been prescribed PrEP once in a 12-month period?
  - Are reasons for missed follow-up appointments recorded in a standardised way?
- Toxicity, drug resistance and seroconversion: **Toxizität, Arzneimittelresistenz und Serokonversion**
  - Among individuals diagnosed with HIV, how many have ever used/been prescribed PrEP?
  - How many people with a history of PrEP use who are newly diagnosed with HIV have evidence of viral resistance mutations associated with tenofovir disoproxil fumarate/emtricitabine use?
  - Is a record of renal function maintained?
  - Is there a record of side effects or medical complications experienced by PrEP users?

Monitoring-Tool der ECDC: Referenzkatalog gemeinsam vereinbarter Indikatoren für die Datenberichterstattung

A recent report from the ECDC [13] outlines a monitoring tool which was informed by a broad panel of clinical, research and community experts from different EU/EEA countries and organisations. It provides countries with a reference set of commonly agreed indicators for data reporting and is intended to be used by PrEP programme implementers or other stakeholders in the design and implementation of national or sub-national PrEP programmes. The indicators are clustered according to their priority (core indicators, supplementary indicators, optional indicators). The tool is structured along three key steps of a care continuum adapted to PrEP:

Einteilung in 3 Kategorien, geclustert nach Priorität

- Pre-uptake,
- Uptake and coverage,
- Continued and effective use of PrEP [13].

The monitoring tool does not set a normative standard but provides guidance on the different options that are available to monitor PrEP programmes. An overview of the included indicators can be found in Table 5-1.

Table 5-1: Overview of indicators from the ECDC monitoring tool

Indicator name	Description	Numerator/Denominator	Rationale for reporting
Domain 1: Pre-Uptake			
PrEP service availability	This indicator aims to describe the availability of PrEP services in different geographical areas within a country.	*Numerator:* the number of facilities that offer PrEP per 100,000 population in a given geographical area within a country *Denominator:* N/A	Geographical access to PrEP services is a prerequisite for uptake. Proximity to facilities that offer PrEP is an aspect of access that may be especially relevant in contexts where PrEP follow-up is conducted through regular (e.g. tri-monthly) in-person visits.
PrEP awareness among potential users	This indicator aims to track the awareness of PrEP as an HIV-prevention option among a specific population group.	*Numerator:* the number of people who report being aware of the existence of PrEP as an HIV-prevention option (regardless of whether PrEP is available to them), among the denominator. *Denominator:* the number of people from a sample population who are questioned about PrEP awareness.	Awareness of PrEP as a valid HIV-prevention option is a necessary first step for potential PrEP candidates towards developing informed opinions on its intended use, which may eventually result in the uptake of PrEP. A broad sense of awareness of PrEP among the general population may contribute to a stigma-free environment related to PrEP and HIV, facilitating PrEP uptake. On a more programmatic level, low levels of PrEP awareness among specific populations may lead to the identification of opportunities for additional demand-creation efforts.
Willingness to use PrEP	This indicator aims to measure whether individuals among a specific population group are willing to use PrEP if it was available/offered to them.	*Numerator:* the number of individuals who report their willingness to use PrEP if it were offered/available to them, among the denominator. *Denominator:* the number of people from a sample population who are questioned about their willingness to use PrEP.	Similar to 'PrEP awareness among potential users', 'willingness to use PrEP' reflects a key step in the thought process of potential PrEP candidates on their trajectory of PrEP uptake. This step is closer to the actual use of PrEP than 'PrEP awareness'. On a programmatic level, this indicator may provide insights into the potential unmet demand for PrEP among certain (surveyed) populations.
Domain 2: Uptake and coverage			
Current PrEP users	This indicator aims to keep track of how many people used PrEP during the reporting period.	*Numerator:* the number of unique individuals who received PrEP for HIV prevention at least once during the reporting period. *Denominator:* N/A (optional for reporting at the EU-level: per 100,000 population)	The number of current PrEP users is key to assess the scope and reach of a PrEP programme at any stage of implementation. If measured repeatedly, it may give an indication of the expansion of the programme over time. Additionally, this indicator can signal possible gaps in PrEP access among certain population groups, or in a given geographical area, if disaggregated by relevant characteristics related to user profiles. Lastly, monitoring this indicator can also be useful to predict future demands for PrEP, which, especially in the early stages of implementing PrEP, might be helpful to ensure the allocation of sufficient (human and infrastructural) resources and an uninterrupted supply of commodities. This indicator does not provide any insight into PrEP use over time.
New PrEP users	This indicator aims to monitor how many people used PrEP for the first time in their lives during the reporting period.	*Numerator:* the number of unique individuals who received PrEP for HIV prevention for the first time during the reporting period. *Denominator:* N/A (optional for reporting at the EU-level: per 100,000 population)	This indicator aims to identify and distinguish people who accessed PrEP for the first time ever (during the reporting period), from PrEP users who continued to use PrEP or re-started PrEP after a gap in use. The number of first-time PrEP users provides insight into the ability of a programme to newly engage people into using PrEP as an HIV-prevention method. In combination with additional information on the profile of new 'PrEP starters', it tracks progress in the accessibility of PrEP for certain population groups. Especially for early-stage PrEP programmes, this indicator may prove useful to track the expansion of the programme in terms of reaching new population groups with PrEP services (e.g. according to key populations or geographical area of residence).
PrEP coverage	This indicator aims to describe how many people currently use PrEP relative to the population in need of PrEP.	*Numerator:* the number of people who used PrEP at least once during the reporting period. *Denominator:* the estimated number of people that are eligible for PrEP, according to local PrEP-eligibility criteria.	Estimates of 'PrEP coverage' provide insights into the extent to which a PrEP programme has reached a target population for PrEP, and conversely, how many people who could benefit from PrEP are currently not accessing it ('unmet need'). Low PrEP coverage may signal potential issues that warrant further investigation, ranging from low PrEP awareness and/or willingness to use PrEP, to more structural barriers to access (e.g. financial or geographical barriers).

Indicator name	Description	Numerator/Denominator	Rationale for reporting
Domain 3: continued and effective use			
Recent PrEP use among people newly diagnosed with HIV	This indicator aims to measure how many people who experienced an HIV seroconversion, recently accessed PrEP.	*Numerator:* the number of people who received PrEP at least once in the 12 months prior to being diagnosed with HIV, and who had at least one follow-up HIV test, among the denominator. *Denominator:* the number of people newly diagnosed with HIV during the reporting period.	This indicator aims to direct attention to situations where an HIV seroconversion took place despite having had (recent) access to PrEP, and hence may flag possible missed opportunities for HIV-prevention programmes. While some of the structural barriers that drive new HIV diagnoses among recent PrEP users are clearly out of the control of service providers, it is important to gain insights into such missed opportunities to address them at a policy or health systems level. Hence, this indicator may help revealing where a PrEP programme did not succeed to engage people who were previously contacted by the programme about using PrEP appropriately. Outcomes may prompt further investigation into the potential reasons for seroconversion, in order to distinguish (exceptional) failures under optimal adherence from situations where PrEP was not used, or inappropriately interrupted.
PrEP continuation	This indicator aims to describe how many people who started PrEP continue to use it in the 12 months after PrEP initiation.	*Numerator:* the number of people who had at least one PrEP refill or follow-up visit in the 12 months after PrEP initiation, among the denominator. *Denominator:* the number of people who were prescribed PrEP for the first time in their lives during the previous reporting period.	Effective PrEP use is not necessarily defined by uninterrupted longitudinal use, given that individuals may use PrEP on-demand and/or 'cycle' in and out of periods of substantial risk of HIV. In the light of this challenge, the ECDC expert panel did not find consensus on a meaningful timepoint up until which to assess PrEP continuation rates in order to evaluate the performance of PrEP programmes. Yet, it was agreed that the time of PrEP initiation provides a useful starting point, since it gives a baseline indication of 'PrEP need', ideally based on a judgement of HIV risk as part of the PrEP eligibility screening process. Given that HIV risk is unlikely to change on the short-term for a large group of people, focusing on sustained PrEP use after initiation might reveal potential shortcomings of a PrEP programme to sufficiently support clients into using PrEP when they need it, or to access follow-up care. When this indicator is disaggregated by user characteristics (e.g. 'key populations' for PrEP), it may reflect whether certain population groups might disproportionately experience barriers to continuous engagement with PrEP. It should be noted that experience with this indicator is currently too low to interpret low continuation rates as 'PrEP programme failures', as users may discontinue PrEP for many different, valid reasons.

Source: [13], (green = core indicator, orange = supplementary indicator, blue = optional indicator)

5.2.5 Barriers to PrEP implementation

zahlreiche Barrieren auf unterschiedlichen Ebenen

Several barriers to PrEP implementation and access have been identified on different levels: patient, provider, and healthcare system levels. Barriers on the individual/patient level include, for example:

Barrieren auf individueller Ebene: z. B. …

- low awareness of PrEP,
- fear of side effects,
- distrust of the medical system: structural racism, transphobia, and negative experiences,
- unwillingness to discuss PrEP with primary care providers,
- actual or perceived lack of privacy,
- stigma and discrimination,
- negative attitudes of healthcare providers,
- travel distance,
- direct and opportunity costs for clients,

… Angst vor Nebenwirkungen, Misstrauen gegenüber Gesundheitssystem, Stigmatisierung, Diskriminierung, Kosten, Wartezeiten etc.

- frequency of required clinic visits for continuation,
- lengthy waiting times,
- inconvenient operating hours [66, 71].

Barrieren auf Ebene des Gesundheitspersonals: z. B. …

On the *healthcare provider level*, the following barriers are mentioned:

… Mangel an PrEP-Wissen, fehlende Ausbildung, Mangel an Zeit und Personal, Bedenken hinsichtlich der Adhärenz etc.

- policy and legal barriers (e.g., policies restricting eligibility),
- lack of PrEP knowledge,
- lack of training,
- disagreement/uncertainty about appropriate PrEP patients,
- concerns/uncertainty about insurance coverage for PrEP,
- concerns about behavioural and health consequences,
- concerns about patient adherence,
- interpersonal stigma,
- biases against patients' race and sexual behaviours,
- concerns about PrEP efficacy, toxicity, and resistance,
- understaffing,
- limited time for interactions with clients,
- stockouts of drugs and supply [66, 71, 72].

"Purview Paradoxon" = Uneinigkeit wer für PrEP-Verschreibung zuständig ist (Hausärzt*innen oder HIV-Spezialist*innen)

In the literature, the so-called Purview Paradox is described as another important barrier to PrEP implementation. This refers to the discordance in beliefs between HIV specialists and primary care providers on who should prescribe PrEP and the optimal clinic setting. The paradox is that neither HIV specialists nor primary care doctors consider PrEP to fall within their clinical domain. HIV specialists, who are best trained and most willing to prescribe PrEP, often do not see HIV-negative patients, while primary care doctors, who regularly care for HIV-negative patients, might lack sufficient training to provide PrEP [71-73].

Barrieren auf Ebene des Gesundheitssystems: z. B. …

The ECDC guidance [9] states that PrEP implementation often starts on a small scale, with a few clinicians prescribing the drug. However, PrEP must be offered and used on a much larger scale to have a measurable effect on HIV incidence in a country. A large number of socio-cultural and healthcare system factors can influence PrEP implementation. Barriers to PrEP service delivery on a *healthcare-system level* include, for example:

… gesellschaftliche Stigmatisierung & Diskriminierung, Transphobie und Homophobie, widersprüchliche gesundheitspolitische Prioritäten, begrenztes Budget, Mangel an Schulungen & Überweisungspfaden etc.

- societal and community stigma and discrimination against specific population groups, lack of gender-affirming healthcare for transgender women, low prioritisation of PrEP for people who inject drugs, stigma associated with PrEP use and accessing HIV services, the intersection of HIV-stigma with transphobia and homophobia, multiple marginalised identities of PrEP users (for example, migrant MSM and MSM engaging in chemsex),
- conflicting political and public health priorities (at national and local levels), including acute and unexpected issues, such as the COVID-19 pandemic,
- effects of economic instability (for example, as a result of the COVID-19 pandemic),
- limited health budgets to set up and sustain PrEP programmes, lack of insurance coverage and financial assistance programmes,
- existing capacity constraints, staffing and infrastructural issues,

- current knowledge and attitudes of providers (including those outside of the infectious disease speciality),
- lack of effective messaging about PrEP, lack of communication between healthcare providers and community-based organisations,
- current access to HIV and STI testing and treatment,
- lack of training, referral systems, or established reimbursement levels for care and drugs,
- legal constraints to providing PrEP for youth, including mandates to involve parental figures in working with minors,
- lack of access to care: inadequate transportation, inflexible work schedules, inconvenient locations dispensing PrEP, time constraints on medical appointments, lack of medical insurance and limited insurance networks, lack of patient confidence and perseverance to access care [9, 29, 71].

weitere Barrieren auf Länder-Ebene: Kosten, Bedenken bzgl. STIs

According to the ECDC progress report, barriers mentioned by the countries that had not yet developed PrEP guidelines include, e.g., cost of the drug, concerns about increased transmission of other STIs, costs of service delivery, concerns about lower condom use, as well as concerns about adherence [74].

PrEP in kommunalen Settings & außerhalb von Gesundheitseinrichtungen → könnte Barrieren tw. beseitigen, mehr Wahlmöglichkeit

The WHO implementation guidance states that it can be feasible and appropriate to deliver oral PrEP in community settings and outside of healthcare facilities. This could overcome barriers to PrEP access and use and also expand choice and increase convenience for PrEP users according to their individual preferences for location and service type. Regarding the feasibility of delivering CAB-LA outside of healthcare facilities, more implementation research is needed [66].

Vorteile der injizierbaren PrEP: z. B. keine tägliche Pilleneinnahme, größere Diskretion, höhere Sicherheit bei bestehenden Nierenerkrankungen

Barrieren: z. B. Kosten, Abneigung gegen Injektionen

In a global survey conducted by the WHO in 2021, PrEP providers were asked about current service delivery practices as well as values and preferences regarding new PrEP products (i.e., CAB-LA). A range of perceived benefits of CAB-LA was reported that can be viewed as facilitators to uptake and implementation. There was a consensus among the interviewed PrEP providers that the main benefit is the elimination of the need to take a pill every day at the same time, which can be significantly challenging for many people for a variety of reasons. Further benefits/facilitators include greater discretion, greater safety for patients with kidney-related co-morbidities as well as client enthusiasm (clients are already asking for this product). Perceived barriers to implementation were also reported by the interviewed providers. These include, e.g., costs (including of testing and routine clinic visits), a lack of national PrEP policies and guidance, aversion to injections, stigma, and safely stopping CAB-LA [75].

Barrieren spezifisch für Frauen: Leitlinien, priorisieren MSM, mangelndes Wissen über Nutzen für Subgruppen von Frauen

A European survey aimed to explore PrEP availability and implementation for women specifically. In addition to general barriers to PrEP access (e.g., lack of information, lack of political support, high cost for the individual), some specific barriers to PrEP access for women were also reported, including guidelines prioritising MSM, women not being seen as a target population for PrEP, and lack of knowledge about which subgroup of women would benefit most from PrEP [76].

5.2.6 Experiences with PrEP implementation in other countries

Current implementation status in the WHO European Region

WHO Europäische Region (2022): 23 von 55 Ländern mit öffentlicher Erstattung der PrEP, weitere 15 Länder: PrEP erhältlich, aber nicht (vollständig) erstattet (u. a. Österreich)

According to the ECDC progress report based on data collection in 2022, PrEP has been increasingly available through healthcare systems in countries in the WHO European region since 2016. In 2022, 23 of 55 countries reported that PrEP was available and reimbursed through their healthcare system, either through insurance or paid by the public sector[10]. A further 15 countries indicated that generic PrEP was available but not fully reimbursed by the public sector (e.g., Austria). However, certain key populations (e.g., people who inject drugs, prisoners, and undocumented migrants) remain ineligible for PrEP in many countries [11].

Germany

Deutschland: Anspruch auf PrEP für gesetzlich Krankenversicherte mit substanziellem HIV-Infektionsrisiko seit 09/2019

In Germany, people with statutory health insurance and a substantial risk of HIV infection, are entitled to HIV PrEP since September 2019 within the 'Terminservice- und Versorgungsgesetz' (§ 20j SGB V). The introduction of PrEP is being accompanied and evaluated within the framework of a research project financed by the German Federal Ministry of Health and led by the Robert Koch Institute (RKI). The project aims to evaluate the effects on the incidence of HIV infections as well as on other relevant sexually transmitted infections (STI), the number of PrEP users as well as consultations and prescriptions, based on several different studies and data analyses [77]. In Germany, PrEP can be prescribed by doctors in HIV specialist centres and doctors with additional qualifications.

Evaluationsbericht: 47 HIV-Zentren mit 4.620 PrEP-Nutzer*innen

99 % männlich, meist MSM; medianes Alter 38 J., 80 % tägliche Einnahme

For the evaluation report, a total of 47 HIV centres in Germany reported data on PrEP use of 4,620 people in the time period between September 2019 and December 2020. The majority of this population was male (99.2%), MSM (88.0%) or MSM in combination with other risks as PrEP indication (98.6%), and was aged between 30-49 years (67.0%), median age of 38 years (IQR 32-45). Overall, 82.5% of PrEP users were under 50 years of age. There were 39 non-males in this sample. The mode of PrEP use was reported as permanent/daily use for 80.9% (3,737 people) and on-demand/event-driven for 18.9% (874 people) [77].

4 HIV-Infektionen unter PrEP (Gründe: niedrige Adhärenz, FTC-Resistenz, 1 Infektion vor PrEP-Beginn)

The median duration of PrEP exposure was 451 days (IQR 357-488), resulting in a total of 5,132 person-years. Among the 4,620 individuals, 4 HIV infections were observed in MSM, aged 26-33 years, corresponding to an incidence of 0.087% and an incidence rate of 0.078/100 person-years (95% confidence interval CI 0.029-0.208). For two of the four incident infections, suboptimal adherence was reported, and in the third case, suboptimal adherence and resistance to emtricitabine were observed. One infection was likely acquired before PrEP start [77].

Rückgang der HIV-Neuinfektionen in D in den letzten Jahren

The number of new HIV diagnoses as well as the estimated number of new HIV infections decreased continuously in Germany and in the MSM group in recent years. In 2020, the number of estimated new HIV infections among

[10] Belgium, Bosnia and Herzegovina, Croatia, Denmark, Finland, France, Georgia, Germany, Iceland, Ireland, Kazakhstan, Kyrgyzstan, Liechtenstein, Luxembourg, Monaco, Northern Macedonia, Norway, Portugal, Slovenia, Spain, Sweden, Ukraine, United Kingdom

MSM was about 1,100, which was a decrease of 300 new HIV infections compared to the previous year. According to the authors of the evaluation report, it cannot yet be assessed if the number of PrEP users in Germany is sufficient to sustainably reduce HIV incidence in the medium and long term due to the influence of the COVID-19 pandemic. The same is the case for the incidence of STI (chlamydia, gonorrhoea, syphilis) that did not increase over the course of the study but, in some studies, even decreased or remained almost the same. However, these results can also not be clearly separated from the influence of the COVID-19 pandemic. In assessing the course of HIV and STI incidence in 2020, a number of factors need to be considered, including changes in sexual behaviour, as well as reduced availability of testing and prevention services and reduced health care utilisation. Further analyses are needed to determine and evaluate the impact of HIV PrEP on testing and diagnosis of HIV and STIs with more validity [77].

STI-Inzidenz nicht gestiegen/tw. gesunken, jedoch Einfluss der Pandemie unklar

A common reason for not initiating PrEP, according to the German evaluation report, was the fear of side effects. In contrast, side effects were rare in the data on reasons for interrupting or discontinuing PrEP, which means that the fear of side effects was significantly more pronounced than the frequency of documented side effects. This shows a need for education to enable people interested in PrEP to make an informed, fact-based decision, as well as a potential for further dissemination of PrEP among people at increased risk of HIV. A need for information on PrEP for people outside the MSM community also became apparent. Needs-based offers and information on PrEP would be necessary for target groups with increased HIV risk, as they exist in other countries (USA, Australia, France), e.g. for people within the trans*/nonbinary communities, for sex workers and for people from the African community. There is also evidence that PrEP needs were not adequately met in rural areas where there are fewer PrEP prescribers and that even in the big cities, many MSM do not express a need for PrEP of their own accord, even though the criteria for a PrEP indication are present. In view of the high concentration of PrEP provision in the five largest cities in Germany as well as the identified barriers to not using PrEP despite an indication (for approx. 35% too much effort to obtain PrEP, for approx. 22% no prescribers available), it must be assumed that provision in line with demand has not yet been achieved nationwide [77].

genannte Barrieren: Angst vor Nebenwirkungen, zu hoher Aufwand, keine PrEP-Dienste in der Nähe

Bedarf an Information und Aufklärung für PrEP-Interessierte

bundesweite bedarfsgerechte Versorgung noch nicht umgesetzt

Overall, the authors conclude that PrEP is a very effective HIV prevention method, and the feared negative influences on STI rates have not been confirmed in this study so far. However, longer observation periods are needed for a more comprehensive assessment. Therefore, the RKI established the continuation of monitoring of HIV PrEP provision in Germany from 2022, within the project 'Surveillance of the provision of HIV PrEP in Germany' (PrEP-Surv) which is funded by the Ministry of Health [77].

PrEP als wirksame Präventionsmethode, befürchtete negative Auswirkungen auf STI-Raten bisher nicht eingetreten; längere Beobachtungszeiträume notwendig

In February 2023, the RKI published the first results of the half-yearly survey of a selection of HIV specialist centres, including data from 14,688 PrEP users in the year 2021. In this sample, 17 new HIV infections were reported after PrEP initiation, mostly due to low adherence, especially in combination with on-demand use or PrEP breaks. The authors concluded that these results again show the effectiveness in real-life settings. However, the interviewed centres still report structural barriers, e.g. service gaps in rural areas, insufficient number of centres and insufficient number of PrEP prescribers [129]. The RKI currently estimates a minimum total number of 30,000 PrEP users in Germany, according to media reports [130].

erste Ergebnisse der halbjährlichen Befragung der HIV-Schwerpunktzentren

Schätzung: derzeit mind. 30.000 PrEP-Nutzer*innen in D

France

Frankreich: Einführung und Kostenerstattung seit 01/2016

ca. 42.000 Nutzer*innen zwischen 01/2016 und Mitte 2021

97.5 % männlich, ø 36 J., 74 % leben in großem städtischem Ballungsraum, nur 7 % sozioökonomisch benachteiligt

seit 2021 PrEP-Verschreibung durch alle Ärzt*innen möglich

In France, oral PrEP has been available and fully reimbursed for people at high risk of sexually acquired HIV infection since January 2016. A study using data from the French National Health Data System, which covers 99% of people residing in France, assessed the roll-out of PrEP use in France from its implementation in January 2016 until mid-2021. A total of 42,159 individuals have initiated PrEP in France. 97.5% of PrEP users were men, with an average age of 36 years, the majority living in a large metropolitan area (74%). Only a minority (7%) of PrEP users were socioeconomically disadvantaged. Women accounted for only 2.5% of PrEP users, which probably means that PrEP is rarely offered in situations where women are at high risk of HIV infection (e.g., injecting drug use, sex workers, vulnerability to condomless sex in a context of high HIV prevalence or exposure). In France, PrEP management includes quarterly HIV and STI screening and promotion of PrEP adherence and condom use. PrEP prescriptions are made for a maximum of 3 months with monthly dispensing of the drug. Since June 2021, PrEP initiation is no longer reserved for physicians with experience in HIV management practising in hospitals or sexual health centres but has been extended to all prescribing physicians, including general practitioners (GPs). The study authors conclude by highlighting the need for further measures to expand access to PrEP to all potential beneficiaries, including women, socioeconomically disadvantaged people and those living in remote areas, as well as to improve adherence [78].

1. Jahr: 4 HIV-Infektionen unter PrEP-Einnahme bei ca. 2.800 Nutzer*innen

An analysis of data from 2,774 PrEP programme participants during the first year of implementation in France showed that four breakthrough infections were reported. Two of them were due to low adherence, one was already infected at PrEP initiation, and one became infected despite good adherence early after PrEP initiation, but infection prior to PrEP initiation cannot be excluded [79].

Scotland

Schottland: 2017 Implementierung eines nationalen PrEP Programms

99 % männlich, davon 98 % MSM

Programm erfolgreich bei MSM mit hohem Risiko, aber Verbesserung nötig bei anderen Gruppen, z. B. Frauen, heterosexuelle Männer, trans Personen, PWID

As the first country in the UK and one of the first worldwide, Scotland implemented a national PrEP programme in July 2017, making PrEP freely available via the NHS for people at high risk of HIV infection through sexual transmission who meet risk-based eligibility criteria. The programme is delivered through sexual health services. An evaluation report was published by the NHS to present data from the first two years of implementation. In the first two years of Scotland's PrEP programme (1 July 2017 to 30 June 2019), a total of 11,289 PrEP prescriptions were recorded, which corresponds to 3,354 individuals who received one or more PrEP prescriptions during this two-year period. Approximately 100 new individuals have started on PrEP each month since January 2019. Of the 3,354 individuals prescribed PrEP at least once during these two years, almost all were male (99%) and, of these, 98% were men who have sex with men. 41% of PrEP users were aged 20-29 years at the time of their first PrEP prescription, and 4% were younger than 20 years. Over one-quarter of PrEP users (28%) were aged 50 years and over. By the end of the second year, the PrEP programme has encouraged almost 1,000 individuals who have not previously attended sexual health services. The authors of the evaluation report conclude that the programme has been successful in reaching a large number of MSM at high risk, but work is ongoing to improve PrEP awareness among women, trans people, non-binary people, heterosexual men and people who inject drugs [80].

Rates of HIV seroconversions during PrEP use are available for the first year of implementation. 1,872 individuals were prescribed PrEP at least once in the first year of the Scottish NHS PrEP programme. Of these, less than five (1 to 4) HIV seroconverted. However, further analyses showed that drug levels were below protective levels at the time of suspected HIV infection. Regarding other STIs, no final conclusions could be drawn. An increase in the number of those diagnosed with gonorrhoea and chlamydia has been detected; however, the increase could be attributed to either improved detection, an actual increase in the incidence of infection or (most likely) a combination of both [81].

1. Jahr: 1-4 Serokonversionen bei rund 1.800 PrEP-Nutzer*innen

Einfluss auf STI-Raten unklar

5.3 Cost/Economic Domain

The aim of the Costs and Economic evaluation domain within HTA is to inform value-for-money judgements about health technologies with information about costs, health-related outcomes and economic efficiency [28].

Kosten/ökonomische Domäne

This section provides several recently published data related to prices, cost-effectiveness and budget impact analyses on oral (daily or on-demand) and injectable PrEP in different countries around the world. Cost-effectiveness and budget impact analyses from one country are not transferable to other countries, but some elements are relevant for all healthcare settings, like the most important drivers of cost.

Informationen zu Preisen, Kosten-Effektivitäts- und Budget-Impact-Analysen zu PrEP aus anderen Ländern

Data related to prices of oral and injectable PrEP

According to the recently published ECDC 2023 report on HIV PrEP in Europe and Central Asia [11], countries in Europe and Central Asia were able to purchase oral PrEP at different **prices**, with a median price of €30.50 per package for one month for generic PrEP and €305 for branded PrEP. The lowest purchase price reported for 28-30 tablets of TDF/FTC, a generic version of PrEP, was €0 (a donation from the private sector), and the highest purchase price was €434. Truvada was generally more expensive than the generic forms of PrEP: the lowest government purchase price for 28-30 tablets of Truvada was €165, and the highest purchase price in one country was €6,041 [11].

große Preisspanne der PrEP in den versch. Ländern

Median-Preis pro Packung für 1 Monat: 30 € für Generikum, 300 € für Truvada®

In the US, the estimated monthly price of Descovy (tenofovir alafenamide/emtricitabine) is US$1,800 [82]. A generic version is not yet available. The list price of CAB-LA in the US is $22,000 annually per person. A generic version is also not yet available; it is under patent protection until 2031.

Descovy® (TAF/FTC): 1.800 US$ pro Monat; CAB-LA: 22.000 US$ pro Jahr

Data related to cost-effectiveness analyses of oral PrEP

Data related to **cost-effectiveness analyses** are derived from a recently published systematic review of economic analyses in 2019 [30] and from selected recently published primary studies in different countries (Table 5-2).

Kosten-Effektivitäts-Analysen zu oraler PrEP

A recently published systematic review of economic analyses embedded within an HTA report in 2019 [30] included 18 studies from ten different countries related to oral PrEP (Table 5-2) [87-104]. Seventeen studies investigated PrEP use in gay, bisexual and other MSM, and one study focused on people who inject drugs (PWID). No study investigated the cost-effectiveness of PrEP in heterosexuals at high risk of HIV acquisition or serodifferent couples.

SR als Teil eines HTA-Berichts: 18 Studien aus 10 Ländern (davon 17 zu MSM, 1 zu PWID)

Table 5-2: Cost-effectiveness analyses: Systematic review and recently published primary studies (oral PrEP)

Source/Countries	Population	Intervention/Comparator	Results
Systematic Review [30]			
6 studies from United States, 5 from Europe (France, Netherlands, Spain, and the UK), 2 from South America (Brazil and Peru), 2 from Canada, 2 from Australia and 1 from Thailand	17 studies in MSM, 1 in PWID	PrEP free of charge vs no PrEP	Mixed: from cost saving to €339,791 per Quality-Adjusted Life Year (QALY) gained
Primary studies			
Ireland [29, 30]	MSM	Publicly funded PrEP programme (medications + frequent monitoring) vs no PrEP	Cost-effective, cost saving
Barcelona [83]	MSM	Daily generic PrEP vs non-implementation	Cost-effective, cost saving
Japan [84]	MSM	PrEP programme vs programme without PrEP	Cost-effective
Asia [85]	MSM	Generic-brand daily dosing of PrEP vs generic event-driven dosing (15 days a month and generic versus branded PrEP for China)	Cost-effective
US [86]	MSM	Branded tenofovir alafenamide emtricitabine vs generic tenofovir disoproxil fumarate/emtricitabine for HIV daily PrEP	Not cost-effective

Vergleich kostenlose PrEP mit keiner PrEP

meist PrEP Medikament allein, nicht als Teil eines Programms

2 Studien: PrEP kostensparend

6 Studien: ICER unter 45.000 €; 3 Studien: ICER über 45.000 €

wichtige Einflussfaktoren: jährliche PrEP-Kosten, Schätzung der Wirksamkeit

All studies compared the intervention of providing PrEP free of charge against the comparator of the status quo ('No PrEP'). The infrastructure and costs for providing PrEP differed between studies due to different standards pertaining to screening, monitoring and counselling. Many studies investigated the cost-effectiveness of PrEP medication alone and not as part of a programme. Fifteen studies evaluated PrEP taken daily, and three studies assessed PrEP taken 'on demand'. The annual cost of daily PrEP medication in MSM and PWID studies ranged from €232 to €14,659 per person (mean €6,543). Costs were lower in European compared with North American studies (mean annual PrEP cost of €6,419 versus €7,702). The mean annual cost of on-demand PrEP was €4,313. Parameter estimates for the efficacy of PrEP in reducing the risk of HIV transmission in MSM ranged from 44%-99%. In nine of the seventeen MSM studies, the efficacy was equal to or above 86%. The efficacy of PrEP was 49% in the PWID study. PrEP was considered cost-saving in two studies. Six studies reported an incremental cost-effectiveness ratio (ICER) below €45,000, and three studies estimated an ICER above €45,000. Evidence of cost-effectiveness was inconsistent due to differences in the study input parameters and design, with ICERs ranging from cost saving to €339,791 per Quality-Adjusted Life Year (QALY) gained. Evidence from sensitivity analyses suggests that the annual cost of PrEP and the estimate of effectiveness used are important drivers within individual studies [30].

weitere 5 rezente Kosten-Effektivitäts-Analysen aus Irland, Barcelona, Japan, Asien und USA

A further five recently published cost-effectiveness analyses were identified from **Ireland** [30, 105], **Barcelona** [83], **Japan** [84], several countries in **Asia** [85], and the **US** [86] (see Table 5-2). Detailed results from these studies can be found in Appendix (see Table A-9). The populations were MSM in all studies. Three analyses compared PrEP programmes versus no PrEP, and two studies compared either different dosings (daily vs event-driven PrEP) or different drugs (TAF/FTC vs TDF/FTC). In four analyses, PrEP was cost-effective, and in two of them, even cost-saving [30, 83, 105]. In one analysis from the US, PrEP with branded TAF/FTC was not cost-effective [86].

Authors from Ireland found that daily oral PrEP programme was cost-saving; the ICER was €4711/QALY (highly cost-effective). Event-based dosing (administration during high-risk periods only) was associated with additional cost savings. The ICERs were also sensitive to key cost parameters, including the cost of HIV care and the cost of PrEP. PrEP was still considered cost-saving over a range of plausible costs [30, 105].

Irland: tägliche orale PrEP kostensparend, bei anlassbezogener PrEP noch zusätzliche Einsparungen

Authors from Spain concluded that short-term investments in the promotion of PrEP will result in important cost savings in the long term [83]. The introduction of PrEP to an MSM cohort in Japan would be cost-effective over a 30-year time horizon [84]. For Asia (Cambodia, China, India, Indonesia, Myanmar, Nepal, Thailand, and Vietnam), authors concluded that implementing PrEP may be cost-effective in settings with increasing HIV prevalence among MSM, and if PrEP drug costs can be reduced, PrEP could be more cost-effective over longer timeframes [85].

Spanien: kurzfristige Investitionen, langfristige Einsparungen

Asien: kosteneffektiv

According to data relevant to the US [86], branded TAF/FTC was not cost-effective in the US compared to generic TDF/FTC for HIV daily PrEP, even in populations at the highest risk for TDF/FTC adverse events.

TAF/FTC (Descovy®): nicht kosteneffektiv

Data related to cost-effectiveness analyses of long-acting cabotegravir

Data related to cost-effectiveness analyses of injectable PrEP are derived from selected recently published primary studies in different countries as examples (Table 5-3). Detailed results from these studies can be found in Appendix (Table A-9).

Kosten-Effektivitäts-Analysen zu CAB-LA

Table 5-3: Cost-effectiveness analyses: Recently published primary studies in US, Canada and South Africa (injectable PrEP)

Source/Countries	Population	Intervention/Comparator	Results
US, Canada, South Africa [106]	MSM in US and Canada; cisgender men and women in Africa	Long-acting injectable cabotegravir vs tenofovir disoproxil fumarate and emtricitabine	Possibly cost-effective in places with high HIV incidence (Atlanta); unlikely to be cost-effective in low-incidence settings (Montreal); CAB-LA could be more cost-effective than oral PrEP only if CAB-LA is priced within 2x the price of oral PrEP
US [107]	MSM and transgender women	Long-acting injectable cabotegravir vs generic or branded tenofovir disoproxil fumarate and emtricitabine	CAB-LA too costly at current price vs generic daily oral emtricitabine-tenofovir disoproxil fumarate (CAB-LA could achieve an ICER of at most $100 000 per QALY vs generic F/TDF at a maximum price premium of $1100 per year over generic F/TDF (CAB-LA price <$1500 per year)
South Africa [108]	Heterosexual adolescents and young women and men aged 15-24 years, female sex workers, and MSM	Long-acting injectable cabotegravir vs tenofovir disoproxil fumarate and emtricitabine	Cost per CAB-LA injection needed to be less than twice that of a 2-month supply of tenofovir disoproxil fumarate and emtricitabine to remain as cost-effective, with threshold prices ranging between $9.03 per injection (high coverage; maximum duration) and $14.47 per injection (medium coverage; minimum duration)

Recently published modelled economic evaluations in the **US**, **Canada** and **South Africa** showed mixed results related to long-acting injectable cabotegravir PrEP relative to daily oral emtricitabine-tenofovir disoproxil fumarate [106-108]. Authors of modelled economic evaluations in the US and Canada [106] showed that long-acting injectable cabotegravir PrEP expansion could be highly efficient and possibly cost-effective in places with high HIV incidence (like Atlanta, compared to branded oral PrEP; not more cost-effective than generic oral PrEP) but are unlikely to be cost-effective in low-incidence settings (like Montreal). Another cost-effectiveness analysis from the US [107] found that CAB-LA is too costly at its current price versus generic daily oral

unterschiedliche Ergebnisse von ökon. Evaluationen aus USA, Kanada & Südafrika; mögliche Kosteneffektivität in Regionen mit hoher HIV-Inzidenz, Preis von CAB derzeit noch zu hoch im Vergleich zu TDF/FTC Generika

TDF/FTC for HIV PrEP. Authors of another economic analysis in South Africa [108] concluded that for CAB-LA implementation to be financially feasible across low-income and middle-income countries with high HIV incidence, it must be reasonably priced.

Kostentreiber: jährl. Medikamenten-Kosten, Verfügbarkeit anderer Maßnahmen sowie HIV-Behandlung

Important drivers of cost included the annualized cost of long-acting PrEP and the availability of other effective HIV prevention options, service delivery and uptake, as well as the availability of HIV treatment.

Data related to budget impact analysis of introducing a publicly funded pre-exposure prophylaxis programme in Ireland

Budget-Impact Analyse aus Irland

The Irish HTA report and O'Murchu et al. 2021 [30, 105] conducted the **budget impact analysis** of introducing a publicly funded PrEP programme in **Ireland**. The authors estimated that 1,705 individuals (95% CI: 617-3,452) would join the programme in year 1.

Schätzungen 1. Jahr: 1,1 Mio. € für PrEP-Medikament, 0,4 Mio. € für Monitoring-Programm (= Zusatzkosten für Personal und Labor)

In the first year, PrEP medications alone are estimated to cost €1.1m (95% CI: €0.4m to €2.2m), and the monitoring programme is estimated to cost €0.4m (95% CI: €0.2m to €0.9m). Over five years, PrEP medications are estimated to cost €5.3m (95% CI: €2.3m to €10m) and the monitoring programme is estimated to cost €2.2m (95% CI: €0.9m to €4.1m). The monitoring programme costs consist of the additional clinic visits (staff resource use and laboratory investigations) by PrEP users compared with 'usual care' of MSM at substantial risk.

inkrementeller Budget-Impact: 5,4 Mio. € über 5 Jahre; Vermeidung von 173 HIV-Infektionen

The incremental budget impact of PrEP programme was €1.5m (95% CI: €0.5m to €3m) in the first year and €5.4m over five years (95% CI: €1.8m to €11.5m), with 173 cases of HIV averted over five years. The incremental budget impact takes all costs into consideration, including the increased cost associated with a potential rise in STIs (other than HIV) and the decrease in costs associated with a reduction in the requirement for HIV treatment and post-exposure prophylaxis after sexual exposure.

kostensparend im 8. Jahr, "break even point" im 14. Jahr

Deterministic sensitivity analysis showed that the parameters that determined the number of participants in the programme (such as PrEP eligibility and uptake rate) had the greatest impact on the incremental budget. When extending the budget impact analysis beyond five years, the yearly incremental budget impact becomes cost-saving by year 8, and the aggregate budget impact becomes cost-saving ('break even' point) by year 14 (all programme and medication costs will have been recouped) relative to no PrEP.

5.3.1 Cost implications for Austria

ökonomische Analysen nicht direkt auf Ö übertragbar

The results from economic analyses from other countries are not transferable to the Austrian context. Primary cost-effectiveness and budget impact analyses relevant to the Austrian setting were not found. This chapter aims to give a brief overview of components of a PrEP programme that would create costs and to reflect on data and information regarding costs that would be needed to estimate the budget impact for the PrEP implementation in Austria.

Überblick über Komponenten, die Kosten verursachen

The following components of a PrEP programme (according to the German-Austrian [18] and WHO guidelines [1]) and their related costs need to be considered:

- **Before PrEP initiation**:
  - Initial consultation with a healthcare professional for counselling, HIV risk assessment and eligibility
  - Fourth-generation HIV testing (repeated test four weeks after initiation)
  - Testing for replicative hepatitis B (HBV) infection using serology or testing for HBV immunity
  - Hepatitis C (HCV) serology, syphilis serology, and STI (smear tests for Chlamydia trachomatis and Neisseria gonorrhoeae: pharyngeal, genital/urine, and anorectal)
  - Testing of kidney function by measuring eGFR

vor PrEP-Beginn:
Erstgespräch zur Beratung & Risikoassessment, Tests auf HIV, Hepatitis B & C, andere STIs, Prüfung der Nierenfunktion

- **During PrEP use**:
  - Cost of the drug itself: daily or on-demand ('off-label') use of oral TDF/FTC, injectable PrEP CAB-LA (not yet approved by the EMA)
  - Regular consultation with a healthcare professional for risk reduction, diagnostic evaluation, and medical history (indicating symptoms of an STI)
  - Laboratory tests: HIV and syphilis every three months, gonorrhoea and chlamydia every 3(-6) months, hepatitis C every 6-12 months, serum creatinine for examination of eGFR depending on age and risk factors

während PrEP-Einnahme: Kosten des Medikaments, regelmäßige Follow-up Termine & Labortests (HIV, Syphilis, Gonorrhö, Chlamydien, Hepatitis C, ggfs. Nierenfunktion)

- **At the end of PrEP:**
  - HIV testing at six weeks after last risk contact

nach PrEP-Beendigung: HIV-Test

Further costs relate to the setting up of a PrEP programme, which can include:

weitere Kosten bei Implementierung des Programms,

- Training and further education of healthcare professionals
- Development of integrated care and referral pathways
- Set-up of a monitoring system

z. B. Aus- und Fortbildung, Entwicklung von Versorgungspfaden, Monitoring-System, spezifische Interventionen zur Erreichung der Zielgruppen

Additionally, to reach at-risk individuals from key population groups, it is necessary to raise awareness of HIV PrEP among key populations at risk, healthcare professionals, as well as professionals working in community-based organisations, patient organisations or in other settings with relevant key populations. Interventions could include information campaigns or community-based activities and can also involve peer support.

To estimate the budget impact for Austria, two types of information would be needed to calculate the costs: information on quantities and the prices of all those cost components. To calculate quantities, more details on epidemiological parameters are needed. This includes, for example, exact data on the current users, the expected new users per year, as well as the duration of use. Similar to Germany (see chapter 5.2.6), these data may be collected alongside implementation as part of the monitoring suggested by the WHO (see chapter 5.2.4). The prices or tariffs for the above-listed components (e.g., counselling, laboratory tests, price of the drug itself) would also be needed, and costs for the implementation of a PrEP programme in the various relevant bodies and organisations would have to be estimated.

für Abschätzung des Budget Impact in Ö nötig: Mengen/epidemiologische Parameter und Preise der Komponenten (z. B. Labortests, Preis des Medikaments)

5.4 Patient/social Domain

Werte und Präferenzen der Nutzer*innen

Different values and preferences among end users regarding PrEP, as well as stigmatisation related to their use, could be related to the introduction of these new oral and injectable pharmaceuticals for PrEP and their potential use/non-use within current care.

Values and preferences of participants from key populations regarding PrEP (gay and bisexual men and other men who have sex with men, sex workers, people who inject drugs, trans people, and people in prisons or other closed settings)

Interviews und Fokusgruppen mit Teilnehmer*innen aus den relevanten Bevölkerungsgruppen

As published in the WHO Values and preferences report 2022 [109], a total of 61 individual semi-structured interviews and 32 multi-country focus group discussions were conducted with participants from key populations (gay and bisexual men and other men who have sex with men, sex workers, people who inject drugs, trans people, and people in prisons or other closed settings), selected by the global key population networks through their regional and country-based networks, with attention given to balancing representation by region, gender, age, and HIV status. PrEP was acknowledged as an effective HIV prevention method, but many participants across networks reported a lack of knowledge surrounding these prevention technologies, as well as low availability of PrEP. Participants preferred to receive HIV prevention services and commodities in a range of settings, including mobile clinics, harm reduction settings, drop-in centres, and through peer outreach.

PrEP als wirksame HIV-Prävention akzeptiert, aber tw. mangelndes Wissen sowie unzureichende Zugänglichkeit

bisher v. a. orale PrEP bekannt, aber großes Interesse an injizierbarer PrEP (angenehmer, diskreter, einfacher einzuhalten)

Participants across all key population networks expressed a growing interest in PrEP as an HIV prevention method. Most participants also reported that PrEP remains widely inaccessible in their communities. When asked about preferences regarding different PrEP dosing regimens and modalities (daily oral, injectable long-acting, event-driven, and the vaginal Dapivirine ring), most participants were only familiar with daily oral PrEP. Although many participants were not previously familiar with injectable, long-acting PrEP, participants indicated that this would be one of their preferred dosing regimens. Injectable long-acting PrEP was perceived as being more convenient, discreet, affordable, and easier to adhere to than daily oral PrEP.

mangelnde Information und Wissen zu sicherer und korrekter Anwendung sowie Interaktion mit anderen Medikamenten (z. B. Hormontherapie) oder Drogen

mangelndes Wissen bzgl. PrEP und STIs; Druck auf Sexarbeiter*innen

Stigmatisierung und Diskriminierung weiterhin große Barrieren

Another common theme expressed across communities was a lack of information and knowledge surrounding PrEP, including its safe and correct use, efficacy, and potential interactions with other drugs and medicines. Participants noted ongoing gaps in the evidence base in relation to the efficacy and suitability of PrEP for people who inject drugs. For trans people undergoing gender-affirming hormone therapy, participants pointed to gaps in research about the efficacy of PrEP, as well as misinformation about PrEP intake regimens increasing the risk of HIV infection (i.e., PrEP on demand is currently not recommended for trans people undergoing gender-affirming hormone therapy). Participants additionally cautioned that the growing number of PrEP users, especially in communities of men who have sex with men, has increased pressure and financial incentives from sex workers' clients to provide services without condoms, increasing the risks of STIs and unwanted pregnancy. This trend has been exacerbated by the fact that many sex workers were not provided with adequate information on PrEP and may falsely believe that PrEP also protects them from other STIs. PrEP was supported by participants across networks, but some participants stressed that what they

viewed as the increasing promotion of PrEP among key populations must not come at the expense of other evidence-based HIV prevention services, such as community-led programming. Across all key populations, stigma, discrimination, and criminalization were emphasized as persistent barriers to accessing health services and remaining in treatment, as well as driving factors in perpetuating vulnerability, human rights abuses, and poor health outcomes [109].

Values and preferences on long-acting injectable cabotegravir (CAB-LA)

Akzeptanz, Werte und Präferenzen hinsichtlich injizierbarer PrEP

Evidence on acceptability, values and preferences for long-acting injectable cabotegravir (CAB-LA) was used from the recently published WHO guidelines on long-acting injectable cabotegravir for HIV prevention [14]. Below, evidence from a systematic review of publications on injectable PrEP [110] and a study on the perspectives of PrEP providers are presented [111].

Values and preferences among end users

Interesse und tw. Präferenz für injizierbare PrEP (Privatsphäre, Diskretion, keine tägliche Einnahme)

aber auch Bedenken (Angst vor Nadeln, Schmerzen an Injektionsstelle, Bedenken bzgl. der Wahrnehmung regelmäßiger Termine)

A systematic review included 99 articles, meeting the inclusion criteria for the values and preferences analysis [110]. Most studies were observational, cross-sectional and qualitative and were conducted in North America. Men who have sex with men were the most researched respondent group. Most examined injectable PrEP generally, including hypothetical injectables or placebo products; six studies examined CAB-LA specifically. The review found that there was overall interest in and some preferences for injectable PrEP, although there was variation within and across groups and regions. The findings show that injectable PrEP presents an opportunity to address adherence-related challenges associated with daily or event-driven dosing required for oral PrEP and may be a better lifestyle fit for individuals seeking privacy, discretion and infrequent dosing. Potential users reported concerns related to fear of needles, injection site pain and location, logistical challenges with regularly attending appointments and concerns about waning or incomplete protection.

Values and preferences among PrEP providers

Gesundheitspersonal: geringere Belastung bzgl. Adhärenz, langanhaltende Schutzwirkung, große Motivation der Nutzer*innen; aber auch Bedenken wegen hoher Kosten, Arbeitsbelastung, Re-Medikalisierung

A global online survey (n=1,353 surveys submitted and n=849 fully completed) and in-depth interviews (n=30) among PrEP providers across all regions found generally high levels of support for the addition of CAB-LA as PrEP [111]. In the survey, 48% reported that they had heard of CAB-LA, and 71% would consider providing it if and when it receives regulatory approval. The main benefits include reduced adherence burden for clients and the long-acting protective effect, privacy, and enthusiasm expressed by clients, which likely supports uptake and continuation. Primary concerns raised by providers are costs and additional workload, HIV testing requirements and drug resistance, how to safely stop CAB-LA, weak commodity management in some settings and the (re-)medicalization of PrEP.

5.5 Ethical Domain

ethische Aspekte

The introduction of these new health technologies, oral PrEP and injectable PrEP and potential use/non-use within current care may cause some ethical issues related to equity, acceptability and factors that could prevent their use.

Ungleichheiten bei Zugang zur PrEP, z. B. bei Personen mit Migrationshintergrund, Personen in ländlichen Gegenden

According to the ECDC 2023 report on HIV PrEP in Europe and Central Asia [11], certain key populations, such as people who inject drugs, prisoners and undocumented migrants, remain ineligible for PrEP in many countries in the European Region. Within countries, inequalities have quickly emerged in PrEP access. There are divergent rates of PrEP uptake along racial and ethnic, socioeconomic, geographical, age, and self-identity lines. In western high-income countries, uptake has typically been highest among gay men connected to urban gay communities and lower among minority ethnic groups, migrants, nongay-identifying MSM, those with little access to health care, and those living in less urban areas [112, 113]. Even within groups with high levels of access, there is still a substantial gap between the estimated number suitable for or in need of PrEP and the number who have ever accessed it [114].

Bsp. Personen, die aus Haft entlassen werden: zahlreiche Barrieren für tägliche Medikamenteneinnahme, z. B. Substanzkonsum, psychische Erkrankungen, Stigma, Misstrauen in Gesundheitssystem

Priorisierung für Studien zu injizierbarer PrEP in dieser Population

Akiyama et al. 2022 [115] stated that although most people with HIV who are incarcerated have access to antiretroviral therapy (ART) that keeps the virus suppressed during confinement, about three-quarters of them don't have suppressed viral loads after incarceration. Using long-acting antiretrovirals in carceral settings could help to end the US HIV epidemic. People being released from jail face numerous barriers to continuing to take daily medications, such as PrEP for HIV. Such barriers include high rates of substance use and serious mental illness, competing social needs, stigma, and medical mistrust. If long-acting injectable PrEP is to benefit people involved in the criminal-legal system, barriers to uptake and continued use will have to be addressed. People who are members of historically marginalized racial or ethnic groups, who identify as transgender, who use drugs, or who have a mental illness are overrepresented in carceral settings and are more likely to be living with or at risk for HIV than members of the wider community. Addressing the needs of people involved in the criminal-legal system for long-acting injectable therapies will therefore be key to achieving health equity as part of efforts to end the HIV epidemic. Authors believe that research on implementing long-acting injectable ART and PrEP in this population, including studies investigating feasibility, acceptability, effectiveness, and cost-effectiveness, should be prioritized.

schwangere & stillende Frauen unterrepräsentiert in klin. Studien

According to Davey et al. 2022 [116], pregnant and breastfeeding populations as at substantial risk of acquiring HIV in some settings, are underrepresented in clinical trials of new PrEP agents. The authors suggested that research on new PrEP agents should include pregnant and breastfeeding populations to avoid delays in reaching those who could benefit from PrEP after efficacy is established.

auch Jugendliche sollten in entsprechenden geeigneten Studien berücksichtigt werden

Nachman et al. 2019 [117] suggested that the needs of children, adolescents, and pregnant and lactating women are considered when developing long-acting formulations. Research should focus not only on how best to transition long-acting products to these populations but also on early engagement across sectors and among stakeholders. A parallel rather than sequential approach is needed when establishing adult, adolescent, and paediatric clinical trials and seeking regulatory approval. Pregnant and lactating women should be included in adult clinical trials. An adolescent-friendly trial design is needed to improve the recruitment and retention of young people.

PrEP-Nutzen geht über körperliche Gesundheit hinaus: höhere Autonomie in Bezug auf sexuelle Gesundheit, weniger Belastung durch Angst vor HIV-Infektion

The authors of the HTA report published in Ireland [30] discussed oral PrEP in the context of benefit—harm balance, autonomy and vulnerability, justice and access, as well as professional values. For some individuals, the benefits of PrEP extend beyond physical health to relief from the burden of fear of HIV infection and greater autonomy in relation to one's sexual health. Many of the individuals who stand to benefit most from PrEP are from vulnerable groups who have unique healthcare needs and are subject to stigma and discrimination. PrEP is a prevention approach that is prescribed for uninfected and typically healthy individuals. Although it can be considered as safe, it is not free of risks. That means that the benefit-harm balance has to be considered carefully to be sure that only those truly at risk of HIV infection take PrEP.

Medikalisierung durch PrEP als mögliche Barriere

Another issue that has been discussed in the context of ethical aspects and equity is the medicalisation of HIV prevention (e.g., PrEP) and of homosexual sexual relationships. It has been argued that PrEP is a worrying form of medicalisation or pharmaceuticalisation of HIV prevention and sex. Although these critiques have also been challenged, this issue may still present a barrier affecting uptake of PrEP as well as adherence [118, 119].

Menschen mit hohem HIV-Risiko haben häufig nur schwer Zugang zum Gesundheitssystem und zu effektiver HIV-Prävention

breite PrEP Akzeptanz in verschiedenen Populationen

According to the WHO Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring [16], preventing HIV among PrEP users will contribute to equitable health outcomes by sustaining their health and the health of their sexual partners. People at substantial risk of HIV are often underserved, have barriers to accessing health services and have few effective HIV prevention options. Access to PrEP provides opportunities to engage these individuals in health care, including sexual and reproductive health services. Broadening PrEP recommendations beyond narrowly defined groups (such as men who have sex with men and serodiscordant couples) enables more equitable access and is likely to be less stigmatizing than targeting specific risk groups. Effective PrEP services will reduce future treatment costs overall by preventing HIV infection in populations with high incidence. PrEP acceptability has been reported in multiple populations, including cisgender women (and pregnant and breastfeeding women), serodiscordant couples, female sex workers, young women, people who inject drugs, transgender people and men who have sex with men.

Stigmatisierung = wichtiger Faktor, könnte je nach Umsetzung zu- oder abnehmen

Stigma is a driver of HIV and could decrease or increase depending on how PrEP is implemented. PrEP should be promoted as a positive choice among people for whom it is suitable and their communities, in conjunction with other appropriate prevention interventions and services, including sexual and reproductive health services. Legal environments in which the rights of people at substantial risk of HIV are violated may represent an important barrier to PrEP implementation [16].

injizierbare PrEP als zusätzliche Option um mehr Menschen zu erreichen

According to the recently published WHO guidelines on long-acting injectable cabotegravir for HIV prevention [14], an additional PrEP option could increase equity by reaching more individuals who could benefit from PrEP and who would prefer injectable PrEP over other options. Inequality in health outcomes could be exacerbated globally through differences in access to CABLA between and within countries.

Empfehlung der deutsch-österr. Leitlinie

As written above, according to the German-Austrian HIV PrEP consensus guideline [19], oral HIV PrEP should be offered as a preventive measure for people at substantial risk of becoming infected with HIV and should only be prescribed in combination with risk reduction counselling concerning HIV, sexually transmitted infections (STIs), and viral hepatitis.

5.6 Legal Domain

rechtliche Aspekte

The introduction of these new health technologies (oral and injectable PrEP) and potential use/non-use within current care may raise some legal issues in Austria related to the regulation for the acquisition and use of PrEP.

2 Präparate (TAF/FTC, CAB-LA) bisher nicht in EU zugelassen

Two of these new technologies (one oral and one injectable medication) are pharmaceuticals that are not yet licensed in the EU for the PrEP, as well as so-called on-demand (intermittent) use of PrEP ('off-label use').

anlassbezogene Dosierung ebenfalls nicht zugelassen → „off-label use"

Off-label prescribing is defined as prescribing a registered medicine for a use that is not included or is disclaimed in the product information and is not approved by the regulatory authorities, such as use in a different indication or age group, at a different dose or by a different route. In situations where no authorised treatment is available, physicians are ethically obliged to find alternatives; for responsible off-label prescribing, physicians should find sufficient evidence to justify off-label use, ask for research when evidence is lacking and inform patients about uncertainties, safety and potential costs. In a case of serious harm, they are exposed to civil liability claims for fault/negligence or even criminal and disciplinary sanctions [120-123]. Individual patient values and preferences should always be considered.

off-label Verschreibung auf EU-Ebene nicht geregelt

Off-label prescription is not regulated on the European Union (EU) level and, therefore, not harmonised in the EU Member States. Off-label prescribing by physicians in Europe is generally allowed, but individual Member States have their own rules on prescribing and reimbursement. In some, this is regulated by law and in others by good practice guidance such as treatment guidelines, general professional recommendations and reimbursement decisions [19, 124].

laut deutsch-österr. Leitlinie: nur zugelassene Medikamente, anlassbezogene Dosierung in spezifischen Fällen als off-label use möglich

As already mentioned above, according to the German-Austrian HIV PrEP consensus guideline published in 2019, only drugs approved in Europe should be prescribed for PrEP. The oral combination drug tenofovir disoproxil fumarate *(or any other chemical salts of tenofovir disoproxil)*/emtricitabine (TDF/FTC) should be used for PrEP. PrEP should be prescribed as a continuous, once-daily intake of TDF/FTC. Intermittent intake of PrEP may be considered for specific cases, although this prescription is outside approval ('off-label use') [19].

Österreich: präventive Arzneimittel „nicht-erstattungsfähig"

bei Entscheidung für Erstattung der PrEP Einigung auf Kostenträger nötig

In Austria, the reimbursement of medicines in the outpatient sector is decided by the Federation of Social Insurances ('Dachverband der Sozialversicherungsträger'). In the case of a positive decision, the medicine is included in the outpatient code of reimbursement ('Erstattungskodex', EKO). However, some categories of medicines are not eligible for reimbursement ('nicht-erstattungsfähige Medikamente'), including e.g., medicines for prophylactic and primary preventive use [125, 126]. This means that in the case of the reimbursement of PrEP medicines, Austrian stakeholders would need to agree on a payer.

6 Discussion

Summary and critical reflection of the results on effectiveness and safety

High-quality evidence from RCTs demonstrated that oral PrEP (tenofovir disoproxil fumarate/emtricitabine) is highly effective at preventing HIV infection in MSM and serodiscordant couples. PrEP effectiveness is rising with increased adherence. One trial with high adherence found PrEP to be effective in preventing HIV infections in heterosexuals but was not effective in trials with low adherence. One study found that oral PrEP was effective in PWID [44]. A limitation of this study is that investigators were not sure if the transmission was parenteral or sexual. On-demand oral PrEP regimen was highly effective at preventing HIV infection in MSM. Daily tenofovir alafenamide (approved by FDA, but not EMA) has proven non-inferior efficacy to daily tenofovir disoproxil fumarate for HIV prevention in MSM.

tägliche orale PrEP mit TDF/FTC: hohe Wirksamkeit, v. a. bei MSM und serodiskordanten Paaren; bei MSM auch anlassbezogene off-label Dosierung; TAF/FTC nicht weniger wirksam (keine EMA-Zulassung)

Oral PrEP was found to be safe, and there was no difference in adverse event rates comparing single-agent tenofovir with tenofovir/FTC in combination. Some studies noted a transient elevation of creatinine with resolution on discontinuation of the study drug, which is in line with results of a recently published systematic review and meta-analysis of published literature and a multi-country meta-analysis of individual participant data (IPDMA) related to kidney function in tenofovir disoproxil fumarate-based oral pre-exposure prophylaxis users [127]. The authors concluded that risks of kidney-related adverse events among tenofovir disoproxil fumarate-based oral PrEP users are increased but generally mild and small. Their global PrEP user analysis found varying risks by age and baseline creatinine clearance. Kidney function screening and monitoring might focus on older individuals, those with baseline creatinine clearance of less than 90ml/min, and those with kidney-related comorbidities. Less frequent or optional screening among younger individuals without kidney-related comorbidities may reduce barriers to PrEP implementation and use [127]. Tenofovir alafenamide has better renal and bone safety compared to tenofovir disoproxil fumarate but is associated with small increases in weight. These better renal and bone safety improvements do not justify a switch for the majority of those already on the tenofovir disoproxil fumarate formulation, but just for those with serious renal or bone adverse events [82]. The FDA approval for tenofovir alafenamide only covers at-risk men and transgender women; cisgender women were excluded from the indication.

orale PrEP ist sicher; in manchen Studien vorübergehender Anstieg des Kreatinins → Risiko von UEs in Bezug auf Nieren erhöht, aber gering

Monitoring der Nierenfunktion v. a. für ältere PrEP-Nutzer*innen und jene mit Erkrankungen der Nieren relevant

TAF/FTC: nur für jene mit schwerwiegenden UEs der Nieren oder der Knochen

High-quality evidence from two large RCTs demonstrated that injectable PrEP (not yet EMA approved) is safe and highly effective at preventing HIV infection in MSM, transgender women who have sex with men, and women. Most reported injection site reactions (ISRs) were mild, and event rates for ISRs decreased over the course of the study. There were no studies identified related to effectiveness and safety in sex workers, people who inject drugs or other groups at risk.

injizierbare PrEP (CAB-LA, bisher keine EMA-Zulassung): sicher und wirksam bei der Prävention von HIV-Infektionen

While uncommon, viral drug resistance mutations may occur during oral and injectable PrEP.

Resistenzmutationen können auftreten

keine Veränderung des sexuellen Verhaltens oder Anstieg von STIs in klinischen Studien; Monitoring nötig

In clinical studies, PrEP did not alter sexual behaviour (as self-reported, prone to reporting bias) or lead to a rise in STI diagnoses, which is probably due to the risk reduction support offered to trial participants. As placebo-controlled trials are not sufficient to measure behaviour change associated with PrEP, monitoring of STIs when PrEP is implemented in real-world settings is required. Quality of life was not assessed in any of the included trials.

bisher keine Unterschiede bei Schwangerschafts-Outcomes, weitere Daten nötig

Currently, no differences were found in pregnancy or perinatal outcomes associated with oral or injectable PrEP exposure. More research and safety surveillance in pregnancy is needed to monitor adverse pregnancy and infant outcomes, especially rare adverse events, through the surveillance of PrEP within larger surveillance programmes or antiretroviral pregnancy registries.

WHO-Empfehlungen für orale (TDF/FTC) und injizierbare PrEP

The WHO recommends oral PrEP (containing tenofovir disoproxil fumarate) as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high certainty of evidence). Long-acting injectable cabotegravir may be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches (conditional recommendation, moderate certainty of evidence).

TAF/FTC und CAB-LA bisher nicht in EU zugelassen

anlassbezogene Dosierung als „off-label use"

Oral tenofovir alafenamide/emtricitabine and long-acting injectable cabotegravir are pharmaceuticals that are not yet licensed in the EU for the PrEP, as well as so-called on-demand (intermittent) use of PrEP (off-label use). The updated WHO document stated that oral event-driven PrEP can be used to prevent sexual acquisition of HIV by cisgender men and trans and gender-diverse people assigned male at birth who are not taking exogenous estradiol-based hormones [66]. The German-Austrian HIV PrEP consensus guideline stated that only drugs approved in Europe should be prescribed for PrEP, and off-label use may be considered for specific cases [19].

Other key aspects related to PrEP and its implementation

zentrale Themen abseits von Wirksamkeit und Sicherheit

This report not only summarises the currently available evidence on effectiveness and safety but also provides information on other important domains, i.e. organisational, economic, ethical, legal and patient/social aspects. In the following, some key issues beyond effectiveness and safety will be pointed out.

Gerechtigkeit: Nicht-Erstattung des Medikaments kann gesundheitliche Ungleichheit verstärken

finanzielle Aspekte oft als Barriere genannt

One of those key topics is the equity aspect. Not publicly reimbursing this drug may reinforce health inequalities, and those affect already disadvantaged groups. The Austrian patient organisations reported that there are groups at risk who might benefit most from PrEP, like MSM (with low income, migrants, students), heterosexual people at risk of HIV acquisition (e.g., sex workers, chemsex users), people with changing sex partners, people that cannot use condoms, as well as groups that currently have very limited options for PrEP. People who live under financial constraints can often not afford PrEP, and PrEP medication might be ordered through the internet without quality assurance and medical supervision. Financial issues have been mentioned as an important barrier both by patient organisations and in the literature. This not only includes the cost of the drug itself but also, e.g., travelling expenses (and time) if there is no PrEP prescribing service nearby.

PrEP als effektive HIV-Präventionsmethode von Gruppen mit hohem HIV-Risiko anerkannt

From the perspectives of the key populations at HIV risk, PrEP was acknowledged as an effective HIV prevention method. Many of them reported a lack of knowledge surrounding these prevention interventions, as well as low availability of PrEP. Literature data show that there is interest in injectables for

PrEP among end users, and CAB-LA could be a good choice for people who value discretion, are familiar and comfortable with needles and/or have difficulty storing or taking oral PrEP. Costs could be a barrier to equitable access [110].

Interesse auch an injizierbarer PrEP

Certain key populations, such as people who inject drugs, prisoners and undocumented migrants, still remain ineligible for PrEP [11]. Pregnant and breastfeeding populations, as well as children and adolescents, are underrepresented in clinical trials of new PrEP pharmaceuticals. More research is needed on the specific needs of transgender women, transgender men and non-binary people, including additional support for adherence in this population and integration of gender-affirming care with HIV services, including PrEP. Research involving transgender men and non-binary people is particularly lacking, including how to improve awareness and uptake of and adherence to PrEP. PrEP awareness and use among people who use drugs is limited, and more research on improving the engagement of people who use drugs with PrEP services is needed [16].

manche Risikogruppen in bisherigen Studien unterrepräsentiert

mehr Forschung nötig, auch zu spezifischen Unterstützungsmaßnahmen, besserem Zugang etc.

Another key issue is that the implementation of PrEP not only consists of reimbursing and ensuring the supply of the drug, but a thorough implementation concept is needed, addressing activities beyond prescribing the drug and making sure to avoid regional disparities. PrEP programmes involve regular HIV testing, screening for other STIs, supporting adherence, advice on safer sex practices, counselling for individuals at substantial risk of infection and linking to treatment services for people with a positive HIV test before starting PrEP or seroconverting while using PrEP. Therefore, PrEP should be offered as part of a comprehensive testing, prevention and treatment service.

PrEP = nicht nur Erstattung der Kosten des Medikaments, sondern umfangreiches Implementierungskonzept nötig

Different settings and healthcare providers can be involved in PrEP service delivery. Ideally, PrEP services should be integrated into settings which are already attended by the target population for other purposes, e.g., sexual health. Possible settings include sexual health clinics, family planning services, services for sex workers, services for MSM and transgender people, family practitioners, gynaecological care providers or pharmacies. The most common settings for PrEP provision in European countries were infectious disease clinics, followed by private providers, the internet, sexual health clinics and primary care [11]. There is growing expert opinion that follow-up visits, after the initial consultation for PrEP eligibility, could be provided by non-HIV specialists and in non-medicalised settings. However, community- and primary care-based models of PrEP service delivery are not yet common in Europe [9].

unterschiedliche Settings und Gesundheitsberufe können involviert sein

Integration in bereits genutzte, bestehende Einrichtungen empfohlen

Regarding the involved healthcare providers, the literature on barriers to PrEP implementation mentions the so-called Purview Paradox, which means that neither HIV specialists nor primary care doctors consider PrEP to fall within their clinical domain. HIV specialists, who are best trained and most willing to prescribe PrEP, often do not see HIV-negative patients, while primary care doctors, who regularly care for HIV-negative patients, might lack sufficient training to provide PrEP [71-73]. The list of doctors and clinics currently prescribing PrEP in Austria includes, e.g., general practitioners, doctors specialised in pulmonology, internal medicine and sexually transmitted disease, so there already seems to be some variability regarding the specialisations of doctors and settings providing PrEP in Austria. However, half of the providers listed are located in Vienna and in one federal province (Lower Austria), there are no providers at all yet. Additionally, one of the patient organisations criticised that there is still a lack between testing, treatment and prevention in Austria, as there is no 'one-stop shop' (like sexual health clinics).

Frage der Zuständigkeit: HIV-Spezialist*innen oder Primärversorgung?

in Ö bisher unterschiedliche Setting und Ärzt*innen involviert, jedoch regional unterschiedliche Versorgung

kein „One-Stop-Shop"

aktives Adressieren der Barrieren

Many other barriers on different levels (individual, healthcare provider, healthcare system) exist which need to be actively addressed in order to decrease inequalities.

Wichtigkeit von Aus- und Fortbildung, auch Training der Kommunikationsfähigkeiten

As lack of training and knowledge about PrEP is a significant barrier, appropriate training and continuing education for all (potential) PrEP providers is described as a key component of facilitating PrEP programmes, which also aims to raise awareness among healthcare professionals. Training should include, e.g., PrEP delivery according to clinical guidelines, PrEP eligibility assessments, prescribing and management, counselling and HIV risk assessment, and other HIV prevention interventions. Additionally, healthcare providers involved in PrEP services need adequate training and support to be able to have respectful and sensitive conversations on HIV prevention needs and preferences with the various key populations. A strong patient-carer relationship is helpful in enabling the discussion of barriers and facilitators regarding adherence and self-care [16]. In Austria, a PrEP training programme is offered by the Austrian AIDS society (ÖAG).

potentiell weitere positive Effekte von PrEP-Programmen neben HIV-Prävention

z. B. regelmäßiges Testen auf STIs, Möglichkeit psychische Gesundheit zu verbessern

Apart from preventing HIV infections, PrEP programmes can also have additional positive effects, for example, the possibility to regularly test a group at high risk for STI, to treat infections and thus to quickly interrupt infection chains due to the necessary regular follow-up examinations. Another positive side effect is the opportunity to improve other health areas that have an impact on HIV risk, such as mental health, through regular follow-up visits with a healthcare professional within the PrEP programme [128]. A recently updated Swiss guidance recommends combining screening for mental health problems with PrEP consultations which has two advantages. On the one hand, people who have a higher risk for HIV often belong to sexual and other minorities who are known to be at a higher risk for mental health problems such as depression or addiction disorder. On the other hand, mental health problems have been shown to influence adherence to PrEP intake. The guidance, therefore, recommends screening for mental health during regular PrEP visits, either in direct conversation or using a validated screening tool [69].

Qualitätssicherung und Monitoring-System nötig

Another important organisational aspect of PrEP programme implementation is quality assurance and monitoring. It is recommended that PrEP programmes should deliver services in a monitored system to be able to measure basic data on, e.g., people on PrEP, stopping PrEP, breakthrough infections, new STI infections, and drug resistance [9].

Erfahrungen mit Implementierung von PrEP-Programmen aus 3 Länder-Beispielen (Deutschland, Schottland, Frankreich)

Examples from three European countries (Germany, Scotland, and France, in which PrEP is fully reimbursed) give some insights into experiences with PrEP programme implementation. In all three countries, the majority of PrEP users were MSM. PrEP was used mainly in metropolitan areas, and only a minority were socioeconomically disadvantaged. Rates of HIV seroconversion during PrEP were reported to be low and mostly related to low adherence or suspected to be acquired before PrEP initiation. It is reported that the programme has been successful in reaching a high number of MSM at risk (Scotland), but there is a need for further measures to also reach and raise awareness among at-risk women, heterosexual men, trans people and PWID.

orale PrEP (TFD/FTC) in Studien aus mehreren Ländern kosteneffektiv bzw. sogar kostensparend

Cost-effectiveness and modelling analyses support the cost-effectiveness or even cost-saving of oral PrEP containing tenofovir disoproxil fumarate/emtricitabine as a prevention strategy in several developed countries [83, 84, 105]. Estimates of cost-effectiveness were dependent on the effectiveness and adherence of PrEP, the incidence of HIV, the cost of PrEP, the reduction in price due to generics and the lifetime cost of HIV. On-demand PrEP (not currently

a licensed indication) may be preferentially used to minimise costs and toxic effects, assuming that the effectiveness of daily versus event-based PrEP remains the same in future studies [30]. According to data relevant to the US [86], using prices from 2020, branded tenofovir alafenamide/emtricitabine compared to generic tenofovir disoproxil fumarate/emtricitabine was not cost-effective, even in populations at highest risk for TDF/FTC adverse events.

Studien nicht direkt auf Ö übertragbar, aber ähnliche Ergebnisse wahrscheinlich

Different countries have different willingness-to-pay thresholds. Primary cost-effectiveness and budget impact analyses relevant to the Austrian setting were not found. Results from economic analyses relevant to other countries cannot be transferred to Austria, but chances are high that results would be similar because of the high consistency of cost-effectiveness in other countries. While we do not know the budget impact for Austria, we identified several cost categories that would have to be considered in addition to the drug costs, thus being aware that introducing PrEP would raise costs in the short run, especially in the implementation phase but – based on international experience – breaking even in the medium- and long-run due to reduced costs for HIV treatment.

Budget-Impact für Ö: Identifizierung von Kostenkategorien

kurzfristige Kosten für Implementierung, langfristig reduzierte Kosten für HIV-Behandlung

Results of economic evaluations are mixed related to long-acting injectable cabotegravir PrEP compared to daily oral emtricitabine-tenofovir disoproxil fumarate. According to some literature data, it could be cost-effective or cost-saving when prioritized among certain populations, particularly women, and/or offered along with complementary products.

injizierbare PrEP: Ergebnisse aus ökonom. Evaluationen uneinheitlich

An important topic is also the general societal context (e.g., the attitude towards certain sexual behaviours and prejudices) that needs to be actively addressed if barriers to access are to be overcome. Austrian patient organisations report that stigma, including self-stigma, discrimination (e.g., in the healthcare system or at the workplace) and social exclusion, are still present in the context of HIV/AIDS, and these factors also hugely affect PrEP uptake.

gesellschaftl. Kontext: Stigmatisierung & Diskriminierung → auch Einfluss auf PrEP-Nutzung

All those activities related to the implementation and delivery of PrEP programmes require clearly defined responsibilities and coordination among different actors. At present, it seems unclear who would be responsible for paying for the drug, for setting up a pathway of care, or for developing and conducting information campaigns if a PrEP programme is to be embedded into the Austrian structure. It is unlikely that all these responsibilities would reside with one body, but they will probably lie with very different bodies, which makes a clear definition of responsibilities and coordination even more important.

klar definierte Verantwortlichkeiten & Koordination zwischen versch. Akteuren für PrEP-Programm nötig

Limitations

We are aware of two main limitations of our report. First, we did not pool RCTs identified from the update literature search but analysed them descriptively. Thus, the 'summary of findings' tables are heterogenous, depending if they are taken from the already published systematic review or newly created with the data from the new RCTs. However, as different comparisons were used in the newly identified studies, pooling of the data would not have been possible in most cases. Second, only the results for effectiveness and safety are based on a systematic literature search and selection. For the description of additional important aspects ('other domains'), including the cost/economic domain and the experiences with PrEP implementation from other countries, we did not conduct a systematic literature search but selected a few examples to give a first impression; therefore, important studies might be missing.

2 Limitationen:

kein Poolen der Ergebnisse der neuen RCTs, daher GRADE Tabellen heterogen

systematische Literatursuche nur für Wirksamkeit & Sicherheit, nicht für andere Domänen

7 Conclusion

High-quality evidence has demonstrated that daily oral PrEP and injectable PrEP are both safe and highly effective at preventing HIV infection in a number of high-risk groups. On-demand oral PrEP regimens have also demonstrated effectiveness. Effectiveness has mostly been tested in MSM, less often in serodiscordant couples and rarely in transgender persons, women, or heterosexuals for whom confidence in the effectiveness is less certain. For some groups (e.g., sex workers), evidence on effectiveness and safety is currently lacking.

Evidenz hoher Qualität zur Wirksamkeit und Sicherheit der PrEP v. a. für MSM, serodiskordante Paare; für andere Gruppen weniger bzw. keine Evidenz

Potential users have acknowledged the drug's effectiveness and expressed a high willingness to use it, including injectables for PrEP, which have so far not been approved in Europe. International economic evaluations on oral PrEP medication mostly showed favourable results, often even demonstrating cost savings in the long run. Various guidelines based on high-quality evidence have clearly recommended to implement PrEP into national HIV prevention programmes. Not reimbursing PrEP restricts access to high-income and highly educated groups, thus substantially increasing health inequalities in often already vulnerable and disadvantaged groups.

Akzeptanz potentieller Nutzer*innen

Nicht-Erstattung der PrEP verstärkt potentiell gesundheitliche Ungleichheit

Based on these international findings on the benefit of the drug but also for equity and ethical reasons, we recommend reimbursement of daily oral PrEP (tenofovir disoproxil fumarate/emtricitabine) for Austria. However, the following aspects need to be considered in case of a reimbursement decision for PrEP:

Erstattung der PrEP empfohlen, jedoch Berücksichtigung zahlreicher Aspekte notwendig:

- A thorough implementation concept is needed, addressing activities beyond prescribing the drug — **Implementierungskonzept**
- PrEP needs to be offered as part of a comprehensive testing, prevention and treatment service, according to current guidelines, with clear responsibilities and pathways — **PrEP als Teil einer integrierten Versorgung**
- The setting for PrEP service delivery should be easily accessible and accepted by different key populations; current regional disparities need to be reduced — **Niederschwelligkeit**
- Appropriate training and further education of health care professionals is crucial, also targeting communication skills — **Aus- und Fortbildung**
- Specific efforts are necessary to provide information and raise awareness among specific populations at risk, e.g., MSM with migration background or low income, women and heterosexual men at high risk for HIV infection (e.g., sex workers) — **Information und Sensibilisierung für spezif. Risikogruppen**
- A monitoring system has to be set up so that an evaluation of the programme can be conducted — **Monitoring, Evaluation**
- Implementing PrEP according to evidence-based recommendations will incur costs beyond PrEP drug costs in the short term, while monetary benefits (e.g., reduced costs for treatment of HIV infections) will occur later — **kurzfristige Kosten für Implementierung, Einsparungen später**
- Since responsibilities for reimbursing, implementing and monitoring are currently unclear in Austria, these responsibilities and related coordination activities need to be defined before reimbursement decisions are made — **Definition von Zuständigkeiten, Koordination**

injizierbare PrEP sowie TAF/FTC evt. als zusätzliche Optionen (im Falle einer Zulassung in EU)

Long-acting injectable cabotegravir may be offered in the future, in the case of marketing authorisation in the EU, as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches. The same is true for oral tenofovir alafenamide/emtricitabine, but probably just for those with serious renal or bone adverse events, due to the current high price of branded formulation without available generic equivalents.

anlassbezogene PrEP als off-label Verwendung möglich

According to the recently published WHO guideline, so-called on-demand (intermittent) use of oral PrEP (off-label use) can be used to prevent the sexual acquisition of HIV by cisgender men and trans and gender-diverse people assigned male at birth who are not taking exogenous estradiol-based hormones. The German-Austrian HIV PrEP consensus guideline stated that such a regimen may be considered for specific cases.

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Appendix

Study characteristics of 2 new RCTs related to effectiveness and safety of oral PrEP

Table A-1: Study characteristics of RCTs related to effectiveness and safety of oral PrEP; one RCT (2 references) as non-inferiority RCT that compared two different types of oral tenofovir-containing PrEP, tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC; one RCT that compared oral daily vs on-demand PrEP with oral tenofovir disoproxil fumarate 300mg/emtricitabine 200mg (TDF/FTC) tablets

	Tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC	**Oral daily vs on-demand PrEP: tenofovir disoproxil fumarate 300mg/emtricitabine 200mg (TDF/FTC)**
Study name/Study ID/ Author, year, reference number	**DISCOVER**, NCT02842086 Mayer 2020 [39] Ogbuagu 2021 [57]	CCRB Clinical Trials Registry, The Chinese University of Hong Kong CUHK, CUHK_CCRB00606 and Chinese Clinical Trial Registry (Registration number: ChiCTR1800016100), Kwan 2021 [38]
Study design, study phase	RCT (phase 3, double-blind, active-controlled, non-inferiority trial)	RCT (controlled, open-label, crossover trial)
Centres (single centre or multicentre), country, setting	Multicenter/Europe (Austria, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, and the UK) and North America (Canada and the USA)	Single center/Hong Kong
Patient population (number of included patients/Mean age and sex)	High-risk cisgender men who have sex with men (MSM) (99%) and transgender women who have sex with men (1%); 5399 randomised (received emtricitabine and tenofovir alafenamide, n=2700 or emtricitabine and tenofovir disoproxil fumarate, n=2699); median age 34 years (interquartile range, 28 to 43)	Sexually active HIV-negative MSM aged 18 years or above with normal renal function and without chronic hepatitis B infection; n=119, daily-first arm (n=59) and on-demand-first arm (n=60) with an 87% overall completion rate (n=103); Participants in the daily-first arm were put on daily PrEP for 16 weeks, then on-demand PrEP for another 16 weeks. Another arm received PrEP in a reversed regimen sequence. Participants' median age at enrolment was 30 years [interquartile range (IQR) 26-38 years]
Inclusion criteria	Negative for HIV by use of third-generation HIV antibody tests or fourth generation HIV-1 antigen-antibody tests at screening and baseline, and who reported either condomless anal sex with at least two partners in the previous 12 weeks or having syphilis, rectal gonorrhoea, or rectal chlamydia in the previous 24 weeks. Previous or current use of emtricitabine and tenofovir disoproxil fumarate for PrEP was allowed.	MSM, aged 18 years or above, who had had condomless anal intercourse (CLAI) with men in the preceding 6 months, inclined to have CLAI in the coming 6 months, were HIV-negative, not hepatitis B carriers, had a creatinine clearance of at least 60ml/min and occurrence of at least one behavioural risk in the past 6 months, including chemsex engagement, STI diagnosis, had multiple sex partners and had people living with HIV (PLHIV) as sex partners regardless of their viral load status
Exclusion criteria	Suspected or known active serious infection (determination of serious was at the individual investigator's discretion); acute hepatitis A, B, or C infection, or chronic hepatitis B infection; a history of osteoporosis or fragility fractures; or impaired renal function, as defined by an estimated glomerular filtration rate by the Cockcroft-Gault formula ($eGFR_{CG}$) of less than 60ml/min	Unable to communicate in either Chinese or English, were not normally residing in Hong Kong, or had any form of mental illnesses
Intervention (generic drug name and dosage, time frame; number of randomized)	Emtricitabine (200mg) and tenofovir alafenamide (25mg) tablets daily, n=2700	Daily oral tenofovir disoproxil fumarate 300mg/emtricitabine 200mg (TDF/FTC) tablets
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized)	Emtricitabine (200mg) and tenofovir disoproxil fumarate (300mg) tablets daily, n=2699	On-demand oral tenofovir disoproxil fumarate 300mg/ emtricitabine 200mg (TDF/FTC) tablets
Primary Outcome(s)	Incident HIV infection	PrEP coverage of days with coverage of condomless anal intercourse (CLAI), reflecting prevention-effective adherence during the two regimen periods

	Tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC	Oral daily vs on-demand PrEP: tenofovir disoproxil fumarate 300mg/emtricitabine 200mg (TDF/FTC)
Patient-relevant secondary or tertiary outcome(s)	Secondary safety outcomes, measured as percentage changes from baseline to week 48, included: (1) hip bone mineral density; (2) spine bone mineral density; (3) urine β2-microglobulin to creatinine ratio; (4) retinol-binding protein to creatinine ratio; (5) changes in the distribution of urine protein to creatine ratio above the clinically significant threshold of 22.6mg/mmol at 48 weeks; and (6) change in serum creatinine from baseline; incidence of treatment-emergent adverse events; other laboratory abnormalities, including changes in blood lipids from baseline; changes in weight from baseline; adherence by self-reporting, pill counts, and dry blood spots (DBS) testing; tenofovir diphosphate concentrations in peripheral blood mononuclear cells (PBMCs); and HIV antiretroviral drug resistance in participants who acquired HIV infection	(1) uptake of TDF/FTC derived from the percentage of days on PrEP and retention rate; (2) STI diagnoses through testing; and (3) regimen preferences and risk perception. Safety outcomes included adverse events graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events and change in creatinine clearance level.
Follow-up (weeks, months)	48 weeks (all participants) to 96 weeks (half of all participants)	16 weeks + 16 weeks
Sponsor/lead institution	Gilead Sciences funded the study, collected and analysed the data, interpreted the results in consultation with the other authors of the Article, and helped to write the report	AIDS Trust Fund (MSS 292 R); Gilead Sciences for providing the study drugs

Study characteristics of 2 new RCTs related to effectiveness and safety of injectable cabotegravir PrEP vs tenofovir disoproxil fumarate/emtricitabine PrEP

Table A-2: Study characteristics of RCTs related to effectiveness and safety of injectable cabotegravir vs tenofovir disoproxil fumarate/emtricitabine PrEP

Study name/Study ID/ Author, year, reference number	**HPTN 083**, NCT02720094 [58, 59] Stopped early for efficacy*	**HPTN 084**, NCT03164564 [41, 60] Stopped early for efficacy**
Study design, study phase	RCT (phase 2b-3, double-blind, double-dummy, active-controlled noninferiority trial)	RCT (phase 3, double-blind, double-dummy, active-controlled, superiority trial)
Centres (single centre or multicentre), country, setting	Multicentre/US, Latin America, Asia, Africa	Multicentre/sub-Saharan Africa
Patient population (number of included patients/Mean age and sex)	At-risk cisgender men who have sex with men (MSM) and transgender women who have sex with men (570, 12.5%); 4570 (2283 CAB-LA vs 2287 TDF/FTC); median age 26 years (interquartile range, 22 to 32)	Female sex at birth; 3224 randomised (1614 CAB-LA vs 1610 TDF/FTC); 3219 (99.8%) of 3224 self-identified as female; median age 25 years (IQR 22-30)
Inclusion criteria	Adults (≥18 years of age) in general good health as determined by clinical and laboratory assessments, negative HIV serologic test at enrolment, undetectable blood HIV RNA viral load within 14 days before trial entry, creatinine clearance of 60ml or more per minute, at high risk for HIV infection	Assigned female sex at birth, aged 18-45 years, reported at least two episodes of vaginal intercourse in the previous 30 days, at risk of HIV infection based on an HIV risk score, agreed to use a long-acting reversible contraceptive method with a failure rate of less than 1%; non-reactive test results at the site with at least one HIV rapid antibody test cleared by the US Food and Drug Administration, a laboratory-based antigen-antibody test, and were required to have undetectable HIV RNA up to 14 days before enrolment

Study name/Study ID/ Author, year, reference number	**HPTN 083**, NCT02720094 [58, 59] Stopped early for efficacy*	**HPTN 084**, NCT03164564 [41, 60] Stopped early for efficacy**
Exclusion criteria	Use of illicit intravenous drugs within 90 days before enrolment, previous participation in the active treatment group of an HIV vaccine trial, coagulopathy, buttock implants or fillers, a seizure disorder, corrected QT interval of greater than 500 msec, positive results on a hepatitis B virus surface antigen test or hepatitis C virus antibody test	Pregnant or breastfeeding; substantial renal, hepatic, or cardiovascular disease; history of seizures, coagulopathy, or allergy to any of the study products; previously enrolled in an HIV vaccine or monoclonal antibody trial
Intervention (generic drug name and dosage, time frame; number of randomized)	Long-acting injectable cabotegravir (CAB-LA) 600mg i.m every 8 weeks, n=2283	Long-acting injectable cabotegravir (CAB-LA) 600mg i.m every 8 weeks, n=1614
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized)	Daily oral tenofovir disoproxil fumarate 300mg – emtricitabine 200mg (TDF–FTC), n=2287	Daily oral tenofovir disoproxil fumarate 300mg – emtricitabine 200mg (TDF–FTC), n=1610
Primary Outcome(s)	Incident HIV infection; grade 2 or higher clinical or laboratory adverse event according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (version 2.1)	Incident HIV infection; grade 2 or higher clinical or laboratory adverse event according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (version 2.1)
Patient-relevant secondary or tertiary outcome(s)	HIV incidence across all three steps of the trial and in pre-specified subgroups by region, age, race, ethnicity, baseline risk, and gender identity, Adherence; Drug resistance mutations; changes in renal function, liver function, and bone mineral density (BMD); acceptability of and preferences for CAB LA vs. oral TDF/FTC; association between levels of adherence and HIV incidence; changes in sexual-risk behaviour as measured by self-report and rates of incident gonorrhoea, chlamydia, and syphilis; resource utilization and programmatic costs of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India; use mathematical simulation to project the short- and long-term clinical impact, cost projections, budgetary impact, and incremental cost-effectiveness of long-acting injectable PrEP vs. daily oral PrEP vs. no PrEP for HIV uninfected MSM and TGW in the US, Brazil, South Africa and India	HIV incidence across all three steps of the trial and in pre-specified subgroups by age, contraceptive use method, body-mass index (BMI), acceptability and willingness to use the study product; Sexual risk behaviours, Incident sexually transmitted infections, Pregnancy incidence and outcomes, Weight, and HIV drug resistance
Follow-up (weeks, months)	153 weeks (median follow-up of 1.4 years (interquartile range IQR, 0.8 to 1.9)	24 months (median follow-up time 1.24 years (interquartile range IQR 0.92-1.56)
Sponsor/lead institution	Division of AIDS of the National Institute of Allergy and Infectious Diseases, ViiV Healthcare and Gilead Sciences donated trial medications and matching placebos; ViiV Healthcare provided additional funding and contributed to the design of the trial.	National Institute of Allergy and Infectious Diseases, ViiV Healthcare, and the Bill & Melinda Gates Foundation. Additional support was provided through the National Institute of Mental Health, the National Institute on Drug Abuse, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. ViiV Healthcare and Gilead Sciences provided pharmaceutical support.

* *On review of the results of the first preplanned interim end-point analysis, the Data and Safety Monitoring Board concluded that the results met the prespecified criteria for stopping the trial on the basis of efficacy;*

** *On review of the results of the second preplanned interim end-point analysis, the Data and Safety Monitoring Board concluded that the results met the prespecified criteria for stopping the trial on the basis of efficacy*

Risk of Bias

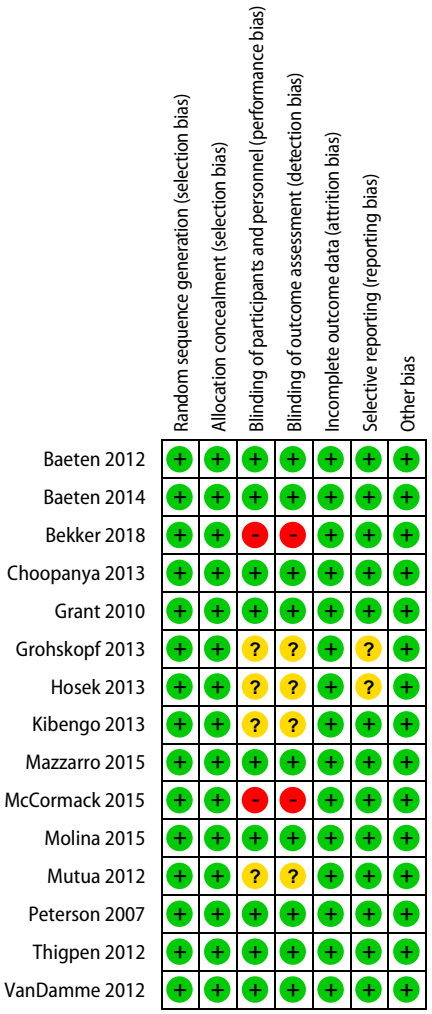

Figure A-1: Risk of Bias summary: RCTs from already published SR with 15 RCTs included (Sources: [29, 30])

Table A-3: Risk of bias 2 (ROB2) summary of 4 new RCTs related to oral and injectable PrEP

Studies	Randomisation process	Deviations from the intended interventions	Missing outcomes	Measurement of the outcome	Selection of reported results	Overall bias
Trial NCT02720094, Landovitz 2021	low	low	some concerns [a]	low	low	some concerns
Trial NCT03164564, Delany-Moretlwe 2022	low	low	low	low	some concerns	some concerns
Trial DISCOVER, NCT02842086, Mayer 2020, 48 weeks, Ogbuagyn 2021, 96 weeks	low	low	some concerns [c]	low	low	some concerns
Trial ChiCTR1800016100, Kwan 2021	low	High [d]	some concerns [e]	High [f]	low	high

[a] *Participant retention was 86.5% at 1 year, so data not available for all or nearly all participants randomized.;*

[b] *Describes the primary outcomes and provides brief information for many of the secondary and tertiary study outcomes; additional information will be reported elsewhere.;*

[c] *Primary analysis, when 100% of participants completed 48 weeks of follow-up and 50% of participants completed 96 weeks. Longer-term (96-week) secondary efficacy and safety outcomes. Randomly assigned 5399; 4257 completed at week 96 (78.8%);*

[d] *Open-label, crossover trial;*

[e] *119 randomized; weeks 16 and 32 completion rates were 94% and 87%, respectively, without interarm significant difference;*

[f] *Unblinded study: open-label (participants, physicians, research support staff and investigators were not masked to the study arm allocation), crossover trial; sexual behaviours and diary data were self-reported – social desirability and recall bias*

Effectiveness and safety results of oral PrEP

Table A-4: Effectiveness results of the two new RCTs on oral PrEP

	Tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC	Oral daily vs on-demand PrEP tenofovir disoproxil fumarate 300mg/ emtricitabine 200mg (TDF/FTC)
Study name/Study ID/Author, year, reference number	**DISCOVER,** NCT02842086 Mayer 2020 at 48 weeks [39], Ogbuagu 2021 at 96 weeks [57]	CCRB Clinical Trials Registry, The Chinese University of Hong Kong CUHK, CUHK_CCRB00606 and Chinese Clinical Trial Registry (Registration number: ChiCTR1800016100), Kwan 2021 [38]
Incidence of HIV infection	***At 48 weeks:*** total 22; 7 in emtricitabine and tenofovir alafenamide group (0.16 infections per 100 person-years [95% CI 0.06-0.33]) vs 15 in emtricitabine and tenofovir disoproxil fumarate group (0.34 infections per 100 person-years [0.19-0.56])* HIV incidence rate ration IRR 0.47 [95% CI 0.19-1.15] ***At 96 weeks:*** 8 HIV infections in emtricitabine and tenofovir alafenamide group (0.16 infections per 100 person-years [95% CI 0.07-0.31]) vs15 in emtricitabine and tenofovir disoproxil fumarate group (0.30 infections per 100 person-years [0.17-0.49]) HIV incidence rate ration IRR 0.54 [95% CI 0.23-1.26])	*N.A. Not written as outcome*
Adherence	***At 48 weeks:*** 96-98% participants reported taking drug >80% of the time Median pill count adherence: 98% (IQR 93.4-99.8) emtricitabine and tenofovir alafenamide group vs 98% (93.5-99.9) emtricitabine and tenofovir disoproxil fumarate group. DBS analysis (subset of participants at each visit): 84-96% had tenofovir diphosphate concentrations consistent with taking four or more tablets per week ***At 96 weeks:*** 78-82% participants reported taking study medication >95% of the time Median pill count adherence at week 96: 98% (IQR 93-100%) in both study groups. DBS analysis through the primary endpoint; at each visit, 84-96% participants had tenofovir diphosphate concentrations consistent with taking at least four tablets per week	Median number of days with CLAI: 13 (IQR of 4-28), 11 (IQR: 3-20) of which were covered by PrEP Differences in the numbers of CLAI-days (p=0.94), PrEP-covered CLAI days (p=0.97) and the proportions of days with PrEP-covered CLAI (p=0.93) not statistically significant between two arms. The median number of days with PrEP: 129 (IQR: 97-167), equivalent to about 73% (IQR: 59-85%) of the person-days. The median number and percentage of days on PrEP: 93 (IQR: 64-106) days or 96% (88-100%) during daily vs 45 (IQR: 25-70) days or 54% (32-75%) during on-demand period
Drug resistance mutations	***At 48 weeks:*** Emtricitabine resistance in 4 participants (all in the emtricitabine and tenofovir disoproxil fumarate group, 0 vs 4) No resistance to tenofovir ***At 96 weeks:*** genotypic testing in 20 (87%)/23 infected with HIV; 4(20%)/20 emtricitabine resistance detected (M184V or M184I), all in the emtricitabine and tenofovir disoproxil fumarate group, suspected to have been infected before study enrolment No resistance to tenofovir	*N.A. Not written as outcome*
STI	Rate per 100 person-years Described as safety outcome	47%, 53/113 at least one incident STI, incidence rate 87.46 per 100 person-years; no significant difference between groups (p=0.072)
Gonorrhoea rectal	***At 48 weeks:*** 22 infections per 100 person-years in the emtricitabine and tenofovir alafenamide group vs 21 infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group, p=0.2791	incidence rate of all-site NG: 45.95/100 py (n=32/112, 29%)
Chlamydia rectal	28 infections per 100 person-years in the emtricitabine and tenofovir alafenamide group vs 28 infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group, p=0.5381	incidence rate of all-site CT: 50.29/100 py (n=35/113, 31%)

	Tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC	Oral daily vs on-demand PrEP tenofovir disoproxil fumarate 300mg/ emtricitabine 200mg (TDF/FTC)
Syphilis	10 infections per 100 person-years in the emtricitabine and tenofovir alafenamide group vs 10 infections per 100 person-years in the emtricitabine and tenofovir disoproxil fumarate group, p=0.227 ***Week 96:*** STI rates high and similar across groups: 21 per 100 person-years vs 20 per 100 person-years for rectal gonorrhoea; 27 per 100 person-years vs 27 per 100 person-years for rectal chlamydia;10 per 100 person-years vs 9 per 100 person-years for syphilis	incidence rate of 17.74/100 py (n=13/113, 12%)
Weight increase	***At 48 weeks:*** emtricitabine and tenofovir alafenamide group significantly greater mean change in bodyweight between baseline and 48 weeks vs emtricitabine and tenofovir disoproxil fumarate group (p<0.0001) ***At week 96:*** more weight gain in emtricitabine and tenofovir alafenamide group (median weight gain 1.7 kg vs 0.5 kg, p<0.0001)	*N.A Not written as outcome*
Intention to continue PrEP for HIV prevention		96%, 105/109) indicated intention to continue PrEP for HIV prevention. 16 (15%) participants accepted both daily and on-demand PrEP; 44 (40%) and 43 (39%) showed preference only for daily and on-demand PrEP
Perceived risk of HIV infection		Lowered perceived risk of HIV infection: 39% vs. 17% baseline 18 (17%) participants who considered themselves as having high risk of HIV infection at the endpoint more likely to have sex partners on PrEP at the baseline (p=0.012), report STI diagnosis at Week 16 (p=0.026) and have an emotionally attached partner at Week 24 (p=0.016)

* *One (0.04%) participant in the emtricitabine and tenofovir alafenamide group and four (0.15%) participants in the emtricitabine and tenofovir disoproxil fumarate group who tested negative for HIV at the screening visit, but who tested positive at week 4, were suspected to have acquired HIV infections before baseline. A sensitivity analysis of the primary endpoint excluding these five participants maintained noninferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate (IRR 0.55 [95% CI 0.20-1.48]*

Table A-5: Safety results of the two new RCTs on oral PrEP

	Tenofovir alafenamide plus FTC versus tenofovir disoproxil fumarate (TDF) plus FTC	Oral daily vs on-demand PrEP tenofovir disoproxil fumarate 300mg/emtricitabine 200mg (TDF/FTC)
Safety outcomes/RCT/Ref	**DISCOVER,** NCT02842086 Mayer 2020 *At 48 weeks* [39] Ogbuagu 2021 *At 96 weeks* [57]	**Kwan 2021** [38]
Six prespecified secondary safety endpoints	***At 48 weeks:*** significant difference (p<0.0001) between the two groups in all six prespecified bone mineral density and renal biomarkers (in favour tenofovir alafenamide) ***At week 96:*** Emtricitabine and tenofovir alafenamide: superiority over emtricitabine and tenofovir disoproxil fumarate in all but one of the six prespecified bone mineral density and renal biomarkers (with the exception of study drug-emergent urine to protein creatinine ratio of more than 22.6mg/mmol). More weight gain in emtricitabine and tenofovir alafenamide group (median weight gain 1.7 kg vs 0.5 kg, p<0.0001)	N.A
Any AEs	***At 48 weeks:*** E + t alafenamide 2498 (93%)/2694 E + t disoproxil fumarate 2494 (93%)/2693 Most common adverse events in both groups: diarrhoea (135 [5%] of 2694 participants in emtricitabine and tenofovir alafenamide group vs160 [6%] of 2693 participants in emtricitabine and tenofovir disoproxil fumarate group); nausea (114 [4%] of 2694 participants in emtricitabine and tenofovir alafenamide group vs 125 [5%] of 2693 participants in emtricitabine and tenofovir disoproxil fumarate group) ***Week 96:*** 94% AEs in both groups Most grade 1 (mild) or 2 (moderate), most common bacterial sexually transmitted infections Study drug-related adverse events in 564 (21%) participants in the emtricitabine and tenofovir alafenamide group vs 654 (24%) in the emtricitabine and tenofovir disoproxil fumarate group	<1/3 (36%, n=43) different grades of adverse events, most common diarrhoea, headache, nausea and dizziness 3/4 (77%, n=33) with daily regimen only, 9/37 participants persistent symptoms throughout the entire 16 weeks 5/10 participants (during on-demand period) reported grade 1 adverse events.
Grade 3 or higher laboratory abnormality	***At 48 weeks:*** Any: 196 (7%) vs 206 (8%) ***Week 96:*** 9% in each group (246 in the emtricitabine and tenofovir alafenamide group vs 240 in the emtricitabine and tenofovir disoproxil fumarate group) grade 3 or higher laboratory abnormalities	
Drug discontinuation	***At 48 weeks:*** 36 (1%) vs 49 (2%) ***Week 96:*** 40 (1%) of 2694 participants in emtricitabine and tenofovir alafenamide group vs 51 (2%) of 2693 in the emtricitabine and tenofovir disoproxil fumarate group	None reported
Serious adverse events	***At 48 weeks:*** 169 (6%) vs 138 (5%) ***Week 96:*** 202 [7%] in emtricitabine and tenofovir alafenamide group vs 186 [7%] in emtricitabine and tenofovir disoproxil fumarate group	None reported
Renal	***At 48 weeks:*** 263 (10%) participants in the emtricitabine and tenofovir alafenamide group vs 266 (10%) of participants in the emtricitabine and tenofovir disoproxil fumarate group; study drug-related renal events in 14 (0.5%) participants in emtricitabine and tenofovir alafenamide group vs 26 (1%) participants in emtricitabine and tenofovir disoproxil fumarate group ***Week 96:*** 18 (1%) participants in emtricitabine and tenofovir alafenamide group vs 36 (1%) participants in emtricitabine and tenofovir disoproxil fumarate group Renal adverse events leading to discontinuation: 2 in emtricitabine and tenofovir alafenamide group vs 6 in emtricitabine and tenofovir disoproxil fumarate group	Change of creatinine clearance over time: –0.39ml/min (95% CI: –0.49 to –0.28, p< 0.0001) per week from an intercept of 120.12 (95% CI: 115.48-124.75, p< 0.0001), no difference between the two arms
Fracture events	***Week 96:*** In each study group, 60 participants had fracture events; 1 (2%) in the emtricitabine and tenofovir alafenamide group vs 2 (3%) in the emtricitabine and tenofovir disoproxil fumarate group were nontraumatic (pathological)	
Death	***At 48 weeks:*** 1 (0.04%) vs 1 (0.04%) ***Week 96:*** 3 (<1%) vs 2 (<1%)	None reported

Effectiveness and safety results of injectable vs oral PrEP

Table A-6: Effectiveness results of the two new RCTs on injectable vs oral PrEP

Effectiveness outcomes/ RCT/Ref	Landovitz 2021 [58] HPTN 083, NCT02720094	Delany-Moretlwe 2022 [41] HPTN 084, NCT 03164564
Incidence of HIV infection	Total 52; 13/3205 in cabotegravir group (incidence, 0.41 per 100 person-years) vs 39/3187 in TDF–FTC group (incidence, 1.22 per 100 person-years)* Hazard Ratio (HR) 0.34 (95% confidence interval [CI], 0.18 to 0.62; p<0.001)	Total 40; 4/1956 HIV infections in cabotegravir group (HIV incidence 0.20 per 100 person-years [95% CI 0.06-0.52]) vs 36/1942 in TDF/FTC group (1·.85 per 100 person-years [1.3-2.57] HR 0.12 [0.05-0.31]; p<0.0001) Risk difference –1.6% [–1.0% to –2.3%]
Adherence	91.5% of person-years injectable CAB-LA vs 74.2% or 86.0% TDF–FTC group (in randomly selected subgroup of 390 participants in the TDF–FTC group, 74.2% had tenofovir concentrations >40 ng per milliliter, consistent with the receipt of daily TDF–FTC doses in previous week; 86.0% had concentrations above the lower limit of quantitation, 0.31 ng per milliliter)	3349 (93.1%) of 3599 person-years on study (1678 [93.0%] of 1805 in cabotegravir group vs 1671 [93.1%] of 1794 in TDF/FTC group) covered by injections, i.e., cabotegravir or placebo injections were received on time or with a delay of less than 2 weeks 1084 (55.9%) of 1939 evaluated samples with quantifiable plasma tenofovir concentrations (≥0.31ng/mL): 812 (41.9%) of 1939 tenofovir concentrations consistent with daily use (≥40ng/mL) (samples from a randomly selected cohort of 405 participants in the TDF/FTC group were evaluated for adherence to TDF/FTC)
Drug resistance mutations	Cabotegravir group (INSTI resistance mutations): 4 of 9 incident cases that had a resistance test result TDF–FTC group: 2 of 39 incident cases in which the drug concentrations that were measured were consistent with good PrEP adherence	Cabotegravir group (INSTI resistance mutations): 0 in 4 incident cases TDF/FTC group: NRTI resistance in 1 of 36 incident cases (poor adherence to TDF/FTC); several (9 according the Eshleman 2022) had NNRTI mutations
	Marzinke 2021 [59] Integrase strand transfer inhibitors (INSTI) resistance mutations in 5 cases in the CAB arm (4 with INSTI resistance only and 1 with INSTI and nonnucleoside reverse-transcriptase inhibitor – [NNRTI] resistance)	Eshleman 2022 [60] None had CAB resistance (INSTI- resistance mutations) 9 in the TDF/FTC arm: nonnucleoside reverse-transcriptase inhibitor resistance; 1 had the nucleoside reverse-transcriptase inhibitor resistance mutation, M184V
STI	Rate per 100 person-years Cabotegravir group vs TDF–FTC group	N.A ("will be reported elsewhere")
Overall incidence of new rectal or urethral gonorrhea	13.49 per 100 person-years	7.7 per 100 person-years (6.8-8.7); not vary significantly by study group
Gonorrhea rectal	11.1 vs 11	N.A
Overall incidence of new rectal or urethral chlamydia	21.36 per 100 person-years	19.6 per 100 person-years (95% CI 18-21); not vary significantly by study group
Chlamydia rectal	15.8 vs 17.8	N.A
Hepatitis C	0.49 vs 0.58	N.A
Syphilis	16.6 vs 16.7	N.A

Effectiveness outcomes/ RCT/Ref	Landovitz 2021 [58] HPTN 083, NCT02720094	Delany-Moretlwe 2022 [41] HPTN 084, NCT 03164564
Weight increase	Post hoc analysis: a mean annualized increase in body weight of 1.23 kg per year (95% CI, 1.05 to 1.42) in cabotegravir group vs increase of 0.37 kg (95% CI, 0.18 to 0.55) in TDF–FTC group	Cabotegravir group significant increase in average initial weight gain vs TDF/FTC group (0.4 kg [95% CI 0.27-0.51]; p<0.0001) Subsequently both groups showed weight gain, with a mean increase of 2.4 kg per year (1.9-3.0) in the cabotegravir group compared with 2.1 kg per year (1.9-2.4) in the TDF/FTC group (p=0.041)
Pregnancy incidence	N.A	Overall confirmed pregnancy incidence (1.3 per 100 person-years [95% CI 0.9-1.7]) 49 confirmed pregnancies: 29 in cabotegravir group (1.5 per 100 person-years [1.0-2.2]) and 20 in TDF/FTC group (1.0 per 100 person-years [0.6-1.6]) Outcome data available for 31 (63%) of 49 pregnancies at the time of data lock, with the remainder of pregnancies ongoing: most resulted in a livebirth (13 of 18 in the cabotegravir group and 10 of 13 in the TDF/FTC group), with the remainder ending in pregnancy loss (spontaneous or induced); no congenital anomalies observed

* *Post hoc centralized testing of stored plasma samples resulted in readjudication: 1 of the original 13 incident HIV infections in the cabotegravir group was readjudicated as a base line infection. An analysis that included the post hoc readjudication data provided a revised estimate of incident HIV infection in the cabotegravir group of 0.37 (95% CI, 0.19 to 0.65; hazard ratio, 0.32 [95% CI, 0.16 to 0.58]).*

Table A-7: Safety results of the two new RCTs on injectable vs oral PrEP

Safety outcomes/RCT/Ref	Landovitz 2021* [58] HPTN 083, NCT02720094	Delany-Moretlwe 2022 [41] HPTN 084, NCT 03164564
	Safety population (participants received at least one dose of any of the oral tablets or injections): 4562 participants (2280 in the cabotegravir group vs 2282 in the TDF–FTC group)	Safety population: 3224 participants received at least one dose of study product
AEs		
Grade 2 or higher	4222 out of 4562 (92.5%) Cabotegravir group 2106 (92.4%)/2280 vs TDF/FTC Group 2116 (92.7%)/2282 Most frequent: decreased creatinine clearance overall 3257 (71.4%); 1588 (69.6%) Cabotegravir group vs 1669 (73.1%) TDF/FTC group	2973 (92.2%) of 3224 participants Cabotegravir group 1487 (92.1%)/1614 vs TDF/FTC Group 1486 (92.3%)/1610 Most frequent: decreased creatinine clearance: 1166 (72.2%) Cabotegravir group vs 1197 (74.3%) TDF/FTC group
Grade 3 or higher	1494/4562 participants (32.7%); similar in the two trial groups Cabotegravir group 727 (31.9%)/2280 vs TDF/FTC group 767 (33.6%)/2282 Most frequent: Increased creatine kinase overall 633 (13.9%); 324 (14.2%) Cabotegravir group vs 309 (13.5%) TDF/FTC group	Both study groups (558 [17.3%] of 3224 Cabotegravir group 276 (17.1%)/1614 vs TDF/FTC group 280 (17.4%)/1610 Most frequent: Decreased creatinine clearance; 110 (6.8%) Cabotegravir group vs 125 (7.8%) TDF/FTC group

Safety outcomes/RCT/Ref	Landovitz 2021* [58] HPTN 083, NCT02720094	Delany-Moretlwe 2022 [41] HPTN 084, NCT 03164564
Serious adverse events	241 participants (5.3%)/4562 (balanced between the two groups)	66 participants at least one SAE; 33 (2.0%) cabotegravir group vs 33 (2.0%) TDF/FTC group; six SAEs related to study product (2 in cabotegravir group vs 4 in TDF/FTC group) 2 SAEs in cabotegravir group: hospitalisation for fetal distress and respiratory tract infection; 4 SAEs in the TDF/FTC group: hospital admissions for investigation of hepatotoxicity (n=1) or raised transaminases (n=2), and seizure (n=1)
Drug discontinuation	172 (3.8%); out 2117 participants in active CAB-LA injection, 50 (2.4%) permanently discontinued the injections owing to an injection-related adverse event; discontinuation was strongly associated with increased severity of the injection-site reactions	40 (1.2%) participants (17 [1.1%] in cabotegravir group vs 23 [1.4%] in TDF/FTC group) during steps 1 and 2
Adverse events of special interest	Uncommon, overall frequency similar in the two groups	Overall, one (<0.1%) of 3224
Seizures	Overall, 7 (0.2%) 2 (0.2%) cabotegravir group vs 5 (0.2%) TDF–FTC group	0 cabotegravir group vs 1 (0.1%) TDF–FTC group
Liver related adverse events resulting in discontinuation of the oral tablets or both oral tablets and injections	95 (2.1%) 47 (2.1%) cabotegravir group vs 48 (2.1%) TDF–FTC group	33 (1.0%) 15 (0.9%) cabotegravir group vs 18 (1.1%) TDF–FTC group
Death	11 (7 in the TDF–FTC group and 4 in the cabotegravir group; hazard ratio, 0.57, 95% CI, 0.17 to 1.96) 1 death in the TDF–FTC group that resulted from cardiovascular disease: related to the oral tablets or injections.	3, all in cabotegravir group – 3 (0.2%). None attributed to study product; due to hypertensive heart disease (n=1), a cerebrovascular accident (n=1), and an unexplained headache that could not be further investigated (n=1)
Injection-site reactions	1724 (81.4%) cabotegravir group vs 652 participants (31.3%) TDF–FTC group Mostly mild or moderate in severity and decreased in frequency over time; Of 10,666 injection-site reactions in the cabotegravir group, 6486 (60.8%) were pain and 2530 (23.7%) were tenderness; the events began a median of 1 day (IQR, 0 to 2) after injection and lasted a median of 3 days (IQR, 2 to 6)	577 (38.0%)/1519 in cabotegravir group vs 163 (10.8%) of 1516 TDF/FTC group Grade 2 or worse adverse events in 192 (12.6%) of 1519 cabotegravir group vs 25 (1.6%) of 1516 TDF/FTC group. Pain most commonly reported: 570 (4.4%) of 12 901 injections in cabotegravir group vs 146 (1.1%) of 12825 injections in TDF/FTC group. Most injection site reactions at the first injection, diminished over time. In cabotegravir group, injection site reactions in 438 (28.8%) of 1519 participants at first injection; decreased to 25 (1.9%) of 1322 participants by the fourth injection. No discontinuations of study product due to injection site reactions.

***** *In published article: Included are only adverse events that were assigned Medical Dictionary for Regulatory Activities, version 23.1 (MedDRA) terms by clinical staff. Injection-site reactions and sexually transmitted infections are not included within AE.*

Ongoing RCTs

Table A-8: List of ongoing RCTs on oral and injectable PrEP in ClinicalTrials.gov and EudraCT registries

Study Identifier	Estimated completion date	Study type	Number of participants	Intervention	Comparator	Patient population/Ages	Primary endpoints
NCT04994509 https://ClinicalTrials.gov/show/NCT04994509	July 2027	RCT, phase 3	5,010	Lenacapavir	F/TAF (Descovy®) F/TDF (Truvada®)	Cisgender female, 16 to 25 years	HIV Incidence reported per 100-PY of follow-up
NCT03164564 https://ClinicalTrials.gov/show/NCT03164564	May 2022	RCT, phase 3	3,200	CAB-LA	TDF/FTC	Cisgender female, 18 to 45 years	HIV incidence rate, AEs
NCT04925752 https://ClinicalTrials.gov/show/NCT04925752	April 2027	RCT, phase 3	3,000	Lenacapavir	F/TAF (Descovy®) F/TDF (Truvada®)	Cisgender male, Transgender male, Transgender female, and Gender non-binary, 16 years and older	HIV Incidence reported per 100-PY of follow-up
NCT04652700 https://ClinicalTrials.gov/show/NCT04652700 **EudraCT 2020-003309-79**	September 2024	RCT, phase 3	494	Islatravir	F/TAF (Descovy®) F/TDF (Truvada®)	Male participants and transgender women, 16 years and older	Percentage of participants with Adverse Event (AE), Percentage of participants who discontinued study treatment due to an AE
NCT04644029 https://ClinicalTrials.gov/show/NCT04644029 **EudraCT 2021-001289-39**	July 2024	RCT, phase 3	730	Islatravir	FTC/TDF (TRUVADA™ or generic product emtricitabine/ tenofovir disoproxil)	Assigned female sex at birth and is cisgender, 16 to 45 years	Incidence rate per year of confirmed HIV-1 infections, Percentage of participants with Adverse Event (AE), Percentage of participants who discontinued study treatment due to an AE
NCT05140954 https://ClinicalTrials.gov/show/NCT05140954	May 2025	RCT, phase 2/3	54	25mg TAF/200mg FTC (Descovy)	Different dosing schedule (7doses per week; 4 times per week; twice per week)	Female (Cisgender women), 18 to 30 years	Adherence (perfect; moderate; poor): steady state concentrations of tenofovir for different dosing patterns of DOT TAF/FTC PrEP
NCT04742491 https://ClinicalTrials.gov/show/NCT04742491	November 2024	RCT, phase 2/3	310	F/TAF (Descovy®) F/TDF (Truvada®)	Intermediate intervention arm vs 6 months deferred intervention arm	Transgender women, 18 years and older	PrEP adherence and persistence, Uptake of hormonal therapy and PrEP
NCT04937881 https://ClinicalTrials.gov/show/NCT04937881	September 2023	RCT, phase 2/3	50	200mg emtricitabine (FTC) and 25mg tenofovir alafenamide (TAF)	200mg emtricitabine (FTC) and 300mg tenofovir disoproxil fumarate (TDF)	14-24 weeks pregnant women, 18 years and older	Adherence: Tenofovir diphosphate (TDF-DP) concentrations in plasma and interceullalar levels in pregnant and pospartum women on daily PrEP, comparing the drugs TAF to TDF
EudraCT 2016-000439-42 https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000439-42/GB	N.A	RCT, phase 4	84	Descovy 200/25mg	Truvada 200/245mg	Male and women, 18-64 years	Time to protection and adherence requirements of TRUVADA® and DESCOVY®; determine the minimal dosing requirement for on demand PreP

Patient involvement

The impact of condition – HIV

How does HIV, for which the medicines are being assessed to prevent people at risk, affect patients? What are the experiences of living with HIV?
Untreated HIV infections resulted in sickness and death in almost all cases: immunodeficiency opportunistic infections and cancer are inevitable, resulting in high morbidity, hospitalisations and mortality. Psychosocial implications of HIV/AIDS are as following: severe burden of psychological distress, psychiatric morbidity and social difficulties (stigma including self-stigma, discrimination within the health system and at workplace, social exclusion, poverty, unemployment …). For example, medical treatment or taking ART has a particularly strong impact on the emotional and psychological level of HIV-positive people. For many infected people, taking ART every day at the same time is a great challenge and is associated with a lot of psychological stress, as they are worried that their environment, such as work colleagues, friends or family members, who do not know about the infection, could find out about the infection by taking the medication. Due to the daily use of medication, those affected are repeatedly in need of explanation, which in turn causes great psychological stress. Furthermore, it is very challenging for some affected people to coordinate their daily medication intake with their employment, i.e., it is very difficult for people who work shifts to take their medication regularly because of the irregular working hours. In addition, there is still a great deal of stigmatisation against HIV/AIDS in society, which is why those affected often do not tell anyone or only very close relatives/friends about their infection. As a result, many affected people feel a great deal of shame associated with the infection, as those affected often have the feeling that they have to 'hide' a part of themselves because they cannot or do not want to talk about the infection. Social withdrawal, isolation and social exclusion can be the result. An advanced AIDS disease can have effects on several levels. For example, if the disease is far advanced, people may lose their jobs, which can result in a loss of income. In addition, an advanced AIDS disease can bring with it various physical problems. Sometimes could result in the loss of loved ones who cannot cope with this.
How does HIV affect the daily life of carers and what is the emotional impact for them? What is the burden on care-givers?
Many times, at the beginning, due to lack of knowledge on HIV transmission, there is often a great fear of becoming infected with HIV in everyday life. It is essential to clarify prejudices and misinformation regarding the transmission of HIV and how to deal with the infection in daily life, and thus to reduce potential fears regarding HIV/AIDS. Psychosocial stress of family and carers of people who live with HIV is high, so they need psychological support also.
Are there groups of patients that have particular issues in managing their HIV or preventing HIV?
People with late diagnoses, people who are not prepared for HIV, migrants and vulnerable groups. For example, people with an African migration biography in particular have increased difficulties in dealing with their HIV infection. This is due to the fact that HIV is still strongly stigmatized in Africa and that there are many prejudices and misinformation about the virus, such as the belief that an HIV infection is a certain death sentence. In some cases, those affected have had the experience of being expelled from their family and close environment if they inform relatives about the infection. Because of this, it is increasingly noticeable that those affected with an African migration biography in particular have a very shameful way of dealing with the infection. Not all people may receive information needed due to level of education, access to communities, language barriers, other restrictions, individual resilience … PLWH without health insurance are not provided with antiretroviral medication by the state in Austria, in opposition to most European countries. This a huge shortcoming and should be taken care of immediately. MSM with unprotected sexual activity face higher risks of HIV-acquisition and should be at the center of PrEP. Incurring costs are not affordable for everyone. Free of charge PrEP should be available to all people at risk.

Experience with currently available health interventions for HIV prevention

How well do currently available health interventions work for HIV prevention? How does the use of any type of interventions for HIV prevention affect activities of daily living? What is the effect of any type of intervention on quality of life?
There is a big lack of knowledge on prevention and on sexual health as such. People who are not aware about their risk of infection and people who cannot pay PrEP are areas the current interventions do not address. Information about safer sex and easy access to PrEP is an unmet need for people at risk for HIV. There is still a lack between testing, treating and prevention as there is no one stop shop (like sexual health clinics). PrEP in Austria is only known to Men having sex with Men (MSM) – and there only a group with good financial background is able to use it (as it is quite expensive 59 Euro/month + private prescription from an HIV treatment provider (subject to a charge) – the unmet need is here, that especially vulnerable groups cannot afford it. Still stigma on people being vulnerable, going to a testing site ... On-site work has become more difficult. Despite the fact of already conducted workshops and campaigns on the topic (i.e., prevention workshops in schools, distribution of condoms and flyer in different locations, frequented by MSM), the range of people reached is limited. In cis-communities, 'prevention' often only means birth control. Lack of awareness. PrEP is promoted very little. Most promotion probably is spread by word of mouth within the MSM community. The nowadays used interventions for HIV-prevention have all shown to be very effective (i.e., treatment as prevention, PrEP, consistent condom use) but all of them are associated with barriers to success: Treatment as prevention: high percentage of late diagnosis ('late presenters') resulting in many years of possible HIV-transmission per individual patient; PrEP: main barrier is cost for the drug and the necessary STD-checks; Condoms: are not consistently used (e.g. in the context of chemsex parties). All possible interventions are associated with very little side effects (condoms: allergy, treatment as prevention and PrEP: low rate of intolerance to one of the ARV compounds). Some mentioned side effects associated with currently available interventions for HIV prevention that are distressing or difficult to tolerate.

PrEP (including the necessary monitoring) is too expensive. PrEP, which might be the most effective intervention of all is associated with the highest financial burden (currently 60€ only for the drugs) because costs are not covered by Austrian health insurances (in opposition to most European countries). Lowering barriers to effective HIV-prevention must therefore include free-of-charge Prep for everybody in need! At the same time ART must be accessible free-of-charge for everybody living in Austria (not only for those who enjoy health insurance!).
Are there groups of people that have particular issues using the currently available interventions for HIV prevention? Are there groups of people who currently don't have good access to available interventions for HIV prevention? Are there factors that could prevent a group or person from gaining access to available interventions for HIV prevention?
People with migrant background, people who fear to be discriminated because of their sexual orientation, the group of the classic HIV-Late-Presenter (heterosexual men around 50 from the less urban areas), vulnerable MSM are very hard to reach HIV-prevention. Different factors could prevent from gaining access to interventions for HIV prevention, like stigma, financial issues, language barriers. For example, people who live under financial constraints cannot afford PrEP and will thus not buy it. Or it might be ordered through the internet without quality assurance and without medical supervision.

Experiences with, and expectations of, the medicines being assessed: oral and parenteral medicines for preexposure prophylaxis (PrEP) to prevent HIV in people at risk

For those *with* experience of these oral and parenteral medicines for preexposure prophylaxis (PrEP) to prevent HIV in people at risk, what difference did it make to their lives? How does the use of these medicines affect activities of daily living? What is the effect of these medicines on quality of life? Was the use of these medicines worthwhile?
People using PrEP feel safe in their sexual contacts and are more informed on possible extra-risks – so know a lot about STI transmission and sexual health on the whole. As PrEP can be only received on receipt, regular STD tests are included. They are responsible and prudent about own health and HIV-status. PrEP usage has substantially increased quality of life, as fear of HIV acquisition has considerably dropped. Sexual and social life has definitely improved for PrEP users. They are losing their fear while having sex with different sex-partners and with infected partners under or without treatment. PrEP is mainly used in the group MSM, and more and more MSM are going to use the PrEP to avoid an HIV-infection. Only very few women and heterosexual men are using PrEP. PrEP is especially popular in the age between 25 and 40, as they can afford it (see below when it comes to the financial expenses) and used during sex-parties or holidays and other occasions. Most people that started "on demand" changed to a continuous taking, as it is easier to manage (e.g., desire vs reason). Daily PrEP and PrEP on demand have both worked as effectively. In some cohort no PrEP user has experienced HIV-infection in opposite to some patients who did not use PrEP. People who use PrEP don't see it as burden in their daily life's, it's more perceived as a big support. The intake is without problems/adherence is no issue, as well as safety (no side effects in general, also when using the PrEP for many years). PrEP users are mostly committed about regular use (temporary or permanent) to avoid an HIV-infections and regular check of STI-status via blood test and swaps. No PrEP user receives parenteral PrEP. Sometimes PrEP users struggle with common prejudices and stigma: they are seen as very promiscuous and infected with other diseases (STIs); seen as weak – common insults: 'Too weak to use condoms', 'Not able to hold an erection', and so on … Financial implications to patients and their families (e.g., costs of purchasing the medicines, travelling costs) are high: it ranges from 0 EUR in studies (only very few can participate) to 150 EUR and more per month (including the costs of the medication). Also other expenses and 'time killers': travelling costs and travelling time for example to Vienna or Klagenfurt, if living in Graz. It's an obstacle, that they have to visit the GP/HIV-treaters regularly and that they have to pay for the private practice. Costs are high and not affordable for everyone. People who stopped using PrEP mainly because of the costs (some also: monogamous partnership). Many users are angry about that situation as an infection would cost much more at the end. PrEP use is seen as the 'method to avoid infections for the rich people'. PrEP should be offered for free as well as STI-check. In many cities it is so complicated to get in contact with a doctor that can prescribe PrEP medications. The prescription of PrEP-medications should be available at any general practitioner. For some PrEP-users a long-lasting technique (e.g., injectables) would be preferable to swallowing a pill.
For those *without* experience of these medicines being assessed, what are the expectations of using them? How do patients perceive these medicines under assessment?
Their expectation is the idea of having a more relaxed sex life. Sometimes they are worried because of possible side effects (i.e., kidney function as this is one of the tests to be considered). Big obstacles for people knowing of PrEP but not taking it (mostly MSM) are the costs (financial barrier). Other reasons might be present also, like fear of side effects, fear of being caught taking the pills (fear of disclosure of homosexuality) and others. Still: If I take the PrEP people will think I'm a 'slut' (self-stigma). People not (yet) on PrEP might wish to have (additional) protection against HIV-transmission. As of consequence they hope to have improved their sexual or social life.
Which groups of patients/people at risk might benefit most from these medicines being assessed?
MSM (with low income, migrants, students), heterosexual people at risk of HIV-acquisition (i.e., sex workers, chemsex users ...), people with changing sex partners, people that cannot use condoms, groups that currently have very limited options for PrEP.

Additional information

What information may support patients to make informed decisions about using these medicines? How are treatment choices explained to patients? What specific issues may need to be communicated to patients to improve adherence? Please include any additional information you believe would be helpful to the HTA reviewers (e.g., ethical or social issues, any potential equality issues, information needs about these medicines).
It is important to reach the vulnerable groups with campaigns (also in more languages). More information is needed for heterosexual women and men, but also within health care providers, i.e., general practitioners, gynaecologists … Further efforts are needed to get more physicians into prescribing PrEP. Easy and cheap access is needed. Cost coverage by Austrian health insurance companies is needed, i.e., for the drugs and the necessary lab tests, and the procedures done by the physician) as one single intervention which might have the greatest impact on acceptability and usage of PrEP. As soon as cost coverage is in place this must be communicated by all means (social media, different promotion campaigns …). More information on the transmission paths of the other STDs as well as the risk of taking PrEP medication.

Key messages from patients

To reach the goal to eliminate new HIV-infections by 2030 we have to get the PrEP for all people that need it. We have to reach groups who are vulnerable in this particular field. There should not be any financial obstacles in preventing HIV. The PrEP must be offered free of charge. HIV-medicines (emtricitabine+tenofovir) as PrEP are extremely effective in preventing HIV-infection whether taken daily or on demand. It has been shown to be cost-effective. Costs are a barrier to usage and should therefore be taken over by health insurances as done in most European countries. It is very likely that higher uptake of PrEP will reduce future transmissions and diagnoses of HIV in Austria. PrEP for all who need it would prevent stigma and self-stigma. Access to information must be secured. Regular examinations (checking other STDs) when prescribing the medication, prescription only by a specialist after a detailed consultation.

Primary cost-effectiveness analyses related to oral PrEP and injectable PrEP

Table A-9: Main results from primary cost-effectiveness studies

Authors/Ref	Oral PrEP
O'Murchu et al. 2021 [105] **Health Information and Quality Authority. 2019 [30]**	In recently published cost-effectiveness analysis in **Ireland,** introduction of publicly funded pre-exposure prophylaxis (PrEP) programme (medications + frequent monitoring) for MSM population at high-risk was compared with no PrEP. The primary outcome measure was the incremental cost-effectiveness ratio (ICER). Evidence showed that in the base case, introducing a PrEP programme was considered cost saving and provided significant health benefits to the population. Univariate sensitivity analysis demonstrated that PrEP efficacy and HIV incidence had the greatest impact on cost-effectiveness. Including an increase in sexually transmitted infections had a negligible impact on the results. Efficacy was a significant driver in the model. PrEP was cost saving at all efficacy values above 60%, and at the lowest reported efficacy in MSM (44% in the iPrEX trial), the ICER was €4711/QALY (highly cost-effective). Event-based dosing (administration during high-risk periods only) was associated with additional cost savings. In the scenario where 50% of PrEP recipients follow event-based dosing, the ICER decreases to -€4,594 (95% CI: -€20,158 to €14,150). The ICERs were also sensitive to key cost parameters, including the cost of HIV care and the cost of PrEP. PrEP was still considered cost saving over a range of plausible costs.
López Seguí et al. 2023 [83]	Authors published results of cost-effectiveness analysis of the daily HIV pre-exposure prophylaxis in *men who have sex with men* in **Barcelona**. Authors compared the implementation of HIV pre-exposition prophylaxis using administrative data from MSM who receive the treatment (at the generic price) compared with non-implementation. A deterministic compartmental model and a social perspective with a micro-costing approach over the time horizon 2022-2062 were used. A baseline 86% effectiveness of PrEP is assumed. Results showed that daily oral PrEP was found to be cost-saving: discounted savings in costs are attained after 16 years, and after 40 years the savings reach 81 million euros. In terms of health indicators, 10,322 additional discounted quality-adjusted life-years (QALYs) are generated by the intervention. Results were sensitive to sexual behavioral patterns among MSM, the price of PrEP (reduced if offered on-demand), its effectiveness and the discount rate. Authors concluded that short-term investments in the promotion of PrEP will result in important cost-savings in the long term.
Yamamoto et al. 2022 [84]	Authors evaluated the cost-efectiveness of a pre-exposure prophylaxis programme for HIV prevention for *men who have sex with men* in **Japan** (PrEP has not yet been approved in Japan)**.** A Markov model was developed to describe HIV infection and disease progression in an MSM cohort (n=1000) in Japan receiving a PrEP programme. HIV/AIDS treatment, screening, hospitalization due to AIDS, and PrEP were considered as costs and quality-adjusted life-years (QALYs) gained as utilities. Cost-effectiveness was assessed by comparing the incremental cost-effectiveness ratio (ICER) over a 30-year period against the willingness to pay (WTP) threshold. One-way sensitivity and probabilistic sensitivity analyses were performed. With 50% PrEP coverage, the PrEP programme became dominant against the programme without PrEP, using a threshold of 5.0 million JPY/QALY (45,455 USD). The probabilistic sensitivity analysis showed that the PrEP programme was dominant or at least cost-effective in most cases of 10,000 simulations. Preparing cheaper PrEP pills, which results in PrEP being dominant or ICER being lower than the WTP threshold, is important to make the programme cost-effective. Authors concluded that introduction of PrEP to an MSM cohort in Japan would be cost-effective over a 30-year time horizon.
Ten Brink et al. 2022 [85]	Authors published results relevant for several countries in **Asia** using the Optima HIV model to examine the impact of scaling-up PrEP over five years to cover an additional 15% of *MSM* compared with baseline coverage (target deemed feasible by regional experts). Based on behavioural survey data, authors assumed that covering 15% of higher-risk MSM will cover 30% of all sexual acts in this group. Scenarios to compare the impact of generic-brand daily dosing of PrEP with generic event-driven dosing (15 days a month) were modelled from the start of 2022 to the end of 2026. Cost-effectiveness of generic versus branded PrEP was also assessed for China, the only country with an active patent for branded, higher cost PrEP. The impact on new HIV infections among the entire population and cost per HIV-related disability-adjusted life year (DALY) averted were estimated from the beginning of 2022 to the end of 2031 and from 2022 to 2051. Authors found that if PrEP were scaled-up to cover an additional 15% of MSM engaging in higher-risk behaviour from the beginning of 2022 to the end of 2026 in the eight Asian countries considered (Cambodia, China, India, Indonesia, Myanmar, Nepal, Thailand, and Vietnam), an additional 100,000 (66,000-130,000) HIV infections (17%) and 300,000 (198,000-390,000) HIV-related DALYs (3%) could be averted over the 2022 to 2031 period. The estimated cost per HIV-related DALY averted from 2022 to 2031 ranged from US$600 for event-driven generic PrEP in Indonesia to US$34,400 for daily branded PrEP in Thailand. Over a longer timeframe from 2022 to 2051, the cost per HIV-related DALY averted could be reduced to US$100-US$12,700. Authors concluded that implementing PrEP in Asia may be cost-effective in settings with increasing HIV prevalence among MSM and if PrEP drug costs can be reduced, PrEP could be more cost-effective over longer timeframes.
Walensky et al. 2020 [86]	Authors published results from cost effectiveness analysis in **US** related to branded tenofovir alafenamide/emtricitabine (F/TAF) compared to generic tenofovir disoproxil fumarate/emtricitabine (F/TDF) for HIV daily pre-exposure prophylaxis. Authors used published literature on F/TDF safety (with and without HIV) and the cost and quality of life impact of fractures and end-stage renal disease (ESRD). The target population were age-stratified US *men who have sex with men (MSM)* using PrEP. The study applied a time horizon of five years and a health care sector perspective. Outcome measures were fractures averted, cases of ESRD averted, quality-adjusted life years (QALYs) saved, costs, incremental cost-effectiveness ratios (ICER), and maximum justifiable price for F/TAF. Results of base-case analysis showed that over a 5-year horizon, for the 123,610 MSM on PrEP, compared to F/TDF, F/TAF averted 2,101 fractures and 25 cases of ESRD with an ICER of >$7 million/QALY. At a 50% discount for generic F/TDF ($8,300/year) and a societal willingness to pay up to $100,000/QALY, the maximum fair price for F/TAF was $8,670/year. Results of sensitivity analysis showed that among those >55y, the ICER for F/TAF remained >$3 million/QALY and the maximum permissible fair price for F/TAF was $8,970/year. Results were robust to alternative time horizons and PrEP-using population sizes. Authors concluded that in the presence of a generic F/TDF alternative, the improved safety of F/TAF is worth no more than an additional $370 per person per year.

Authors/Ref	Injectable PrEP
Stansfield et al. 2022 [106]	Authors conducted a comparative modelling analysis of the potential impact of expanding PrEP coverage by offering CAB-LA to i) *men who have sex with men (MSM)* in **Atlanta, USA** and **Montreal, Canada**, cities with concentrated HIV epidemics dominated by MSM transmission, and ii) *cisgender men and women* in **South Africa**, a country with a generalized HIV epidemic. Four independent age- and risk-stratified HIV transmission models were parameterized and calibrated to local data from Atlanta (HPTN model), Montreal (McGill model) and South Africa (Synthesis and Thembisa models). Achieving expansion of overall PrEP coverage to the desired targets after 5 and 10 years were simulated by recruiting additional PrEP users based on current PrEP indication criteria specific to each setting and switching different proportions of TDF/FTC users to CAB-LA starting in 2022. Population effectiveness, efficiency and cost-effectiveness of PrEP expansion were evaluated over 20 years compared to base-case scenarios with current projections of TDF/FTC use only. MSM models: In the base-case scenarios, predicted median overall PrEP coverage rises from 30% to 32% (Atlanta) and from 6% to 10% (Montreal) between 2022 and 2042. Increasing overall PrEP coverage by 8-10 percentage points (pp) to 40% of the Atlanta MSM population by 2027 is expected to avert 35-39% of new HIV infections over 20 years. A substantially larger increase in overall PrEP coverage (~20pp increase to 30%) is needed to avert a comparable fraction of infections in Montreal (preliminary results), where population-level viral suppression is high. Approximately 20 additional person years (PY) on PrEP are needed to prevent one infection in Atlanta where annual HIV incidence is 1.5-2% compared to more than 1000 PYs in Montreal where annual HIV incidence is below 0.2%. Averting one disability-adjusted life year is predicted to cost around US$ 200,000 in Atlanta and millions of US dollars in Montreal. Reaching 50% overall PrEP coverage in 2027 may avert close to 60% of new HIV infections over 20 years in both settings. Authors concluded that offering CAB-LA to MSM in the USA and Canada can impact the HIV epidemic substantially if it leads to increases in overall PrEP coverage. PrEP expansion could be highly efficient and possibly cost-effective in places with high HIV incidence (like Atlanta) but are unlikely to be cost-effective in low-incidence settings (like Montreal). In the base-case scenarios, median overall PrEP coverage in South Africa is currently at or below 1% and not expected to increase by 2042. Increasing overall PrEP coverage to 13% of the male and female adult population in 2027 by recruiting CAB-LA users predominately from high HIV-risk groups is expected to avert ~20% of new HIV infections over 20 years (Thembisa). Achieving 5% overall CAB-LA coverage in 2027 among high-risk groups with targeted PrEP use during periods of substantial HIV risk may avert nearly 50% of new HIV infections over 20 years (Synthesis). Achieving similar expansion with oral TDF/FTC instead of CAB-LA is expected to reduce the impact by up to 20% (Thembisa) and 40% (Synthesis) due to lower efficacy and adherence. Approximately 16-25 additional PYs on CAB-LA are needed to prevent one infection in South Africa with strict risk targeting (Synthesis) compared to more than 100 if CAB-LA is available to all but mostly used by individuals at high risk (Thembisa). In the latter scenario, expanding PrEP coverage with CAB-LA could be more cost-effective than with oral PrEP only if CAB-LA is priced within 2x the price of oral PrEP (i.e., up to US$ 18.80 per injection). This analysis suggests that offering CAB-LA in South Africa can impact the HIV epidemic substantially if adequately used by people at high risk of acquiring HIV. PrEP expansion could be highly efficient and cost-effective if adopted mainly during periods of substantial risk.
Neilan et al. 2022 [107]	Authors published results from a cost-effectiveness analysis which aimed to identify the maximum price premium (greatest possible price differential) that society should be willing to accept for the additional benefits of CAB-LA over tenofovir-based PrEP among *men who have sex with men and transgender women (MSM/TGW)* in the **United States**. Analysis related to CAB-LA versus generic F/TDF or branded F/TAF for HIV PrEP and was from the perspective of the health care system with a time horizon of 10 years, on the target population of 476 700 MSM/TGW at very high risk for HIV (VHR). The study found that over 10 years, costs would total $33.48 billion for no PrEP, $30.67 billion for generic F/TDF, $60.42 billion for branded F/TAF, and $75.84 billion for CAB-LA (assuming the upper bound of its price), inclusive of primary transmissions. Results of base-case analysis showed that CAB-LA increased life expectancy by 28 000 QALYs (26 000 QALYs) among those at very high risk for HIV, compared with generic F/TDF (or branded F/TAF). Branded F/TAF cost more per QALY gained than generic F/TDF compared with no PrEP. At 10 years, CAB-LA could achieve an ICER of at most $100 000 per QALY compared with generic F/TDF at a maximum price premium of $3700 per year over generic F/TDF (CAB-LA price <$4100 per year). Results of the sensitivity analysis showed that in a PrEP-eligible population at high risk for HIV, rather than at very high risk for HIV (n=1 906 800; off PrEP incidence: 1.54 per 100 person-years), CAB-LA could achieve an ICER of at most $100 000 per QALY versus generic F/TDF at a maximum price premium of $1100 per year over generic F/TDF (CAB-LA price <$1500 per year). This cost-effectiveness analysis found that the long-acting injectable form of cabotegravir (CAB-LA) is too costly at its current price versus generic daily oral emtricitabine-tenofovir disoproxil fumarate (F/TDF) for HIV pre-exposure prophylaxis (PrEP).
Jamieson et al. 2022 [108]	Authors provided the results from a modelled economic evaluation and threshold analysis, to evaluate the effect of tenofovir disoproxil fumarate and emtricitabine and long-acting injectable cabotegravir provision to *heterosexual adolescents and young women and men aged 15-24 years*, *female sex workers*, and *men who have sex with men* in South Africa. They estimated the average intervention cost, in 2021 US$, using ingredients-based costing, and modelled the cost-effectiveness of two coverage scenarios (medium or high, assuming higher uptake of long-acting injectable cabotegravir than tenofovir disoproxil fumarate and emtricitabine throughout) and, for long-acting injectable cabotegravir, two duration sub scenarios (minimum: same pre-exposure prophylaxis duration as for tenofovir disoproxil fumarate and emtricitabine; maximum: longer duration than tenofovir disoproxil fumarate and emtricitabine) over 2022-41. Authors showed that across long-acting injectable cabotegravir scenarios, 15-28% more new HIV infections were averted compared with the baseline scenario (current tenofovir disoproxil fumarate and emtricitabine roll-out). In scenarios with increased coverage with oral tenofovir disoproxil fumarate and emtricitabine, 4-8% more new HIV infections were averted compared with the baseline scenario. If long-acting injectable cabotegravir drug costs were equal to those of tenofovir disoproxil fumarate and emtricitabine for the same 2-month period, the incremental cost of long acting injectable cabotegravir to the HIV programme was higher than that of tenofovir disoproxil fumarate and emtricitabine (5-10% vs 2-4%) due to higher assumed uptake of long-acting injectable cabotegravir. The cost per infection averted was $6053-6610 (tenofovir disoproxil fumarate and emtricitabine) and $4471-6785 (long-acting injectable cabotegravir). The cost per long-acting cabotegravir injection needed to be less than twice that of a 2-month supply of tenofovir disoproxil fumarate and emtricitabine to remain as cost-effective, with threshold prices ranging between $9.03 per injection (high coverage; maximum duration) and $14.47 per injection (medium coverage; minimum duration). Authors concluded that for long-acting injectable cabotegravir implementation to be financially feasible across low-income and middle-income countries with high HIV incidence, it must be reasonably priced.

Search strategies

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to November 29, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to November 29, 2022>	
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ID	Search
#1	exp HIV/ (119796)
#2	HIV.ti,ab. (424067)
#3	exp HIV Infections/ (356290)
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#5	aids virus*.mp. (1189)
#6	(human adj5 virus* type iii).mp. (474)
#7	htlv-iii.mp. (1672)
#8	htlv 3.mp. (67)
#9	lymphadenopathy associated virus*.mp. (299)
#10	txid12721.mp. (0)
#11	txid 12721.mp. (0)
#12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (532692)
#13	exp Pre-Exposure Prophylaxis/ (7579)
#14	pre-exposure prophylax*.mp. (10574)
#15	preexposure prophylax*.mp. (1868)
#16	PrEP.ti,ab. (11482)
#17	anti-retroviral chemoprophylax*.mp. (0)
#18	antiretroviral chemoprophylax*.mp. (29)
#19	antiretroviral chemo-prophylax*.mp. (0)
#20	anti-retroviral chemo-prophylax*.mp. (0)
#21	exp Chemoprevention/ (26810)
#22	chemoprevention.mp. (20285)
#23	chemo-prevention.mp. (130)
#24	HIV prophylax*.mp. (337)
#25	exp Tenofovir/ (7066)
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#27	disoproxil.mp. (4712)
#28	viread.mp. (82)
#28	"9-(2-phosphonylmethoxypropyl)adenine".mp. (34)
#30	9-pmpa.mp. (0)
#31	99yxe507il.mp. (0)
#32	f4yu4lon7i.mp. (0)
#33	ott9j7900i.mp. (0)
#34	PMPA.ti,ab. (414)
#35	TDF.ti,ab. (6204)
#36	exp Emtricitabine/ (2597)
#37	emtricitabine.mp. (4909)
#38	emtriva.mp. (23)
#39	coviracil.mp. (10)
#40	beta l 2′,3′ dideoxy 5 fluoro 3′ thiacytidine.mp. (8)
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#42	truvada*.mp. (332)
#43	TAF.ti,ab. (2513)
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#45	Cabotegravir.mp. (550)
#46	CAB.ti,ab. (4820)
#47	Apretude*.mp. (6)
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#49	12 and 48 (19940)
#50	limit 49 to randomized controlled trial (1481)
#51	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) (1753822)
#52	49 and 51 (3084)
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#60	limit 59 to (english or german) (1226)
#61	remove duplicates from 60 (626)
Total hits: 626	

Search strategy for Embase

Search Name: PreP to prevent HIV infection		
Search date: 01.12.2022		
No.	Query Results	Results
#73	#71 NOT #72	691
#72	#71 AND 'Conference Abstract'/it	320
#71	(#63 OR #65 OR #66 OR #68) AND [2020-2022]/py AND ([english]/lim OR [german]/lim)	1,011
#70	(#63 OR #65 OR #66 OR #68) AND [2020-2022]/py	1,014
#69	#63 OR #65 OR #66 OR #68	3,980
#68	#62 AND #67	1,048
#67	('meta analysis (topic)'/exp OR 'meta analysis'/exp OR ((meta NEXT/1 analy*):ab,ti) OR metaanaly*:ab,ti OR 'systematic review (topic)'/exp OR 'systematic review'/exp OR ((systematic NEXT/1 review*):ab,ti) OR ((systematic NEXT/1 overview*):ab,ti) OR cancerlit:ab,ti OR cochrane:ab,ti OR embase:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR cinahl:ab,ti OR cinhal:ab,ti OR 'science citation index':ab,ti OR bids:ab,ti OR ((reference NEXT/1 list*):ab,ti) OR bibliograph*:ab,ti OR 'hand search*':ab,ti OR ((manual NEXT/1 search*):ab,ti) OR 'relevant journals':ab,ti OR (('data extraction':ab,ti OR 'selection criteria':ab,ti) AND review/it)) NOT (letter/it OR editorial/it OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))	716,184
#66	#62 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	764
#65	#62 AND #64	1,373
#64	((double NEXT/1 blind*):de,ab,ti) OR placebo*:ab,ti OR blind*:ab,ti	702,235
#63	#12 AND #61 AND [randomized controlled trial]/lim	2,366
#62	#12 AND #61	35,906

#61	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60	96,863
#60	apretude*	5
#59	cab:ti,ab	4,798
#58	cabotegravir*	846
#57	'cabotegravir'/exp	749
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#55	taf:ti,ab	3,329
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#45	racivir	29
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#43	emtriva	498
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#41	'emtricitabine'/exp	10,129
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#39	ott9j7900i	
#38	f4yu4lon7i	
#37	99yxe507il	
#36	'9 pmpa'	1
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#34	gs1275	
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#32	'9 [2 (phosphonomethoxy) propyl] adenine'	28
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#30	'9 (2 phosphonomethoxypropyl) adenine'	13
#29	viread	1,029
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#23	'chemo prevention'	176
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#8	'htlv 3'	88
#7	'htlv-iii'	1,889
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#1	'human immunodeficiency virus'/exp	214,979

Search strategy for Cochrane

Search Name: PreP to prevent HIV infection	
Search date: 02.12.2022 17:18:31	
Comment: MH/IR 021222	
ID	Search
#1	MeSH descriptor: [HIV] explode all trees
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#24	("HIV prophylaxis") (Word variations have been searched)
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#28	(viread) (Word variations have been searched)
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#30	("9-pmpa") (Word variations have been searched)
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#54	#51 OR #52 OR #53
#55	#50 NOT #54
Total hits: 420	

Search strategy to identify HTA reports (INAHTA)

Search Name: PreP to prevent HIV infection	
Search date: 04.12.2021	
ID	Search query,"Hits","Searched At"
7	(((PrEP) OR (preexposure prophylax*) OR (pre-exposure prophylax*) OR ("Pre-Exposure Prophylaxis"[mhe])) FROM 2020 TO 2022) AND (English OR German)[Language],"1","2022-12-04T22:49:17.000000Z"
6	((PrEP) OR (preexposure prophylax*) OR (pre-exposure prophylax*) OR ("Pre-Exposure Prophylaxis"[mhe])) FROM 2020 TO 2022,"1","2022-12-04T22:43:10.000000Z"
5	(PrEP) OR (preexposure prophylax*) OR (pre-exposure prophylax*) OR ("Pre-Exposure Prophylaxis"[mhe]),"5","2022-12-04T22:41:51.000000Z"
4	PrEP,"3","2022-12-04T22:41:25.000000Z"
3	preexposure prophylax*,"0","2022-12-04T22:41:10.000000Z"
2	pre-exposure prophylax*,"2","2022-12-04T22:40:27.000000Z"
1	"Pre-Exposure Prophylaxis"[mhe],"3","2022-12-04T22:38:52.000000Z"
Total hits: 1	

Search strategy to identify ongoing RCTs

„Pre-exposure prophylaxis to prevent HIV“ Trial register search (Date of search: 30.01.2023)

Search strategies:

ClinicalTrials.gov (Expert Search Mode)

pre-exposure prophylaxis AND AREA[OverallStatus] EXPAND[Term] COVER[FullMatch] ("Recruiting" OR "Not yet recruiting" OR "Active, not recruiting" OR "Enrolling by invitation") AND AREA[ConditionSearch] HIV Infections AND AREA[Phase] EXPAND[Term] COVER[FullMatch] ("Phase 3" OR "Phase 4")

31 Studies identified

WHO ICTRP (Advanced Search Mode)

HIV OR "HIV Infections" *in the Condition*

AND

"pre-exposure prophylaxis" OR PreP *in the Intervention*

Phases are Phase 3, Phase 4

27 (20 further) studies identified

EudraCT (Advanced Search Mode)

(HIV OR "HIV Infections" OR "human immunodeficiency virus") AND ("pre-exposure prophylaxis" OR PreP)

Selected Trial Phase: Phase Three, Phase Four

30 (26 further) studies identified

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