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DISSERTATION

Entwicklung von Methoden zur Vervollständigung der Behandlungskaskade für HIV und Hepatitis C unter Verwendung von Sekundärdaten und Daten aus Langzeitkohorten

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Inhalt

Abkürzungsverzeichnis

AIDS	Akquiriertes Immun-Defizienz-Syndrom
ART	Antiretrovirale Therapie
ATC	Anatomisch-therapeutisch-chemisches Klassifikationssystems
BOC	Boceprevir
CDC	Zentren für die Kontrolle und Prävention von Krankheiten
DAA	Direkt wirkende antivirale Medikamente
DCV	Daclatasvir
DSV	Dasabuvir
ECDC	Europäisches Zentrum für die Prävention und die Kontrolle von Krankheiten
GKV	Gesetzliche Krankenversicherung
HCV	Hepatitis C Virus
HIV	Humane Immundefizienz-Virus
IfSG	Infektionsschutzgesetz
LDV	Ledipasvir
OBV	Ombitasvir
OST	Opiatsubstitutionstherapie
PegIFN	Pegyliertes Interferon α2a und α2b
PTVr	Ritonavir-geboostertes Paritaprevir
PZN	Pharmazentralnummer
RBV	Ribavirin
RKI	Robert Koch-Institut
SGB	Sozialgesetzbuch
SMV	Simeprevir
SOF	Sofosbuvir
TB	Tuberkulose
TVR	Telaprevir
UNAIDS	Gemeinsames Programm der Vereinten Nationen für HIV/AIDS (UNAIDS)
VL	Viruslast
WHO	Weltgesundheitsorganisation

1 Zusammenfassung der Publikationspromotion

1.1 Abstrakt auf Deutsch

Hintergrund

Sowohl für HIV als auch für das Hepatitis C Virus (HCV) existieren Zielvorgaben zum Anteil Diagnostizierter, Behandelter und erfolgreich Behandelter. Diese Anteile lassen sich stufenweise in einer Behandlungskaskade abbilden, die den jeweiligen Anteil zur vorherigen Stufe darstellt. Zur Beurteilung des Erreichens der Zielvorgaben ist also die Bestimmung der Anzahl und des Anteils an Personen in der jeweiligen Stufe und die Erstellung einer Behandlungskaskade wichtig. In Deutschland konnten allerdings bisher noch nicht alle Ziele und Stufen der Behandlungskaskade bestimmt werden. Ziel der Arbeit war die Entwicklung von Methoden zur Vervollständigung der Behandlungskaskade für HIV und HCV und die Bestimmung der Anzahl an Personen und des Anteils in den entsprechenden Säulen.

Methoden

In der vorliegenden Promotionsarbeit wurden Sekundärdaten in Form von Apothekenabrechnungsdaten und Daten aus HIV-Langzeitkohorten genutzt. In einer Vorarbeit wurde eine Methode zur Bestimmung der Anzahl an Personen unter HIV-Therapie mit einem Konzept der Leitsubstanzen für bestimmte Erkrankungen entwickelt. Diese Methode wurde in der vorliegenden Promotionsarbeit weiterentwickelt und an weitere Erkrankungen angepasst. Darüber hinaus wurde ein Modell entwickelt, das anhand von realen Viruslast-Messungen virtuelle Viruslast-Werte und einen individuellen Viruslast-Verlauf generiert. Dieses Modell berücksichtigt zusätzlich den HIV-Therapiestatus und die daraus abgeleitete Viruslast-Dynamik.

Ergebnisse

Es wurden Apothekenabrechnungsdaten zu HCV-Behandlungen zwischen 2010-2015 ausgewertet und die Anzahl an Personen mit HCV-Behandlung und Therapiekosten bestimmt. Die Methoden wurden auf weitere Erkrankungen in einem speziellen Setting angewandt, die Versorgung mit Medikamenten gegen Tuberkulose, HIV, HCV und Opiatsubstitutionstherapien in deutschen Gefängnissen. Schließlich wurde der Therapieerfolg der HIV-Behandlung in Deutschland anhand von Daten aus HIV-Langzeitkohorten untersucht und der Anteil an Personen mit erfolgreicher HIV-Therapie über die Jahre 1999-2018 bestimmt. Die entwickelte Methode für den Therapieerfolg erlaubt zusätzlich die Bestimmung von längeren Zeiten ohne Viruslastkontrolle als Maß für die Anbindung an die klinische HIV-Versorgung.

Diskussion und Schlussfolgerung

Die im Rahmen der vorliegenden Promotionsarbeit entwickelten Methoden zur Bestimmung der Anzahl an Personen unter Therapie mit ausgewählten Medikamenten und Therapiekosten sowie die Methode zur Bestimmung des Therapieerfolgs der HIV-Therapie erlaubten erstmals die Bestimmung wichtiger Stufen in der Behandlungskaskade von HCV und HIV in Deutschland. Die Fragestellungen und Ziele der vorliegenden Promotionsarbeit konnten beantwortet und erfüllt werden. Die entwickelten Methoden zur Anzahl an Therapierten leisteten einen wichtigen Beitrag zur Surveillance von HIV und HCV in Deutschland und werden kontinuierlich in der Surveillance genutzt.

1.2 Abstrakt auf Englisch

Background

For both HIV and hepatitis C virus (HCV), targets exist for the proportion diagnosed, treated, and successfully treated. These proportions can be mapped in stages in a treatment cascade, which represents the respective proportion to the previous stage. To assess whether the targets have been met, it is therefore important to determine the number and proportion of people in each stage and to draw up a treatment cascade. In Germany, however, it has not yet been possible to determine all targets and stages of the treatment cascade. The aim of this work was to develop methods to complete the treatment cascade for HIV and HCV and to determine the number of persons and proportion in the respective columns.

Methods

In this dissertation, secondary data in the form of pharmacy billing data and data from long-term HIV cohorts were used. In a preliminary work a method for determining the number of persons receiving HIV therapy using a lead substance concept for specific conditions was developed. This method was further refined and adapted to additional diseases. Furthermore, a model was developed that uses real viral load (VL) measurements to generate virtual VL values and an individual VL progression. This model additionally considers HIV treatment status and VL dynamics derived from it.

Results

Pharmacy data on HCV treatment between 2010-2015 were analyzed and the number of people with HCV treatment and therapy costs were determined. The methods were applied to additional diseases in a specific setting, the provision of medication for tuberculosis, HIV, HCV, and opioid substitution therapy in German prisons. Finally, the therapeutic success of HIV treatment in Germany was investigated and the proportion of individuals with successful HIV therapy was determined between 1999-2018. The developed method for treatment success additionally allows for the determination of prolonged periods without VL control as a measure of retention to clinical HIV care.

Discussion and Conclusion

The methods developed in this doctoral thesis to determine the number of persons on therapy with selected drugs and therapy costs, as well as the method to determine HIV treatment success, allowed for the first time the determination of important stages in the treatment cascade of HCV and HIV in Germany. The questions and objectives of the dissertation could be answered and fulfilled. The developed methods on the number of persons receiving treatment made an important contribution to the surveillance of HIV and HCV in Germany and are continuously used.

1.3 Einleitung

1.3.1 Hintergrund

Die Überwachung (Surveillance) von Infektionen mit dem Humanen Immundefizienz-Virus (HIV) und Hepatitis C Virus (HCV) in Deutschland beruht im Wesentlichen auf der bundesweiten Meldepflicht für Ärzt*innen und Labore gemäß Infektionsschutzgesetz (IfSG) (1-3). Darüber hinaus existiert in Deutschland kein zentrales Register von Menschen mit HIV oder HCV, aus dem beispielsweise Aussagen zu Behandlung, Krankheits- und Therapieverläufen sowie dem Therapieerfolg ableitbar sind. Die Surveillance über die Meldungen hinaus erfolgt in Form von Studien, darunter Langzeitbeobachtungsstudien (Kohortenstudien), in denen eine kontinuierliche Beobachtung stattfindet (1). Allerdings gibt es bei solchen Studien immer die Gefahr eines Bias beim Einschluss der Personen in die Kohorte oder der Auswahl für die Auswertung.

Hier können weitere Daten, die eine hohe Repräsentativität für die Population besitzen, hilfreich sein. Dies ist häufig bei Sekundärdaten der Fall, da es sich bei diesen oft um eine nahezu oder vollständige Vollerfassung handelt, wie z.B. bei Apothekenabrechnungsdaten von Personen mit gesetzlicher Krankenversicherung (GKV). Allerdings stellen diese anonymen Apothekenabrechnungsdaten nach §300 Sozialgesetzbuch V (SGB V) lediglich die Gesamtzahl der über die GKV abgerechneten Medikamente dar ohne einen Bezug zur Anzahl an Personen, die sie einnehmen oder deren Charakteristika zu erlauben. In einer Vorarbeit wurde eine Methode zur Bestimmung der Anzahl an Personen unter HIV-Therapie entwickelt. Hierbei wurde ein Konzept der Leitsubstanzen für bestimmte Erkrankungen erarbeitet, welches erlaubt aus der Anzahl abgerechneter Medikamente auf die Anzahl an Personen umzurechnen (4).

Im Jahr 2014 wurden in Deutschland direkt wirkende antivirale Medikamente zugelassen, die Heilungsraten von über 90% nahezu nebenwirkungsfrei bei gleichzeitig deutlich verkürzter Behandlungsdauer zeigten und das Potential zu einer deutlichen Reduktion bis hin zur Elimination der HCV in Deutschland hatten. Allerdings blieb zunächst unklar, wie viele Personen damit behandelt und geheilt wurden und zu welchen Kosten für die GKV.

Im April 2016 hat die Bundesregierung die Strategie zur Eindämmung von HIV, Hepatitis B und C sowie anderer sexuell übertragbarer Infektionen ("BIS 2030 – Bedarfsorientiert, Integriert, Sektorübergreifend") beschlossen (5). Diese ist in Übereinstimmung mit der Global Health Sector Strategy on Viral Hepatitis der Weltgesundheitsorganisation (WHO), die neben der Eindämmung von HIV die Eliminierung von Hepatitis B und C bis 2030 fordert (6). Die Ziele für Hepatitis umfassen unter

anderem 90% der Infizierten zu diagnostizieren, 80% von diesen zu therapieren, und die Sterblichkeitsrate um 65% zu senken.

Die 90-90-90 Ziele des Programms der Vereinten Nationen für HIV/AIDS (UNAIDS) aus dem Jahr 2014 zur Beschleunigung des Kampfes gegen HIV und zur Beendigung der AIDS-Epidemie beinhalten, dass bis zum Jahr 2020 90% der Menschen, die mit HIV leben ihre Diagnose kennen, von diesen 90% eine antiretrovirale Therapie (ART) erhalten und wiederum von diesen 90% eine erfolgreiche ART erhalten, welche die Viruslast unterdrückt. Bis zum Jahr 2030 sollen diese Anteile auf 95% erhöht werden (7-9). Durch den jeweiligen Anteil von 90% bzw. 95% zur vorherigen Gruppe ergibt sich insgesamt von der ersten zur letzten Stufe dieser sog. Behandlungskaskade ein Anteil von 73% bzw. 86% erfolgreich Therapierter an allen Menschen mit HIV.

Zur Beurteilung des Erreichens dieser Zielvorgaben ist also die Bestimmung der Anzahl und des Anteils an Personen in der jeweiligen Stufe und die Erstellung einer Behandlungskaskade wichtig. In Deutschland konnten allerdings bisher noch nicht alle Ziele und Stufen der Behandlungskaskade bestimmt werden.

1.3.2 Ziel und Fragestellung

Ziel der vorliegenden Promotionsarbeit war die Entwicklung von Methoden zur Vervollständigung der Behandlungskaskade für HIV und HCV. Es sollte eine Methode zur Bestimmung der Anzahl an Personen unter Therapie gegen HCV sowie den Therapiekosten unter Nutzung von Sekundärdaten entwickelt werden. Nach Einführung der hocheffektiven direkt wirkenden antiviralen Medikamente (engl. direct-acting antivirals, DAA) war die Hypothese, dass sich die Behandlungszahlen erhöhen. Als wichtige Vorarbeit galt hierbei die Entwicklung einer Methode zur Bestimmung der Anzahl an Personen unter HIV-Therapie unter Nutzung von Sekundärdaten und Daten aus HIV-Langzeitkohorten (4). Die Anzahl der behandelten Personen stellt in der klassischen aus drei Säulen bestehenden Behandlungskaskade die zweite Säule dar.
Die entwickelten Methoden und Expertisen sollten auf weitere Fragestellungen und Erkrankungen in einem speziellen Setting angewandt werden, die Versorgung mit Medikamenten gegen Tuberkulose (TB), HIV, HCV und Opiatsubstitutionstherapien (OST) in deutschen Gefängnissen.
Weiteres Ziel war die Entwicklung einer Methode zur Bestimmung des Therapieerfolgs der HIV-Therapie zur Vervollständigung der HIV-Behandlungskaskade (dritte Säule der HIV-Behandlungskaskade).

1.4 Methodik und Datenquellen

1.4.1 Methode zur Bestimmung der Anzahl an Personen unter Therapie gegen Hepatitis C unter Nutzung von Sekundärdaten

Apothekenabrechnungsdaten von gesetzlichen Krankenversicherungen

Die in der vorliegenden Promotionsarbeit genutzten Sekundärdatenquellen waren Verordnungsdaten aus Apothekenabrechnungszentren sowie Daten aus Apotheken, die Gefängnisse mit Medikamenten belieferten.

Bei den Apothekenabrechnungsdaten handelte es sich um in Apotheken eingelöste Rezepte gegen die Infektionskrankheiten HIV und HCV von Personen mit gesetzlicher Krankenversicherung (GKV). Der Anbieter (Firma Insight Health™) gibt für den Untersuchungszeitraum eine Abdeckung von >99% innerhalb des GKV-Verschreibungsmarktes an. Die GKV repräsentiert ~87% der deutschen Bevölkerung. Diese Datenquelle hat damit eine hohe Repräsentativität mit einem geringen zu erwartenden Bias. Allerdings stellen die Apothekenabrechnungsdaten lediglich die kumulative Gesamtzahl der über die GKV abgerechneten Medikamente auf Ebene der Pharmazentralnummer (PZN) dar, ohne einen Bezug zur Anzahl an Personen oder deren Eigenschaften zuzulassen. Zur Berechnung der Anzahl an Personen unter Therapie gegen eine bestimmte Erkrankung benötigt es weitere Überlegungen und Methoden. Hier war die Vorarbeit mit der Methode zur Bestimmung der Anzahl an Personen unter HIV-Therapie und dem Konzept der Leitsubstanzen für bestimmte Erkrankungen wichtig und ausschlaggebend (4).

Für die Bestimmung der Anzahl an Personen unter HCV-Therapie wurden Standard-28-Tagespackungen verschiedener HCV-Medikamente nach den Therapieleitlinien zu Behandlungsregimen kombiniert und die Anzahl der monatlich abgerechneten Regime berechnet. Der Begriff Monatsregime wurde definiert als die Summe der monatlichen Verordnungen des jeweiligen Regimes.

Der Beobachtungszeitraum wurde in drei Zeiträume unterteilt, die sich an den Änderungen und Paradigmenwechseln aufgrund von Neuzulassungen und Empfehlungen bei der antiviralen HCV-Behandlung in Deutschland orientierten. Zu den ausgewerteten Regimen gehörten Therapien mit PEGyliertem Interferon α (PegIFN) 2a and 2b und Ribavirin (RBV), Therapien mit den DAA der 1. Generation Boceprevir (BOC) und Telaprevir (TVR) und Therapien mit DAA der 2. Generation.

Anhand der Therapiedauer einzelner Regime wurde die Anzahl der mit DAA behandelten Personen in der GKV bestimmt. Die Daten zur Behandlungsdauer stammten aus einer großen prospektiven klinischen Kohorte von HCV- und HIV/HCV-infizierten Personen, der GECCO-Kohorte (10, 11). Zusätzlich wurden die Kosten anhand von Apothekenabgabepreisen pro Jahr und die mittleren Therapiekosten pro Person und Behandlung bestimmt.

1.4.2 Bestimmung der Anzahl an Personen unter Therapie mit ausgewählten Medikamenten in Gefängnissen unter Nutzung von Sekundärdaten

Apothekendaten von Medikamenten für deutsche Haftanstalten

Bei den Daten aus Apotheken, die Gefängnisse mit Medikamenten belieferten handelte es sich um Medikamente gegen die Infektionskrankheiten TB, HIV, HCV sowie OST von inhaftierten Personen. Hierzu wurden die Ministerien für Justiz der 16 deutschen Bundesländern, um Zustimmung zur Auswertung gefragt.

Die Auswahl der Medikation und Zuordnung zu den relevanten Infektionskrankheiten erfolgte auf Basis des Anatomisch-therapeutisch-chemische Klassifikationssystems (ATC) nach dem in der Vorarbeit zu HIV entwickelten Konzept der Leitmedikation. Als Leitmedikation wurden Substanzen bzw. Regime definiert, die für die Behandlung der jeweiligen Erkrankung typisch und idealerweise einzigartig sind. Die ausgewählten Leitsubstanzen für die verschiedenen Erkrankungen und OST sind in Tabelle X zusammengefasst. Zur Berechnung der Anzahl an täglich behandelten Personen wurden definierte Tagesdosen (engl. defined daily doses DDD) der Leitsubstanzen verwendet. Für jede Leitsubstanz wurde die kumulative Anzahl von DDD, die durchschnittliche tägliche Anzahl von DDD (DDDd) und die durchschnittliche Behandlungsprävalenz pro Tag in Prozent (adTP) bewertet. Dementsprechend repräsentiert die DDD eine Person, die pro Tag behandelt wird, und die adTP bedeutet den Anteil der pro Tag behandelten Gefangenen. Die Behandlungsprävalenz der Erkrankungen und OST wurde zur Diskussion und Bewertung mit zuvor gemessenen Prävalenzen aus anderen Studien verglichen (12).

1.4.3 Methode zur Bestimmung des Therapieerfolgs der HIV-Therapie anhand von Daten aus Langzeitkohorten zur Vervollständigung der HIV-Behandlungskaskade

1.4.3.1 Modell zur Bestimmung der Virämie und der viralen Suppression (Therapieerfolg) anhand longitudinaler Daten aus Langzeitkohorten

In der vorliegenden Studie wurde ein Modell entwickelt, das anhand von realen Messungen der Viruslast (VL) mit einer maximalen Entfernung von 180 Tagen zueinander virtuelle VL-Werte und einen individuellen VL-Verlauf generiert. Zusätzlich wurde in dem Modell der ART-Status und die daraus abgeleitete VL-Dynamik berücksichtigt. War der Abstand zwischen den realen VL-Messungen >180 Tage, wurde die dazwischen liegende Zeit als sogenannte Lückenzeit (engl. gap time) definiert. Darüber hinaus wurden Blips berücksichtigt, die als eine einzelne nachweisbare VL <1.000 Kopien/ml innerhalb von 180 Tagen definiert wurden.

Die VL-Werte wurden in folgende Gruppen unterteilt: VL <50; 50- <200; 200- <500; 500- <1.000; 1.000- < 10.000; 10.000- <100.000; 100.000- <1.000.000 und ≥1.000.000 Kopien/ml.

Der Therapieerfolg (virale Suppression) wurde gemäß den Deutsch-Österreichischen Leitlinien zur ART als VL <50 Kopien/ml definiert (13). Bei der Bewertung des UNAIDS-Ziels der viralen Suppression für Menschen mit HIV wurde zur Vergleichbarkeit mit anderen Ländern und Studien zusätzlich der Anteil der Personenzeit mit VL <200 Kopien/ml angegeben. Der VL-Wert von <200 Kopien/ml für die Beurteilung und Überwachung der Virämie auf Bevölkerungsebene ist im Einklang mit den Richtlinien und Empfehlungen mehrerer Institutionen, wie den US-amerikanischen Zentren für die Kontrolle und Prävention von Krankheiten (CDC) und dem Europäischen Zentrum für die Prävention und die Kontrolle von Krankheiten (ECDC) (14, 15).

Gemäß der konventionellen Definition zur Bestimmung des Therapieerfolgs der HIV-Therapie in der HIV-Behandlungskaskade wird die virale Suppression anhand nur einer - und zwar der letzten - VL eines Jahres von Personen in medizinischer Versorgung bestimmt. Das entwickelte Modell wurde mit der konventionellen Methode in Bezug auf die Ergebnisse zur viralen Suppression verglichen. Des Weiteren wurden Sensitivitätsanalysen durchgeführt, um eine mögliche Fehlklassifizierung mit der konventionellen Methode weiter zu untersuchen. So wurde die Anzahl und der Anteil von Menschen mit HIV mit kontinuierlicher Virussuppression über einen einjährigen Beobachtungszeitraum auf individueller Ebene bestimmt und mit den Ergebnissen der konventionellen Methode unter Verwendung der letzten VL eines Jahres verglichen.

Wie zuvor beschrieben wurde bei einem Abstand zwischen den realen VL-Messungen von >180 Tagen die dazwischen liegende Zeit als sogenannte Lückenzeit definiert und gezählt. Damit erlaubte das entwickelte Modell neben der Bestimmung der viralen Suppression die Bestimmung und Analyse von Personen mit längeren Zeiträumen ohne VL-Kontrolle (Lückenzeit) als Maß für die Anbindung an die klinische HIV-Versorgung. Separate Sensitivitätsanalysen in der Gruppe der Personen mit Lückenzeit wurden durchgeführt, um den VL-Status in dieser Zeit und den Einfluss auf das Modell zu bewerten. Dafür wurde bei Personen mit Lückenzeit die letzte VL-Messung vor und die erste VL-Messung nach der Lückenzeit analysiert, um den VL-Status der Personen während der Lückenzeit einzuschätzen.

Untersucht wurden Daten aus den zwei großen multizentrischen deutschen Kohortenstudien (HIV-1 Serokonverter und ClinSurv HIV) des Robert Koch-Instituts (RKI). Eingeschlossen wurden Daten zwischen 1999 und 2018 von Personen mit mindestens 2 VL-Messungen.

1.4.3.2 HIV-1 Serokonverter-Kohorte

Die HIV-1 Serokonverter-Kohorte ist eine landesweite, multizentrische, offene Langzeitbeobachtungskohorte von HIV-1-positiven Personen, deren HIV-Infektionsdatum aufgrund labordiagnostischer Parameter bekannt ist. Im Rahmen der HIV-1 Serokonverterkohorte wird zu jeder Person einmal jährlich ein Fragebogen sowie eine Blutprobe an das RKI versandt. Der Fragebogen

enthält soziodemografische und klinische Daten zum Verlauf der HIV-Infektion. Detailliertere Beschreibungen der Studie und Methoden finden sich an anderer Stelle (16-18). Im Untersuchungszeitraum beteiligten sich deutschlandweit 60 Studieneinrichtungen von niedergelassenen Ärzt*innen und Kliniken an der Studie mit kumulativ ~3.500 Personen. Das Studienkollektiv besteht zum Großteil aus Männern, die Sex mit Männern haben (MSM), die in städtischen Gebieten leben.

1.4.3.3 ClinSurv HIV-Kohorte

Die ClinSurv HIV Kohorte ist eine landesweite, prospektive, multizentrische, offene Langzeitbeobachtungskohorte HIV-positiver Menschen, die seit 1999 am RKI durchgeführt wird. Daten zur Demografie, detaillierte Informationen zur Einleitung, Zusammensetzung und zum Abbruch der täglichen ART sowie Laborparameter und klinische Ereignisse werden halbjährlich in einem standardisierten Format gesammelt. ClinSurv HIV ist die deutschlandweit größte Studie von Menschen mit HIV. Das Studiendesign ist an anderer Stelle ausführlicher beschrieben (19). Im Untersuchungszeitraum befanden sich in dieser Kohorte kumulativ ~25.000 HIV-positive Patient*innen aus 13 Studieneinrichtungen von hauptsächlich HIV-Kliniken sowie niedergelassenen Ärzt*innen deutschlandweit.

1.5 Ergebnisse

1.5.1 Methode zur Bestimmung der Anzahl an Personen unter Therapie gegen Hepatitis C mit DAA unter Nutzung von Sekundärdaten

Real-world treatment for chronic hepatitis C infection in Germany: Analyses from drug prescription data, 2010-2015

Von Januar 2010 bis August 2011 war das empfohlene und einzig verfügbare HCV-Behandlungsschema eine Kombination aus PegIFN/RBV. Am Anfang dieses Zeitraums wurden etwa 6500 Regime pro Monat verordnet, die im August 2011 auf 4700 zurückgingen. Während dieses Zeitraums wurden insgesamt 188.900 PegIFN/RBV Monatsregime verschrieben, was einem Durchschnitt von 5900 Monatsregimen entspricht. Von Januar 2010 bis Dezember 2015 sanken die monatlichen Behandlungen mit PegIFN/RBV von ~6500 auf ~650 (siehe Abbildung 1 (20)).

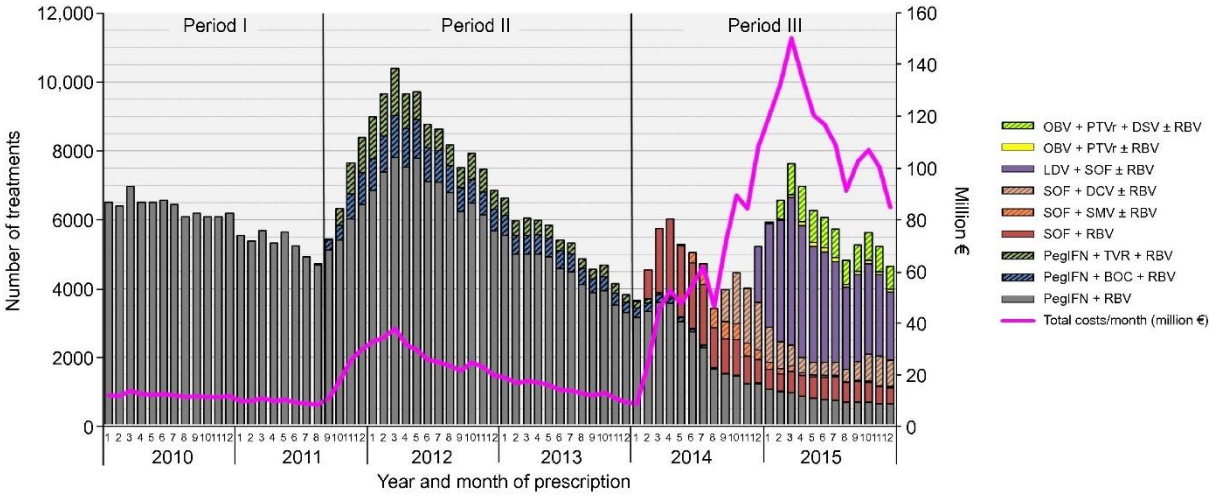

Abbildung 1. Monatliche Verschreibungen von HCV-Regimen (Monatsregimen) und monatliche Gesamtkosten für HCV-Medikamente (01/2010 - 12/2015). Diese Abbildung wurde bereits 2017 im Paper "Real-world treatment for chronic hepatitis C infection in Germany: Analyses from drug prescription data, 2010-2015" von Zimmermann R, Kollan C et al. im Journal of Hepatology veröffentlicht (20). Die Genehmigung zur Verwendung der Abbildung liegt vor.

Pegyliertes Interferon α2a und α2b, PegIFN; Ribavirin, RBV; Boceprevir, BOC; Telaprevir, TVR; Sofosbuvir, SOF; Simeprevir, SMV; Daclatasvir, DCV, Ledipasvir, LDV; Ombitasvir, OBV; Ritonavir-geboostertes Paritaprevir, PTVr; Dasabuvir, DSV.

Mit der Zulassung der DAAs der 1. Genration BOC und TLV in 2011 stiegen die monatlichen HCV-Verschreibungen auf ein Maximum von ~7800 Monatsregimen im März 2012 und gingen danach stetig zurück auf ein Minimum von ~3300 Monatsregimen Ende 2013. Mit der Zulassung der DAAs der 2. Generation in 2014 stiegen die Verordnungen/Monat wieder an. Zunächst erreichten sie im April 2014 einen Höchststand von ~5800 verordneten Monatsregimen, hauptsächlich ausgelöst durch zusätzliche SOF-haltige Regime. Nach der Zulassung weiterer Substanzen gab es ein Maximum von ∼6600 Monatsregimen im März 2015. Anschließend ging die Zahl zurück auf ∼4000 Monatsregime im Dezember 2015.

Insgesamt wurden 25.500 Monatsregime DAA-basierter Verordnungen im Jahr 2014 und 60.900 Monatsregime im Jahr 2015 in den Apothekenabrechnungsdaten erfasst. Nach Berücksichtigung der aus der GECCO-Kohorte abgeleiteten mittleren Behandlungsdauer pro Regime wurden insgesamt 7000 Personen in 2014 und 20.100 Personen in 2015 mit DAA behandelt.

Die Behandlungskosten/Monat lagen stabil bei 12 Mio. EUR zwischen 2010-2011 und stiegen auf ∼38 Mio. EUR im März 2012 im Zusammenhang mit dem Anstieg der PI-basierten Regime in Periode II. Mit dem Rückgang der Monatsregime in Periode II sanken auch die Gesamtkosten auf unter 9 Mio. EUR/Monat bis Ende 2013. Mit der Einführung neuer DAAs in Periode III wurde ein starker Anstieg der monatlichen Gesamtkosten beobachtet, mit einem ersten Höhepunkt im August 2014 mit 62 Mio. EUR/Monat. Danach stiegen die Ausgaben von September 2014 bis März 2015 weiter an, mit einem Maximum von mehr als 150 Mio. EUR/Monat im März 2015. Nach diesem Höchststand sanken die monatlichen Gesamtkosten mit dem Rückgang der monatlichen Verordnungen auf 85 Mio. EUR im Dezember 2015.

Die DAA-Medikamentenkosten/Jahr summierten sich auf ∼664 Mio. EUR in 2014 und ∼1,3 Mrd. EUR in 2015. Der mittlere Preis pro HCV-Behandlung unterschied sich deutlich zwischen den Regimen. Nach Berücksichtigung der Behandlungsdauer pro Regime ergaben sich die höchsten Kosten für SOF/DCV mit 157.365 € pro Behandlung im Jahr 2014 und 105.818 € im Jahr 2015. Der mittlere Preis eines SOF/LDV-Regime sank leicht von 61.713 € im Jahr 2014 auf 60.698 € im Jahr 2015. Im Jahr 2015 lag der mittlere Preis von OBV/PTVr/DSV ± RBV bei 55.131 € und OBV/PTVr ± RBV bei 58.245 € (20). Die detaillierten Ergebnisse sind dargestellt in der Publikation "Real-world treatment for chronic hepatitis C infection in Germany: Analyses from drug prescription data, 2010–2015". Zimmermann R, Kollan C, Ingiliz P, Mauss S, Schmidt D, Bremer V. Journal of Hepatology, Volume 67, Issue 1, July 2017, Pages 15-22 (20).

1.5.2 Bestimmung der Anzahl an Personen unter Therapie mit ausgewählten Medikamenten in Gefängnissen unter Nutzung von Sekundärdaten

High variability of TB, HIV, hepatitis C treatment and opioid substitution therapy among prisoners in Germany

Es wurden Daten von Apotheken bereitgestellt, die Gefängnisse in 11 von 16 deutschen Bundesländern belieferten. Während des Untersuchungszeitraums wurden alle teilnehmenden Gefängnisse und Gefängniskrankenhäuser von drei Apotheken mit TB-, HIV-, HCV- und OST-Medikamenten versorgt. Von den eingeschlossenen Gefängnissen erhielten 41% Medikamente gegen TB, 71% Medikamente gegen HIV sowie 58% Medikamente gegen HCV und OST. Die durchschnittliche tägliche Behandlungsprävalenz (adTP) lag für HIV im Bereich von 0,06% bis 0,94%, für HCV im Bereich von 0,03% bis 0,59% und für OST im Bereich von 0% bis 7,90%. Die Gesamt-adTP für die jeweilige Behandlung betrug 0,39% für HIV, 0,12% für HCV und 2,18% für OST. Bei der TB wurden insgesamt doppelt so viele Leitsubstanzen für die Kontinuitätsphase und die Chemoprävention abgegeben wie für die Initiierungsphase (Isoniazid (H) und Rifampicin (R): 0,09% & 0,07% gegenüber Ethambutol (E) und Pyrazinamid (Z): 0,04% & 0,03%) (12). Die detaillierten Ergebnisse sind dargestellt in der Publikation "High variability of TB, HIV, hepatitis C treatment and opioid substitution therapy among prisoners in Germany". Müller J, Schmidt D, Kollan C, Lehmann M, Bremer V, Zimmermann R. BMC Public Health 17, 843 (2017) (12).

1.5.3 Methode zur Bestimmung des Therapieerfolgs der HIV-Therapie anhand von Daten aus Langzeitkohorten zur Vervollständigung der HIV-Behandlungskaskade

Everything counts - a method to determine viral suppression among people living with HIV using longitudinal data for the HIV care continuum - results of two large, German, multi-center real-life cohort studies over 20 years (1999–2018)

Insgesamt wurden 22.120 Personen in die Analyse der viralen Suppression nach ART-Beginn eingeschlossen. Die mediane Beobachtungszeit unter ART war 5,5 Jahre (Interquartilsabstand, IQR 2,3-9,9). Insgesamt ergaben sich 164.691 Personenjahre (PY) Beobachtungszeit. Mit 88,9% war die Mehrheit der Personen in der ClinSurv-HIV Kohorte eingeschlossen, 8,7% in der HIV-1 Serokonverter-Kohorte, und 2,4% waren in beiden Kohortenstudien. Die Gesamtzahl der realen VL-Messungen betrug 490.352, die mediane Anzahl der VL-Messungen pro Person betrug 17 (IQR 8-32) und die VL-Überwachung erfolgte im Median alle 91 Tage (IQR 70-112). Mit dem Modell wurden 3.974.309 virtuelle VL-Werte generiert. Die realen VL-Messungen und die virtuellen VL-Werte traten in 52.205 Fällen zum gleichen Zeitpunkt auf.

Auf individueller Ebene zeigten insgesamt 94% der Personen (20.849/22.120) jemals eine virale Suppression (VL <50 Kopien/ml) nach ART-Beginn, und 6% (1271/22.120) zeigten nie eine virale Suppression. Bei 86% (19.076/22.120) der Personen wurde zu irgendeinem Zeitpunkt eine Virämie gemessen, und 77% (17.085/22.120) zeigten mindestens einmal eine Virämie mit VL >1000 Kopien/ml.

Entwicklung des Therapieerfolgs von 1999-2018 bei Menschen mit HIV nach ART-Beginn

Basierend auf dem entwickelten Modell stieg der Anteil der Personenzeit mit viraler Suppression über die Beobachtungszeit von 33,6% im Jahr 1999 auf 93,0% im Jahr 2018. Der Anteil der Personenzeit mit VL <200 Kopien/ml stieg von 47,0% im Jahr 1999 auf 96,3% im Jahr 2018. Der Anteil der Personenzeit mit einer Virämie >1.000 Kopien/ml verringerte sich von 37,3% im Jahr 1999 auf 2,6% im Jahr 2018 (Abbildung 2 (21)).

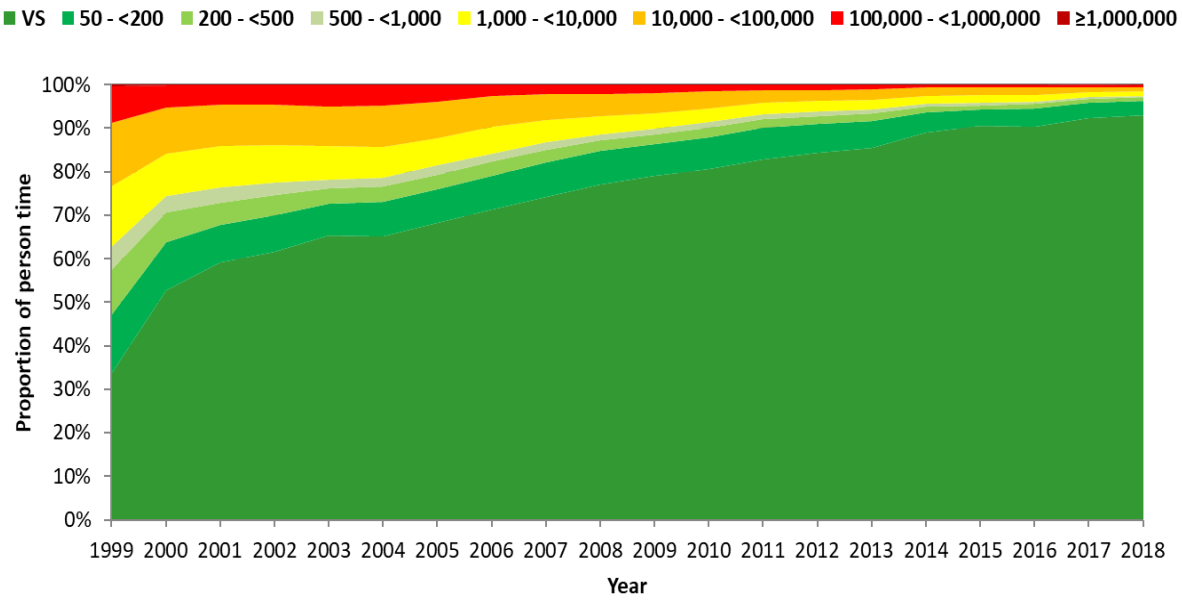

Abbildung 2. Anteil Personenzeit in den Viruslastgruppen von Personen in der Studienpopulation, die jemals eine ART initiiert haben über die Zeit von 1999 bis 2018. Diese Abbildung wurde bereits 2021 im Paper "Everything counts - a method to determine viral suppression among people living with HIV using longitudinal data for the HIV care continuum - results of two large, German, multi-center real-life cohort studies over 20 years (1999–2018) " von Schmidt D, Kollan C, et al. im Journal BMC Public Health veröffentlicht (21). Die Genehmigung zur Verwendung der Abbildung liegt vor.

Entwicklung des Therapieerfolgs von 1999-2018 bei Menschen mit HIV nach ART-Beginn unter Verwendung der letzten VL eines Jahres und Vergleich der Methoden

Der Anteil der Personen mit Virussuppression unter den 22.120 Personen, die jemals ART initiiert hatten und einen dokumentierten VL-Wert hatten, stieg über die Beobachtungszeit von 51,7% im Jahr 1999 auf 93,3% im Jahr 2018. Der Anteil von Menschen mit VL <200 Kopien/ml stieg von 61,1% im Jahr 1999 auf 96,5% im Jahr 2018. Der Anteil der Personenzeit mit einer Virämie >1.000 Kopien/ml verringerte sich von 27,9% im Jahr 1999 auf 2,3% im Jahr 2018.

Der Vergleich zwischen dem entwickelten Modell und der konventionellen Methode ergab einen höheren Anteil mit viraler Suppression bei der konventionellen Methode. Die Abweichung lag bei 18,1% in 1999 und sank dann schnell stetig ab auf 1,8% in 2008 und weiter auf 0,3% in 2018.

In der Analyse der kontinuierlichen viralen Suppression über einen Zeitraum von einem Jahr (2018) hatten insgesamt 88% (10.474/11.837) auf individueller Ebene kein Virusversagen und zeigten bei allen Messungen eine VL <50 Kopien/ml. Die Messung anhand der letzten VL ergab hingegen in 93% (11.044/11.837) der Fälle eine Virussuppression und liegt damit um 5% höher.

Analyse von Personen mit längeren Zeiträumen ohne VL-Kontrolle (Lückenzeit)

Die Analysen von Personen mit längeren Zeiträumen ohne VL-Kontrolle (Lückenzeit) zeigten einen Anteil an Lückenzeit zwischen 18% und 28%. Der Anteil war am niedrigsten in den Jahren 1999 und 2018 mit 18% und am höchsten in den Jahren 2003, 2005 und 2016 mit 28%. Der mediane und mittlere Anteil an Lückenzeit lag bei 24%. In die Analyse der letzten VL vor und der ersten VL nach der Lückenzeit im Zeitraum zwischen 2015 und 2018 wurden 8173 Personen mit 15.892 VL-Messungen eingeschlossen. Die Analyse der ersten VL-Messung nach der Lückenzeit als Maß für die Zeit davor zeigte für 90% (14.293/15.892) eine virale Suppression, 5% (758/15.892) hatten VL zwischen 50-<1.000 Kopien/ml und 5% (841/15,892) VL >1.000 Kopien/ml (21). Die detaillierten Ergebnisse sind dargestellt in der Publikation "Everything counts - a method to determine viral suppression among people living with HIV using longitudinal data for the HIV care continuum - results of two large, German, multi-center real-life cohort studies over 20 years (1999–2018) ". Schmidt D, Kollan C, Stoll M, Hamouda O, Bremer V, Kurth T, Bartmeyer B, the HIV-1 Seroconverter cohort, the ClinSurv HIV cohort. BMC Public Health 21, 200 (2021) (21).

1.6 Diskussion

1.6.1 Methode zur Bestimmung der Anzahl an Personen unter Therapie gegen Hepatitis C mit DAA unter Nutzung von Sekundärdaten

Die Einführung der DAA der 2. Generation in 2014 hat die Therapieoptionen für HCV enorm verbessert. Durch pangenotypische Medikamente mit Heilungsraten von über 90% nahezu nebenwirkungsfrei bei gleichzeitig enormer Verkürzung der Behandlungsdauer wurde die HCV-Behandlung revolutioniert. Allerdings war zunächst unklar, wie der Einfluss auf die Behandlungszahlen ausfällt. Die Hypothese war, dass sich die Behandlungszahlen erhöhen. Die Ziele dieser Studie waren die Entwicklung einer Methode zur Bestimmung der Anzahl und Kosten der HCV-Therapie in Deutschland, die Schätzung der Entwicklung der Behandlungszahlen und Kosten für den Zeitraum 2010-2015 sowie die Bestimmung der Anzahl geheilter Personen nach DAA-Behandlung. Nach unserem Kenntnisstand stellte diese im Rahmen der Promotion entwickelte und publizierte Studie die erste umfassende Beschreibung der Anzahl und Kosten von HCV-Verordnungen mit DAA in Deutschland dar.

Über den Untersuchungszeitraum 2010-2015 wurde ein deutlicher Rückgang der monatlichen PegIFN-Verschreibungen und ein Anstieg der DAA-Verschreibungen beobachtet, entsprechend der Zulassung neuer Substanzen und der Anpassung der deutschen Behandlungsempfehlungen. Insgesamt wurden 7000 Personen im Jahr 2014, und 20.100 Personen im 2015 mit DAA-basierten Regimen behandelt. Die Berechnungen scheinen robust, da Zahlen anderer Institute wie dem GKV-Spitzenverband mit diesen Ergebnissen übereinstimmen (22). Bei einer angenommenen Heilungsrate von 90 % wurden insgesamt 6300 Personen im Jahr 2014 und 18.100 Personen im Jahr 2015 mit DAA von HCV geheilt. Reale Daten aus deutschen Behandlungsregistern bestätigen, dass die Annahme einer SVR von insgesamt 90 % angemessen ist (11, 23, 24). In Deutschland wurden für 2012 ~160.000 Personen mit diagnostizierter virämischer HCV-Infektion geschätzt (25). Da jeder Person mit virämischer HCV-Infektion mit Krankenversicherung ohne Einschränkung auf die Krankheitsschwere DAAs verschrieben werden können, hätten wir seit Markteintritt der DAA der 2. Generation einen viel stärkeren Anstieg der Zahl der monatlich behandelten Personen erwartet.

Wir hätten eine minimale monatliche Behandlungszahl angenommen, die der Ära vor den DAA entspricht, wo im Jahr 2010 zunächst ~6500 monatliche Behandlungen beobachtet wurden. Nach dem erneuten Anstieg der monatlichen Behandlungszahlen Ende 2014 und Anfang 2015 hätten wir zumindest gleichbleibenden Behandlungszahlen erwartet, nicht aber einen Rückgang. Der Rückgang könnte möglicherweise mit teils ungeklärter Kostenregelung sowie Angst vor Regressansprüchen durch die GKV erklärt werden. Darüber hinaus erfolgte wahrscheinlich eine Priorisierung von Personen mit fortgeschrittener Erkrankung durch die Behandelnden (23). Unter den beobachteten Bedingungen

könnten jährlich ~18.000 Menschen geheilt werden, so dass eine deutliche Reduktion der geschätzten ~160.000 diagnostizierten Personen in Deutschland erreicht werden könnte. Dafür ist allerdings politisches Engagement zur weiteren Senkung der DAA-Preise und eine Erhöhung der Behandlungszahlen zu empfehlen.

1.6.2 Bestimmung der Anzahl an Personen unter Therapie mit ausgewählten Medikamenten in Gefängnissen unter Nutzung von Sekundärdaten

In Deutschland ist die medizinische Versorgung von Menschen in Gefängnissen völlig getrennt von der extramuralen Gesundheitsversorgung. Das Ausmaß und die Qualität der medizinischen Versorgung von Menschen in Haft war daher größtenteils unbekannt. Wir haben anhand von Sekundärdaten aus Apotheken die Versorgung mit TB-, HIV-, HCV- und OST-Medikamenten in 11 deutschen Bundesländern zwischen 01/2012 und 03/2013 untersucht mit dem Ziel, die Verfügbarkeit der Behandlungen und den Anteil Behandelter zu bestimmen. Die vorliegende Studie im Rahmen dieser Promotionsarbeit stellt den ersten Versuch dar, die medizinische Versorgung von TB, durch sexuell und durch Blut übertragene Infektionen und OST in Gefängnissen zu beschreiben und zu bewerten.

Die Ergebnisse dieser Untersuchung zeigen, dass in den eingeschlossenen deutschen Justizvollzugsanstalten die medizinische Behandlung aller untersuchten Erkrankungen stattfand. Unter der Annahme, dass die Anzahl der adTP der Anzahl der behandelten Personen pro Tag entspricht, wurden jedoch deutliche Unterschiede in Menge und Umfang der Behandlung zwischen den Bundesländern festgestellt. Anhand der Ergebnisse schienen die Behandlungsraten für TB der erwarteten TB-Prävalenz zu entsprechen, zumindest in Berlin. Eine HIV-Behandlung scheint einem angemessenen Anteil der geschätzten infizierten Gefangenen angeboten worden zu sein. Im Gegensatz dazu war die HCV-Behandlungsprävalenz sehr niedrig. Große Unterschiede zwischen den Bundesländern bei der Bereitstellung aller Behandlungen, insbesondere von OST, deuten auf eine inkonsistente Behandlungspraxis hin, obwohl bundesweite allgemeine (extramurale) Behandlungsrichtlinien für Deutschland existieren. Inwieweit sich Anforderungen und Richtlinien der Ministerien für Justiz auf die Einleitung von Behandlungen und die Gesundheitsversorgung auswirken, scheint nicht nur zwischen den Bundesländern, sondern auch zwischen den Justizvollzugsanstalten innerhalb der Bundesländer unterschiedlich zu sein (26-28). Die Unterschiede in Bezug auf die Behandlung von Krankheiten und die OST in den Justizvollzugsanstalten könnten das dezentrale föderale System in Deutschland widerspiegeln, in dem die Bundesländer möglicherweise unterschiedliche Ansätze in Bezug auf das Management der medizinischen Versorgung verfolgen (29-32).

1.6.3 Methode zur Bestimmung des Therapieerfolgs der HIV-Therapie anhand von Daten aus Langzeitkohorten zur Vervollständigung der HIV-Behandlungskaskade

In der vorliegenden Promotionsarbeit sollte eine Methode zur Bestimmung des Therapieerfolgs der HIV-Therapie zur Vervollständigung der HIV-Behandlungskaskade entwickelt werden. Hierzu wurde ein longitudinales Modell entwickelt, das unter Verwendung klinischer Daten aus Kohortenstudien den individuellen Verlauf der Viruslast von Personen rekonstruiert und damit die Dauer und den Anteil viraler Suppression und Virämie bestimmbar macht. In diesem Modell werden im Gegensatz zur konventionellen Methode alle verfügbaren VL-Messungen einbezogen sowie zusätzlich der ART-Status und die VL-Dynamik berücksichtigt. Die Ergebnisse bieten eine Schätzung der Anzahl und des Anteils von Menschen mit HIV und der Personenzeit mit viraler Suppression für die HIV-Behandlungskaskade, um das UNAIDS-Ziel der viralen Suppression für Deutschland zu evaluieren. Dieses Modell ermöglicht zusätzlich die Bestimmung und weitere Analyse von Personen mit längeren Zeiträumen ohne Beobachtung oder fehlender VL-Kontrolle, definiert als Lückenzeit. Die vorliegende Promotionsarbeit konnte erfolgreich zur Vervollständigung der HIV-Behandlungskaskade beitragen.

Der Anteil an Personen und Personenzeit mit Therapieerfolg und Lückenzeit zwischen 1999 und 2018 wurde anhand der Daten zweier großer nationaler HIV-Kohorten bestimmt. Es wurde ein bemerkenswerter kontinuierlicher Anstieg des Therapieerfolgs beobachtet, sowohl bei Menschen mit HIV nach ART-Beginn als auch in der gesamten Studienpopulation. Das 90%-UNAIDS-Ziel der viralen Suppression ist bei Menschen mit HIV nach ART-Beginn seit 2015 erreicht und in der gesamten Studienpopulation aller diagnostizierten Menschen mit HIV seit 2017. Dies ist wahrscheinlich auf einen insgesamt früheren und weiter verbreiteten ART-Gebrauch zurückzuführen. Unter Verwendung der international vergleichbaren Schwelle von VL <200 Kopien/ml ist das 90% UNAIDS-Ziel bei Menschen mit HIV nach ART-Beginn seit 2011 und in der gesamten Studienpopulation seit 2015 erreicht. Im Jahr 2018 zeigten 93% der Menschen mit HIV nach ART-Beginn virale Suppression mit VL <50 Kopien/ml und 96% hatten VL <200 Kopien/ml. Die Ergebnisse unseres longitudinalen Modells wurden mit denen der konventionellen Methode verglichen. Hierbei konnte vor allem für die früheren Jahre eine mögliche Fehlklassifizierung des Anteils mit viraler Suppression gezeigt werden, wenn nur die letzte VL eines Jahres verwendet wurde. In diesen klinischen „real-life“ Kohortenstudien wurde ein konstant hoher Anteil an längeren Zeiträumen ohne Beobachtung oder fehlender VL-Kontrolle beobachtet. Weitere Analysen wurden durchgeführt, um den VL-Status in dieser sogenannten Lückenzeit zu abzuschätzen. Es konnte gezeigt werden, dass in den letzten Jahren die Lückenzeit nur mit einem geringfügig niedrigeren Anteil viraler Suppression assoziiert war.

1.7 Schlussfolgerungen

Die im Rahmen der vorliegenden Promotionsarbeit entwickelten Methoden zur Bestimmung der Anzahl an Personen unter Therapie mit ausgewählten Medikamenten anhand von Sekundärdaten aus Apothekenabrechnungszentren sowie der Methode zur Bestimmung des Therapieerfolgs der HIV-Therapie anhand von Daten aus HIV-Langzeitkohorten erlaubten erstmals die Bestimmung wichtiger Stufen in der Behandlungskaskade von HCV und HIV.

Dabei diente die ursprünglich entwickelte Methode zur Bestimmung der Anzahl an Personen unter HIV-Therapie mit dem Konzept der Leitsubstanzen als Grundlage für die Weiterentwicklung und Anwendung auf weitere Datenquellen und Indikationen (4). Es handelte sich dabei zum einen um eine Bestimmung der Anzahl an HCV-Therapierten und Kosten der HCV-Therapie (20) sowie um eine Auswertung von Daten aus Apotheken, die Gefängnisse mit Medikamenten gegen die Infektionskrankheiten TB, HIV, HCV sowie OST beliefern (12).

Die Methoden zur Anzahl an Therapierten und Kosten der Therapien gegen HIV und HCV werden kontinuierlich in der Surveillance von HIV und HCV genutzt (2, 3). Durch die Methode und Auswertung des HIV-Therapieerfolgs konnte die HIV-Behandlungskaskade vervollständigt und damit die UNAIDS 90-90-90 Ziele insgesamt für Deutschland evaluiert werden. Insofern hat die vorliegende Promotionsarbeit einen wesentlichen Beitrag zur Verbesserung der verstetigten Surveillance von HIV und HCV geleistet. Die Fragestellungen konnten beantwortet und die Ziele der Arbeit erfüllt werden.

Sowohl die Methodik zur Bestimmung der Anzahl Therapierter als auch das Modell zur Bestimmung des Therapieerfolgs der HIV-Therapie bieten sich an, in Zukunft an andere Untersuchungen, Medikamente oder Parameter angepasst und verwendet zu werden. Deshalb wurde die in der Vorarbeit entwickelte Methodik zur Bestimmung der Anzahl an Personen unter HIV-Therapie und die in dieser Promotionsarbeit entwickelte Methodik zur Bestimmung der Anzahl an Personen unter HCV-Therapie jeweils für ein Kompendium bewährter Praktiken der WHO für die Reaktion des Gesundheitssektors auf HIV und Virushepatitis in der Europäischen Region der WHO eingereicht und darin aufgenommen (33-34).

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2 Eidesstattliche Versicherung

„Ich, Daniel Schmidt, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Entwicklung von Methoden zur Vervollständigung der Behandlungskaskade für HIV und Hepatitis C unter Verwendung von Sekundärdaten und Daten aus Langzeitkohorten; Development of methods to complete the treatment cascade for HIV and hepatitis C using secondary data and long term cohort study data“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

3 Anteilserklärung

Daniel Schmidt hat folgenden Anteil an folgenden Publikationen:

Publikation 1: Ruth Zimmermann, Christian Kollan, Patrick Ingiliz, Stefan Mauss, **Daniel Schmidt**, Viviane Bremer. Real-world treatment for chronic hepatitis C infection in Germany: Analyses from drug prescription data, 2010–2015. *Journal of Hepatology*, Volume 67, Issue 1, July 2017, Pages 15-22

Beitrag im Einzelnen:

- Mitwirkung bei der Entwicklung der Methodik zur Bestimmung der Anzahl HCV-Therapierter aus Apothekendaten, Berechnung der Therapielaufzeit, Berechnung der Anzahl geheilter Personen, Berechnung der Therapiekosten insgesamt und pro Person;
- Mitwirkung bei der Planung der Analysen zur Bestimmung der Anzahl HCV-Therapierter aus Apothekendaten, Berechnung der Therapielaufzeit, Berechnung der Anzahl geheilter Personen, Berechnung der Therapiekosten insgesamt und pro Person;
- Mitwirkung bei der Datenaufbereitung und der Plausibilitätskontrolle;
- Mitarbeit bei der Konzeption des Artikels;
- Mitwirkung bei der Literaturrecherche und Auswahl der relevanten Literatur;
- Mitkonzipierung der Datenauswertung und Mitwirkung bei der Datenauswertung zur Berechnung der Anzahl HCV-Therapierter aus Apothekendaten, Berechnung der Therapielaufzeit, Berechnung der Anzahl geheilter Personen, Berechnung der Therapiekosten insgesamt und pro Person;
- Erstellung von Tabelle 1, 2 und 3 gemeinsam mit Christian Kollan und Ruth Zimmermann, Erstellung von Abbildung 1 gemeinsam mit Christian Kollan;
- Mitwirkung bei der Interpretation der Ergebnisse;
- Mitwirkung bei der Fertigung der Publikation.

Publikation 2: Jana Müller, **Daniel Schmidt**, Christian Kollan, Marc Lehmann, Viviane Bremer, Ruth Zimmermann. High variability of TB, HIV, hepatitis C treatment and opioid substitution therapy among prisoners in Germany. *BMC public health* 17, 843 (2017).

Beitrag im Einzelnen:

- Geteilte Erstautorschaft mit Jana Müller
- Federführung bei der Konzeption des Artikels gemeinsam mit der Erstautorin (J. Müller);
- Durchführung der Literaturrecherche und Auswahl der relevanten Literatur gemeinsam mit der Erstautorin;
- Mitwirkung bei der Datenauswertung zur Bestimmung der Anzahl an Therapierten mit den ausgewählten Medikamenten;
- Erstellung der Abbildung 1, Erstellung von Tabelle 2 gemeinsam mit Jana Müller

- Interpretation der Ergebnisse gemeinsam mit der Erstautorin in Abstimmung mit den Koautoren;
- Gemeinsam mit anderer Erstautorin (J. Müller) Entwurf und Fertigung der Publikation als Erstautor in Abstimmung mit den Koautoren.

Publikation 3: **Daniel Schmidt**, Christian Kollan, Matthias Stoll, Osamah Hamouda, Viviane Bremer, Tobias Kurth, Barbara Bartmeyer, the HIV-1 Seroconverter cohort, the ClinSurv HIV cohort. Everything counts - a method to determine viral suppression among people living with HIV using longitudinal data for the HIV care continuum - results of two large, German, multi-center real-life cohort studies over 20 years (1999–2018). *BMC Public Health* 21, 200 (2021).

Beitrag im Einzelnen:

- Entwicklung der Methodik zur Berechnung des individuellen Viruslastverlaufs, der Bestimmung der Anzahl und des Anteils an Personen und Personenzeit mit viraler Suppression und Virämie, der Bestimmung der Anzahl und des Anteils an Personenzeit und Personen mit Lückenzeit gemeinsam mit Christian Kollan;
- Federführung bei der Planung der Analysen zur Berechnung des individuellen Viruslastverlaufs, der Bestimmung der Anzahl und des Anteils an Personenzeit und Personen mit viraler Suppression und Virämie, Bestimmung der Anzahl und des Anteils an Personenzeit und Personen mit Lückenzeit;
- Federführung bei der Konzeption des Artikels;
- Federführung und Durchführung der Literaturrecherche und Auswahl der relevanten Literatur;
- Federführende Konzipierung der Datenauswertung zur Bestimmung der Anzahl und des Anteils an Personenzeit und Personen mit viraler Suppression und Virämie, Bestimmung der Anzahl und des Anteils an Personenzeit und Personen mit Lückenzeit;
- Federführende Auswertung der Daten;
- Federführende Konzipierung und alleinige Erstellung aller Abbildungen und Tabellen;
- Federführende Interpretation der Ergebnisse in Zusammenarbeit mit den Koautor*innen;
- Entwurf und Fertigung der Publikation als Erstautor.

_____

Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

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Unterschrift des Doktoranden

4 Originalarbeiten als Promotionsleistung

Publikation 1: Ruth Zimmermann, Christian Kollan, Patrick Ingiliz, Stefan Mauss, **Daniel Schmidt**, Viviane Bremer. Real-world treatment for chronic hepatitis C infection in Germany: Analyses from drug prescription data, 2010–2015. *Journal of Hepatology*, Volume 67, Issue 1, July 2017, Pages 15-22

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Publikation 2: Jana Müller, **Daniel Schmidt**, Christian Kollan, Marc Lehmann, Viviane Bremer, Ruth Zimmermann. High variability of TB, HIV, hepatitis C treatment and opioid substitution therapy among prisoners in Germany. *BMC public health* 17, 843 (2017).

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Publikation 3: **Daniel Schmidt**, Christian Kollan, Matthias Stoll, Osamah Hamouda, Viviane Bremer, Tobias Kurth, Barbara Bartmeyer, the HIV-1 Seroconverter cohort, the ClinSurv HIV cohort. Everything counts - a method to determine viral suppression among people living with HIV using longitudinal data for the HIV care continuum - results of two large, German, multi-center real-life cohort studies over 20 years (1999–2018). *BMC Public Health* 21, 200 (2021).

Journal Impact Factor nach ISI Web of Knowledge: 2.521 (2019)

Zimmermann R, Kollan C, Ingiliz P, Mauss S, Schmidt D, Bremer V. Real-world treatment for chronic hepatitis C infection in Germany: Analyses from drug prescription data, 2010–2015. Journal of hepatology. 2017;67(1):15-22.

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RESEARCH ARTICLE Open Access

High variability of TB, HIV, hepatitis C treatment and opioid substitution therapy among prisoners in Germany

Jana Müller[1,2†], Daniel Schmidt[1,2*†], Christian Kollan[1], Marc Lehmann[3], Viviane Bremer[1] and Ruth Zimmermann[1]

Abstract

Background: In Germany, medical care of prisoners is completely separated from extramural health care. The extent and quality of medical care among prisoners in Germany are therefore largely unknown. We performed a secondary data analysis of pharmacy sales data for tuberculosis (TB), HIV, hepatitis C (HCV) and opioid substitution treatment (OST) delivered to prisons in 11 federal states (FS) in Germany between 01/2012 and 03/2013. The aims of this study were to assess (i) the treatment availability for the selected diseases and OST in German prisons, (ii) the proportion of prisoners treated per FS and overall for TB, HIV, HCV and OST during the study period.

Methods: Substances unique to or typically used for the treatment of each disease were defined as marker substances with defined daily doses (DDD).
For each marker substance we assessed the cumulative number of DDD, the average daily number of DDD (DDD_d) and average treatment prevalence per day in percent (adTP). Accordingly, the DDD_d represents one person treated per day and the adTP means the proportion of prisoners treated per day. We compared the adTP of the diseases with previously measured prevalences.

Results: We obtained data from pharmacies supplying prisons in 11 of 16 German FS. Of the included prisons, 41% were supplied with medicines for TB, 71% for HIV and 58% for HCV and OST. Twice as many delivered marker substances for TB were indicated for the continuation phase and chemoprevention than the intensive phase. The HIV adTP ranged from 0.06% to 0.94%, HCV adTP ranged from 0.03% to 0.59% and OST adTP ranged from 0% to 7. 90%. The overall adTP for the respective treatment was 0.39% for HIV, 0.12% for HCV and 2.18% for OST.

Conclusions: According to our findings treatment rates for TB were consistent with the expected TB prevalence, at least in Berlin. HIV treatment seems to be offered to an adequate proportion of estimated infected prisoners. In contrast, the HCV treatment prevalence was low. High variation among FS in provision of all treatments, particularly of OST, point to inconsistent treatment practices, although nationwide extramural treatment guidelines for Germany exist.

Keywords: TB, HIV, HCV, OST, Treatment, Prison health, Intramural, Secondary data

Background

Studies have shown that specific blood- and air-borne and sexually transmitted infections are more common among prisoners than in the general population: in Germany and other European countries, tuberculosis (TB) prevalence was 11 to 81 times higher, hepatitis C virus (HCV) prevalence was 17 to 100 times higher, human immunodeficiency virus (HIV) prevalence was 5 to 24 times higher and opioid dependence was 70 times higher among prisoners in comparison to the general population [1–8]. TB is primarily an airborne disease and the bacteria are usually spread from person to person through infectious droplet nuclei when an infectious pulmonary TB patient coughs or sneezes [9]. Usually, a prolonged and close contact is required for transmission; therefore the prison setting can facilitate the spread of

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the disease. HIV and HCV can be transmitted via unprotected sexual contacts as well as through the widespread intramural practice of unsafe drug use and tattooing involving the sharing of potentially infectious needles, syringes and other paraphernalia [8, 10–16]. Thus transmission risks and infection events are highly increased in prisons, especially due to the absence of sterile drug injecting utensils and restricted access to condoms and other prevention measures.

Nevertheless, the prison setting presents not only challenges, but also opportunities for the prevention and treatment of TB, HIV and hepatitis [17]. Prevention of HIV and HCV by offering testing and counselling, providing condoms and tattooing materials as well as sterile injection equipment for people who inject drugs (PWID) also includes the initiation and continuation of opioid substitution treatment (OST) to reduce injection frequency. Furthermore, the treatment of newly diagnosed and already known infections is important not only for the person infected but also in terms of treatment as prevention [6, 18–23]. Despite various challenges in providing treatment for the mentioned infectious diseases and offering OST in the prison setting, it is practicable, and crucial to reduce transmission within prisons.

Different screening approaches exist to identify infections in prisons; however, systematic screening for infectious diseases is not implemented in the German prison system. Strategies differ among federal states (FS) and singular prisons. TB screening by chest x-ray is performed systematically on all prisoners at entrance in the FS of Berlin [24], and in some other prisons, but in most FS, symptom-based screening strategies are implemented. Screening for sexually transmitted and bloodborne viruses is also diverse, and ranges from test offer to persons with clinical symptoms or risk factors, request by the prisoner to mandatory testing in some prisons or FS [5].

In Germany, treatment guidelines and effective treatment regimens for TB, HIV and HCV as well as OST are available [25–29], and all mentioned treatments are being carried out among patients with statutory health insurance (SHI) extramurally. Upon incarceration SHI is suspended, and health care is provided and paid for by the federal Ministry of Justice (MoJ) of the respective FS. As a result of this transitional period between health care providers treatment interruptions may occur [14, 30].

During the study period from January 2012 to March 2013, 67.607 people were detained in 186 prisons in the 16 FS of Germany [31], corresponding to nearly 0.08% of the total German population. Throughout the study period, five pharmacies supplied all prison hospitals and prisons in Germany with pharmaceuticals. Implementation and provision of health care lays within the responsibility of the MoJ of the respective FS [32]. Nevertheless, according to national laws (Prison Act § 56ff StVollzG; Social Act SGB V), health care in the penitentiary system should take place under the principle of equivalence of care and within the standards of the SHI [14, 33]. Health care is implemented by the prison doctor with the help of the prison administration, both of whom are under the supervision and directives of the FS [14, 34, 35]. Medical care of prisoners is provided by the prison doctor in out-patient care, in special prison wards and correctional hospitals or wherever necessary by extramural specialized medical doctors or hospitals [14]. Since not every prison has a sick ward and only some FS have prison hospitals, contracts and transfer co-operations exist among the states in order to ensure medical care in every FS [34, 36–38].

Because prison health care is not part of the regular public health system in Germany, it is therefore not part of the health reporting system [14]. The extent and quality of TB, HIV, HCV and opioid dependence treatment provided to prisoners in Germany are therefore largely unknown [5, 6, 39].

In order to determine the medical care of infectious diseases and opioid dependence among prisoners in Germany we performed a secondary data analysis of pharmacy sales data for TB, HIV, HCV treatments and OST delivered to prisons in 11 FS in Germany between January 2012 and March 2013. The aims of this study were to assess (i) the treatment availability for the selected diseases and OST in German prisons (ii) the proportion of prisoners treated per FS and overall for TB, HIV, HCV and OST during the study period.

Methods

We asked the MoJ of all 16 FS in Germany to approve and support the planned data collection and analysis for each respective FS in August 2013. Twelve FS agreed to participate in the study; however, one FS was excluded because the respective pharmacy did not provide the data. In the participating FS, all prisons and prisoners of the respective FS were included except one sick ward (5 beds) and one correctional hospital (52 beds) because they were not supplied by one of the contract pharmacies. Throughout the study period, all participating prisons and prison hospitals were supplied by three pharmacies with TB, HIV, HCV and OST medicines.

The pharmacies provided the data for the period from 01/2012 to 03/2013. The dataset contained a minimum of eight variables: the name of the prison, the FS, the trade name of the drug, package size, dosage form, the Anatomical Therapeutic Chemical (ATC) classification code of the drug, the central pharmaceutical number (*Pharmazentralnummer, PZN*), and the number of drug packages supplied per month. The study collected solely prescription data and no individual patient data. No

ethical or data protection concerns were raised. The names of the prisons were pseudonymized.

Substances unique to or typically used for the treatment of each disease were defined as marker substances for the respective disease. We used defined daily doses (DDD) of the marker substances to calculate the number of daily treated persons. The DDD were determined based on current national treatment guidelines, prescribing information according to the German Medicines Act and literature research (Table 1). The number of standard units (e.g. tablets, pens) was determined for each marker substance.

First, we assessed the cumulative number of DDD (DDD_{cum}) of the marker substances for the whole study period (456 days). Then we calculated the average daily number of DDD for each marker substance for the study period (DDD_d). Accordingly the DDD_d represents one person treated with the respective substance per study day. Finally, we calculated the average treatment prevalence per day in percent (average daily treatment prevalence, adTP). Accordingly, the adTP means the proportion of prisoners treated per day with the respective drug to the average number of all prisoners during the study period (Fig. 1). We compared the adTP with previously measured prevalences.

The number of incarcerated persons was obtained from the German Federal Statistical Office, which provides this data in March, August and November each year [31]. Based on these data an average monthly number of prisoners for the months of March 2012, August 2012, November 2012 and March 2013 were calculated for each participating FS and for all participating states in total (Fig. 2).

TB treatment

A standard six month treatment regimen for TB consists of the four antitubercular substances ethambutol (E), pyrazinamid (Z), isoniazid (H) and rifampicin (R). Patients receive all four drugs daily for the first two months (intensive phase), followed by H and R daily for another four months (continuation phase). The marker substances for anti-TB standard treatment were determined to be E, Z, H and R. The determined DDD were 1200 mg for E, 1500 mg for Z, 300 mg for H (except for the formulation 400 mg per pill) and 600 mg for R as recommended in the ATC classification (Table 1). The standard regimen for latent tuberculosis infection (chemoprevention) consists of either (i) H alone or (ii) a combination of H and R or (iii) R alone [26]. For chemoprevention the marker substances were determined to be H (DDD 300 mg) and/or R (DDD 600 mg). R and H fixed-dose combinations were divided into single substances. Pyridoxin as an additive to H was not taken into account. For multidrug-resistant-TB (MDR-TB), protionamide (Pto) and terizidone (Trd) were determined to be the marker substances with a DDD of 750 mg. For HIV-TB-coinfection the marker substance was rifabutin (Rfb) with a DDD of 150 mg (Table 1).

HIV treatment

The standard therapy for HIV during the study period contained exactly one thiacytidine medication (TCM),

Table 1 Marker substances and DDD

Disease	Marker substances	DDD [mg]
Tuberculosis [26, 58]	Ethambutol (E)	1200
	Pyrazinamid (Z)	1500
	Isoniazid (H)	300 [a]
	Rifampicin (R)	600
	Protionamide (Pto)	750
	Terizidone (Trd)	750
	Rifabutin (Rfb)	150
Hepatitis C [27, 58–60]	Pegylated interferon-α (PEG-INF)	0.05, 0.08, 0.1, 0.12, 0.135, 0.15, 0.18
	Boceprevir (BOC)	2400
	Telaprevir (TVR)	2250
HIV [25, 58]	Emtricitabin (FTC)	200
	Lamivudin (3TC)	300
Opioid dependence [29, 61–64]	Methadone,	90
	Levomethadone	45
	Buprenorphine	8
	Buprenorphine/Naloxone	8

[a]For the formulation of 400 mg isoniazid per pill the determined DDD was 400 mg

$$Cumulative\ number\ of\ DDD\ (DDDcum) = \frac{\sum standard\ units}{DDD}$$

$$Daily\ number\ of\ DDD\ (DDDd) = \frac{DDDcum}{456\ d}$$

$$Average\ daily\ treatment\ prevalence\ (adTP\ [\%]) = \frac{(DDDd)}{(average\ number\ of\ prisoners)} \times 100$$

Fig. 1 Cumulative number of DDD, average daily number of DDD and average daily treatment prevalence

either lamivudine (3TC) or emtricitabine (FTC). The marker substances for HIV treatment were determined to be 3TC and FTC (Table 1) [25, 40, 41]. The determined DDD were 300 mg for 3TC and 200 mg for FTC. Drugs with more than one substance were split into single substances.

HCV treatment

The standard therapy for HCV during the study period consisted of peginterferon α-2a (PEG-IFN α-2a) or peginterferon α-2b (PEG-IFN α-2b) in combination with ribavirin (RBV). Furthermore, during the study period a triple-therapy with the substances boceprevir (BOC) or telaprevir (TVR) in combination with PEG-IFN and RBV was available. The marker substances for HCV treatment were determined to be PEG-IFN α-2a, PEG-IFN α-2b, BOC and TVR. We assumed that one pen PEG-IFN correlated with one treated person. The determined DDD were 2400 mg for BOC and 2250 mg for TVR (Table 1).

OST

The marker substances for OST were determined to be methadone, levomethadone, buprenorphine and buprenorphine/naloxone. The determined DDD were 90 mg for methadone, 45 mg for levomethadone, and 8 mg for buprenorphine and buprenorphine/naloxone (Table 1).

Results

By June 2014, of the total 16 German FS, the MoJ of the 12 FS Bavaria, Berlin, Bremen, Hamburg, Mecklenburg-Western Pomerania, Lower Saxony, Rhineland Palatinate, Saarland, Saxony, Saxony-Anhalt, Schleswig-Holstein and Thuringia had agreed to the study. Rhineland Palatinate could not deliver the data and was excluded. In the study period the 11 participating FS with 34,191 prisoners in 97 prisons represented almost half of all German prisoners (N = 67,607) in 186 prisons (Fig. 3).

Detailed results for each disease and FS are shown in Table 2.

TB treatment

About 41% of the 97 prisons were supplied with medicines against TB. There was no TB medicine supply at all to prisons in Saarland. Both marker substances E and Z for the intensive phase were delivered to all investigated FS

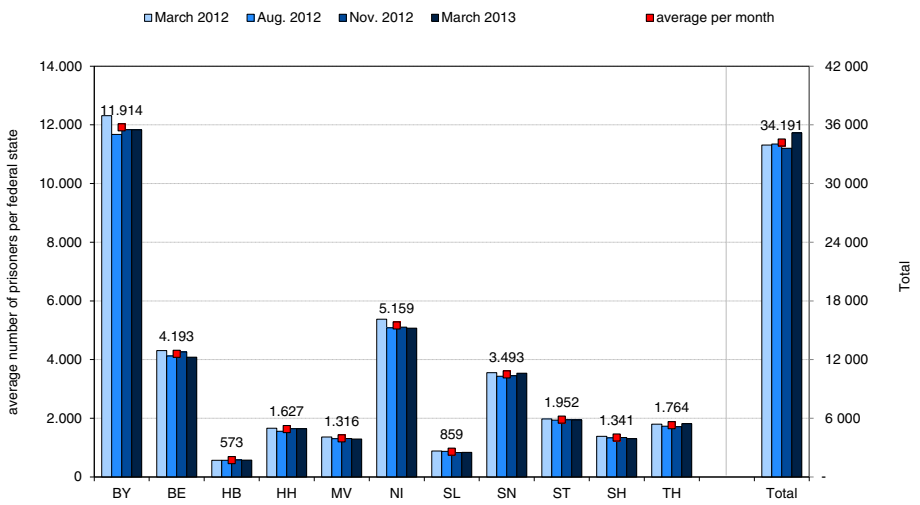

Fig. 2 Average number of prisoners per month in the respective FS and in total during the study period January 2012 and March 2013. Bavaria (BY), Berlin (BE), Bremen (HB), Hamburg (HH), Mecklenburg-Western Pomerania (MV), Lower Saxony (NI), Saarland (SL), Saxony (SN), Saxony-Anhalt (ST), Schleswig-Holstein (SH) and Thuringia (TH)

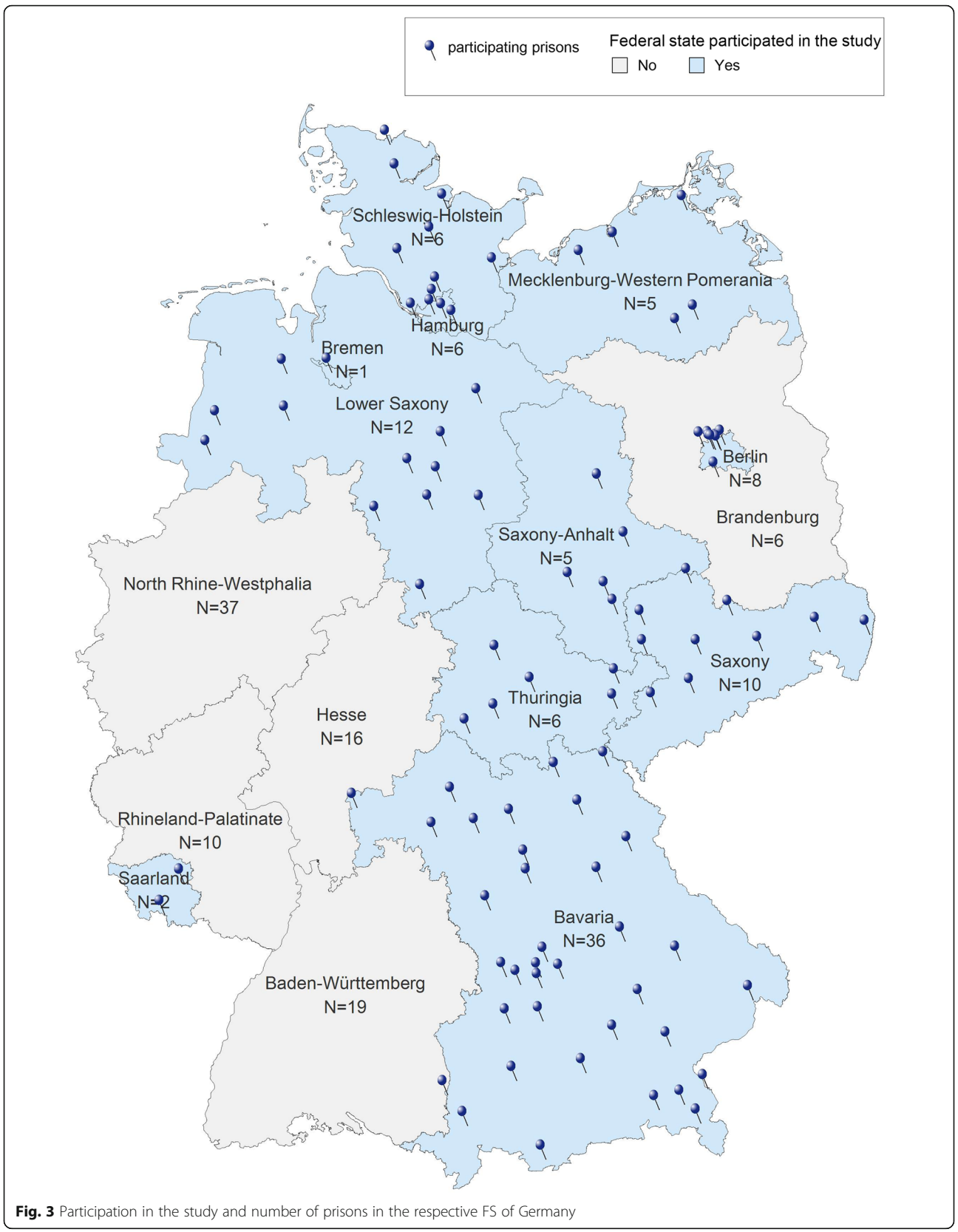

Fig. 3 Participation in the study and number of prisons in the respective FS of Germany

Table 2 Number of prisons, number of delivered prisons, average number of prisoners, cumulative number of DDD (DDD_{cum}), average daily number of DDD (DDD_d) and average treatment prevalence per day in percent (adTP)

Federal state	Bavaria	Berlin	Bremen	Hamburg	Mecklenburg-Western Pomerania	Lower Saxony	Saarland	Saxony	Saxony-Anhalt	Schleswig-Holstein	Thuringia	Overall
Number of prisons	36	8	1	6	5	12	2	10	5	6	6	97
Average number of prisoners (03/2012, 08/2012, 11/2012, 03/2013)	11,914	4193	573	1627	1316	5159	859	3493	1952	1341	1764	34,191
Number of prisons with delivery of TB drugs	13	3	1	4	2	9	0	2	3	3	3	40
H DDD_{cum}	3636	2484	251	1877	167	1734	0	100	2351	500	333	13,432
R DDD_{cum}	4640	2455	293	1633	100	1050	0	140	790	85	0	11,185
E DDD_{cum}	2037	1440	135	1209	0	271	0	242	42	0	104	5480
Z DDD_{cum}	1653	1965	134	1101	0	300	0	67	100	0	0	5319
Pto DDD_{cum}	0	100	0	0	0	0	0	0	0	0	0	100
Trd DDD_{cum}	251	284	0	0	0	0	0	0	0	0	0	534
RFB DDD_{cum}	405	0	0	0	0	0	0	0	0	0	105	510
H DDD_d	8	5	1	4	0	4	0	0	5	1	1	29
R DDD_d	10	5	1	4	0	2	0	0	2	0	0	25
E DDD_d	4	3	0	3	0	1	0	1	0	0	0	12
Z DDD_d	4	4	0	2	0	1	0	0	0	0	0	12
Pto DDD_d	0	0	0	0	0	0	0	0	0	0	0	0
Trd DDD_d	1	1	0	0	0	0	0	0	0	0	0	1
RFB DDD_d	1	0	0	0	0	0	0	0	0	0	0	1
H adTP	0.067	0.130	0.096	0.253	0.028	0.074	0.000	0.006	0.264	0.082	0.041	0.086
R adTP	0.085	0.128	0.112	0.220	0.017	0.045	0.000	0.009	0.089	0.014	0.000	0.072
E adTP	0.037	0.075	0.052	0.163	0.000	0.012	0.000	0.015	0.005	0.000	0.013	0.035
Z adTP	0.030	0.103	0.051	0.148	0.000	0.013	0.000	0.004	0.011	0.000	0.000	0.034
Pto adTP	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001
Trd adTP	0.005	0.015	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.003
RFB adTP	0.007	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.013	0.003
Number of prisons with delivery of HIV drugs	20	7	1	6	3	12	2	7	3	5	3	69
non-TCM DDD_{cum}	42,224	32,784	5060	11,950	3060	24,770	4230	3000	2580	5850	840	136,348
TCM DDD_{cum}	18,900	14,520	2460	6210	660	11,236	1980	960	1290	2730	510	61,456
non-TCM DDD_d	93	72	11	26	7	54	9	7	6	13	2	299
TCM DDD_d	41	32	5	14	1	25	4	2	3	6	1	135
Ratio non-TCM/TCM	2.2	2.3	2.1	1.9	4.6	2.2	2.1	3.1	2.0	2.1	1.6	2.2
HIV adTP	0.348	0.759	0.941	0.837	0.110	0.478	0.505	0.060	0.145	0.446	0.063	0.394

Table 2 Number of prisons, number of delivered prisons, average number of prisoners, cumulative number of DDD (DDD_{cum}), average daily number of DDD (DDD_d) and average treatment prevalence per day in percent (adTP) *(Continued)*

Federal state	Bavaria	Berlin	Bremen	Hamburg	Mecklenburg-Western Pomerania	Lower Saxony	Saarland	Saxony	Saxony-Anhalt	Schleswig-Holstein	Thuringia	Overall
Number of prisons with delivery of HCV drugs	17	6	1	2	1	9	1	8	5	3	3	56
PEG-IFN α-2a DDD_{cum}	3724	1463	1547	1253	0	2198	959	987	1078	1260	448	14,917
PEG-IFN α-2b DDD_{cum}	392	140	0	0	182	315	0	1925	0	7	0	2961
Total PEG-IFN α DDD_{cum}	4116	1603	1547	1253	182	2513	959	2912	1078	1267	448	17,878
BOC DDD_{cum}	70	84	56	0	0	0	0	245	0	0	0	455
TVR DDD_{cum}	147	49	0	0	0	455	0	0	84	84	49	868
PEG IFN α-2a DDD_d	8	3	3	3	0	5	2	2	2	3	1	33
PEG IFN α-2b DDD_d	1	0	0	0	0	1	0	4	0	0	0	6
Total PEG-IFN α DDD_d	9	4	3	3	0	6	2	6	2	3	1	39
BOC DDD_d	0	0	0	0	0	0	0	1	0	0	0	1
TVR DDD_d	0	0	0	0	0	1	0	0	0	0	0	2
PEG-IFN α adTP	0.076	0.084	0.592	0.169	0.030	0.107	0.245	0.183	0.121	0.207	0.056	0.115
BOC adTP	0.001	0.004	0.021	0.000	0.000	0.000	0.000	0.015	0.000	0.000	0.000	0.003
TVR adTP	0.003	0.003	0.000	0.000	0.000	0.019	0.000	0.000	0.009	0.014	0.006	0.006
Number of prisons with delivery of OST	7	6	1	5	3	13	0	6	5	5	5	56
Buprenorphine DDD_{cum}	119	10,738	0	154	2142	910	0	434	3073	1225	1460	20,255
Buprenorphine/Naloxone DDD_{cum}	756	3598	0	0	0	3248	0	175	77		119	7973
Levomethadone DDD_{cum}	222	18,556	222	0	1172	48,937	0	1444	6182	16,512	3043	96,292
Methadone DDD_{cum}	2033	27,967	20,411	47,472		98,590	0			19,579		216,052
Total OST DDD_{cum}	3131	60,859	20,633	47,626	3314	151,684	0	2053	9332	37,316	4622	340,571
Buprenorphine DDD_d	0	24	0	0	5	2	0	1	7	3	3	44
Buprenorphine/Naloxone DDD_d	2	8	0	0	0	7	0	0	0	0	0	17
Levomethadone DDD_d	0	41	0	0	3	107	0	3	14	36	7	211
Methadone DDD_d	4	61	45	104	0	216	0	0	0	43	0	474
Total OST DDD_d	7	133	45	104	7	333	0	5	20	82	10	747
Buprenorphine adTP	0.002	0.562	0.000	0.021	0.357	0.039	0.000	0.027	0.345	0.200	0.182	0.130
Buprenorphine/Naloxone adTP	0.014	0.188	0.000	0.000	0.000	0.138	0.000	0.011	0.009	0.000	0.015	0.051
Levomethadone adTP	0.004	0.970	0.085	0.000	0.195	2.080	0.000	0.091	0.695	2.700	0.378	0.618
Methadone adTP	0.037	1.463	7.812	6.399	0.000	4.191	0.000	0.000	0.000	3.202	0.000	1.386
OST adTP	0.058	3.183	7.897	6.419	0.552	6.448	0.000	0.129	1.048	6.102	0.575	2.184

except for Mecklenburg-Western Pomerania, Schleswig-Holstein and Thuringia. Both marker substances H and R for the continuation phase and chemoprevention were supplied to all FS except Thuringia. Mecklenburg-Western Pomerania and Schleswig-Holstein only received the marker substances H and R, Thuringia only the substances E and H. Substances for the treatment of drug resistant or complicated or severe TB were provided in the FS Bavaria, Berlin and Thuringia.

The adTP of E and Z in the initial stage ranged from 0% in Mecklenburg-Western Pomerania, Saarland, Schleswig-Holstein and Thuringia (Z) to 0.16% (E) and 0.15% (Z) in Hamburg. The adTP of H and R in the continuity stage ranged from 0% in Saarland and Thuringia (R) to 0.26% in Saxony-Anhalt (H) and 0.22% in Hamburg (R). In total, twice as many delivered marker substances were indicated for the continuation phase and chemoprevention than the intensive phase (H & R: 0.09% & 0.07% vs. E & Z: 0.04% & 0.03%). The formulation 400 mg isoniazid per pill played only a marginal role in Lower-Saxony, Saxony-Anhalt and Schleswig-Holstein. Pto as a marker substance for MDR-TB treatment was only delivered in Berlin (adTP 0.01%). Trd also as a marker substance for MDR-TB was delivered in Bavaria (adTP 0.01%) and Berlin (adTP 0.02%). Rfb as marker substance for the TB treatment of patients with HIV-TB-coinfection was delivered in Bavaria (adTP 0.01%) and Thuringia (adTP 0.02%).

HIV treatment

Overall, 71% of the included prisons in the respective FS were delivered with drugs for HIV treatment. HIV DDD_{cum} ranged from 510 in Thuringia to 18.900 in Bavaria. HIV DDD_d ranged from 1 in Thuringia to 41 in Bavaria. HIV adTP ranged from 0.06% in Saxony to 0.94% in Bremen. The overall HIV adTP was 0.39%.

Nucleoside reverse transcriptase inhibitor (NRTI) substances and protease inhibitor (PI) substances were supplied to all participating FS. With the exception of Thuringia, all other FS were supplied with non-nucleoside reverse transcriptase inhibitor (NNRTI) substances and the integrase inhibitor (INI) raltegravir. The entry inhibitor (EI) maraviroc was supplied exclusively to Bavaria and Berlin.

HCV treatment

In total, 58% of the represented prisons were delivered with drugs for HCV treatment. In the FS of Bremen and Saxony-Anhalt, all prisons were supplied with HCV drugs. HCV DDD_{cum} ranged from 182 in Mecklenburg-Western Pomerania to 4.116 in Bavaria. HCV DDD_d ranged from 0 in Mecklenburg-Western Pomerania to 9 in Bavaria. HCV adTP ranged from 0.03% in Mecklenburg-Western Pomerania to 0.59% in Bremen. The overall HCV adTP was 0.12%. BOC DDD_{cum} ranged from 0 in seven FS to 245 in Saxony. BOC DDD_d ranged from 0 in seven FS to 1 in Saxony. BOC adTP ranged from 0% in seven FS to 0.02% in Bremen. TVR DDD_{cum} ranged from 0 in five FS to 455 in Lower-Saxony. TVR DDD_d ranged from 0 in five FS to 1 in Lower-Saxony. TVR adTP ranged from 0% in five FS to 0.02% in Lower-Saxony.

OST

Regarding opioid substitutions, 58% of the included prisons in the respective FS were supplied with drugs for OST. OST DDD_{cum} ranged from 0 in Saarland to 151.684 in Lower-Saxony. OST DDD_d ranged from 0 in Saarland to 333 in Lower-Saxony. OST adTP ranged between 0% in Saarland and 7.90% in Bremen. The overall OST adTP was 2.18%.

Discussion

The results show that medical treatment of all investigated diseases took place in German penal institutions. However, under the assumption that the number of adTP corresponds to the number of treated people per day, differences in quantity and extent of treatment were observed among the FS. To what extent requirements and directives of the MoJ affect the initiation of treatment and health care seems to differ not only among FS but also among prisons within the FS [35, 42, 43]. The differences regarding treatment of diseases and OST in prisons might reflect the decentralized federal system in Germany, in which the states may pursue different approaches with respect to the management of medical care [5, 6, 39].

TB treatment

Our data suggests intensive and continued tuberculosis treatments as well as chemoprevention in prisons of all participating FS except Saarland, where no TB medicine supply was observed. The treatment of resistant, complicated or severe TB was carried out in the FS Bavaria, Berlin and Thuringia. The federal city-states Berlin, Bremen and Hamburg showed high treatment prevalences for all TB substances, which implies largely initiated and continued TB treatment in those penal institutions. In Mecklenburg-Western Pomerania, Saarland and Schleswig-Holstein TB treatment was not initiated since these FS were not supplied with E and Z. However, Mecklenburg-Western Pomerania, Lower-Saxony, Saxony-Anhalt and Schleswig-Holstein showed high adTP of H and R which suggest mostly continued TB treatment and chemoprevention. In addition, Thuringia showed solely high H adTP, which might also indicate chemoprevention. A further indication of H is the treatment of R-resistant TB. However, since the proportion of corresponding E and Z is too low in the respective FS this may play only a marginal role [26].

Further, we observed a ratio of the marker substances for the intensive and continuation phase that might indicate incomplete standard six-month regimen in most FS. However, since imprisonment can begin or end during the course of a treatment, our observation period did not necessarily capture the entire treatment time.

In all penal institutions in Berlin, each newly incarcerated person is screened for TB by chest x-ray [24]. This active case-finding when entering prison can be equated with the prevalence of TB at the time of imprisonment [24]. Bös and Hauer found a TB prevalence of 0.11% through active case-finding by chest x-ray examinations in 2007–2010 in Berlin's penal institutions and 0.21% in 1996–1998 [24, 44]. Our work found an adTP in Berlin of 0.08% and 0.10% for the marker substances E and Z, respectively. Comparing the most recent TB prevalence seen in Berlin's penal institutions to the adTP from our analysis, treatment rates for TB were at least in Berlin consistent with the expected TB prevalence. The most important reason for not treating a prisoner in the study by Bös et al. was a too short duration of imprisonment [24]. We found an almost equal distribution of the adTP for H and R possibly explained by the active case-finding in Berlin with no need for chemoprevention.

Treatment of Multidrug-Resistant-TB and of complicated or severe TB were each observed in only two FS, Berlin and Bavaria and Thuringia and Bavaria, respectively. This was possibly due to a transfer of patients to prison hospitals with necessary existing technical and logistical conditions.

The large range of the provision of drugs for TB treatment among the FS could be explained by co-operations between FS. Especially the co-operation of Saarland with Bavaria and North Rhine-Westphalia might be the reason why there was no TB treatments at all supplied to prisons in Saarland. According to this arrangement Saarland transferred TB infected male prisoners to Bavaria and TB infected female prisoners to North Rhine-Westphalia for treatment. Also Thuringia had a co-operation with Bavaria and transferred TB infected prisoners to Bavaria. However, TB treatments were still carried out in Thuringia with H, E and Rfb, and the latter is indicated for HIV-TB-coinfected patients. We speculate the reason why TB treatments were still carried out in Thuringia despite existing co-operations could be overcrowding or other factors that would need further investigation.

HIV treatment

HIV treatments were carried out in prisons of all participating FS, with highest treatment prevalences found in the federal city-states Bremen, Hamburg and Berlin. The higher HIV adTP compared to the HCV adTP is remarkable, especially considering that studies found a much lower HIV prevalence compared to the HCV prevalence among prisoners. Radun et al. found an HIV antibody prevalence of 0.7% [3]. Schulte et al. came to an HIV prevalence of 1.2%. In this study, 147 prisoners were treated against HIV per year corresponding to 1.0% of all represented prisoners and to 89% of the infected prisoners [5]. In a study by Reimer et al., 300 prisoners were treated corresponding to about 1.0% of the represented prisoners and to about 94% of the infected prisoners [39]. Our results are in accordance with these previous studies, and the treatment prevalence of 0.39% for HIV matches more or less the expected prevalence of infection. HIV treatment seems to be the only of the four investigated treatments that is offered to an adequate proportion of estimated infected prisoners.

The combination of the agents and drug classes suggest treatment according to treatment guidelines which recommend a combination of two NRTI with either a NNRTI, PI or INI for first line therapy. The proportion of NRTI DDD_{cum} to total NNRTI, PI and INI DDD_{cum} suggests standard regimen distribution. Additionally, within the drug classes the DDD_{cum} of the drugs correspond to a standard regimen. Substances differing from the standard therapy were rarely administered. This applies, for example, to the older NRTI substance didanosin and the nowadays less frequent PI substance fosamprenavir. On the other hand, newer substances were also prescribed rather infrequently, which could indicate a hesitation to apply them. This is clearly seen in rilpivirin in the substance group of the NNRTI. Furthermore, we found indication for continuation and switch of ART of previously treated prisoners. This can be seen through the delivery of etravirin in Bavaria, Hamburg and Saarland, which is indicated for the treatment in antiretroviral treatment-experienced patients.

HCV treatment

Our data suggest that HCV treatments were provided in prisons of all participating FS. Overall, during the observation period, only 0.12% of prisoners were treated per day with HCV antivirals. This HCV treatment prevalence appears to be too low considering that studies have shown HCV prevalences to be about 14% to 21% among prisoners [3, 5, 39]. In the comparison of the FS, Bremen showed the highest HCV treatment prevalence, followed by Saarland and Schleswig-Holstein. In the two other federal city-states Berlin and Hamburg very low HCV treatment prevalences were observed, which is not consistent with the high HIV treatment prevalence in both cities. The one third lower adTP in Berlin compared to the overall adTP was therefore surprising considering Berlin has the highest incidence of newly diagnosed HCV of all FS [45], and risk group populations are disproportionately present. We assume that the prevalence of HCV and the need of treatment among prisoners differ

from prison to prison depending on the proportion of prisoners from FS with higher HCV prevalence, the proportion of PWID among prisoners, as well as the proportion of prisoners originating from countries with high HCV prevalence. Also, intra- and extramural co-operations among FS may at least partially explain the different treatment prevalences [46]. Although studies found a much higher HCV prevalence than HIV prevalence among prisoners [3, 5, 39] the amount of HCV treatment per prisoner is much lower than of HIV treatment.

Furthermore, the observed HCV treatment prevalence in view of the high HCV antibody prevalence of 20.6%, 14.3% and 15.0% found among prisoners in surveys is much too low [3, 5, 39]. These studies in German prisons found low HCV treatment rates and support our findings, only 111 (0.8% of the represented prisoners) and 400 (1.4% of the represented prisoners) prisoners were treated per year [5, 39]. According to Schulte et al., the main exclusion criteria for HCV treatment were short duration of imprisonment and drug abuse [5]. Also in comparison to the prevalence of injecting drug use (IDU) by Radun et al. (29.7%) and Schulte et al. (21.9%), the HCV adTP of 0.12% appeared to be too low considering that studies have shown HCV antibody prevalences of 57.6% among PWID [3, 5, 27]. Furthermore according to current guidelines, IDU is no contraindication for HCV therapy [27].

At the time of the analysis, HCV was treated in particular with a dual combination of PEG-IFN and RBV according to the respective guidelines at that time. There was also the option of a triple therapy with one of the two protease inhibitors BOC or TVR in combination with PEG-IFN and RBV. However, this treatment was cost extensive and rich in side effects and assumedly therefore played virtually no role for the HCV treatment in prisons. Triple therapies containing BOC or TVR accounted for only 7.8% of all HCV treatments. Sligthly more triple therapies were observed in Berlin and about two times more in Bremen, Lower Saxony and Saxony. In 2013, new promising direct-acting antivirals (DAAs) against HCV had already been announced. It is possible that the low treatment numbers are partially related to the awaiting of upcoming treatment options as an analysis of drug prescription data of the general German population also suggests [47]. Furthermore, due to the relative ineffectiveness and often serious side effects of interferon-based treatment, it seems plausible that prisoners are even less likely to wish to undergo debilitating treatment than non-prisoners. However, it is unknown to what extent costly DAA regimens have been prescribed since 2014 in the prison setting. An investigation of that would be a valuable follow-up assessment of the extent and quality of medical treatment in German prisons.

OST

We found a large range of the OST adTP between 0% in Saarland and 7.9% in Bremen. Thus, in some FS OST seems to be provided to a high proportion of prisoners, indicating a more liberal and harm-reduction-led politic. In the northern FS more prisoners had access to OST compared to Saarland and Bavaria and the eastern FS [46]. None of the prisons in Saarland and only seven penal institutions in Bavaria were supplied with OST medicines. The amount of OST doses suggests therapy in the northern FS and an abstinence and denial approach in Saarland, Bavaria and the eastern FS. This imbalance and therapy slope among the FS was already described by Keppler et al. [33, 46].

The low number of OST-supplied penal institutions in Bavaria is remarkable. Although OST needs no special medical tools or rooms and is simple to carry out only 7 of the 36 prisons were supplied with OST substances in Bavaria, corresponding to an OST adTP of 0.06%. Due to this low OST adTP, we assume a practice of denial or withdrawal rather than substitution treatments offered to prisoners in Bavaria [48]. The number of 133 DDD_d OST we found in Berlin correlates well with the number of 154 and 120 OST reported for Berlin prisons by Keppler in Lehmann et al. [46] and by Jakob et al. [35]. According to this, 3.6% of the prisoners in Berlin received OST compared to 3.2% in our study [46]. Schulte et al. accounted for 1,137 OST per year altogether, which corresponds to 8.0% of the represented prisoners and to 37% of the PWID in prison [5]. In Reimer's work, 320 long time opioid substitutions correspond to about 1.1% of the represented prisoners [39]. The overall OST adTP of 2.18% we found in our study approximately matches the OST treatment prevalence of Schulte et al. and Reimer. However, given the IDU prevalence of 29.7% and 21.9% among prisoners found in other studies [3, 5], even in the FS with a comparably high OST prevalence it can be concluded that only a minority of prisoners in need receive OST. Reporting on the prevalence of opioid dependence among people in prison was recently implemented in Germany, but the data is not yet published. It might be assumed that IDU mostly consists of opioid consumption. It is possible that some people coming into prison want to use the opportunity to be treated and to stop injecting but that others might prefer a cold withdrawal or do not want to reveal their addiction to avoid stigmatization or disadvantages concerning their prison conditions. Nonetheless our data show a need for scaling up OST, at least in some of the FS.

About 25% of the male and 50% of the female prisoners in Germany are PWID [33]. OST provided during incarceration reduces the level of IDU in prison and thus the possibility of HIV and HCV transmission via unsafe use [49]. OST as an approved effective therapy functions

well in a prison setting, e.g. supervised application, regularity of intake and structured daily life [33]. OST, particularly in combination with other harm-reduction strategies, is an evidence-based measure of HIV and HCV prevention [16, 50, 51]. In addition, people who receive OST often show an increased compliance regarding antiviral and antiretroviral treatment [52, 53]. For the above mentioned reasons and its protective effects, it is incomprehensible that OST is not offered in every prison. According to information provided by several prison doctors a certain proportion of PWID and thus, people in potential need of OST, are among every prison population, and no distribution of PWID to special prisons takes place. Further, this would not explain the high range of OST among the FS, suggesting an abstinence-oriented and denial approach in some FS.

IDU in prison is often unsafe due to the unavailability of sterile materials and is therefore one of the main transmission routes and major risks for HCV. Studies have shown an HCV antibody prevalence of 57.6% among PWID [3] therefore, the HCV adTP of 0.12% appeared to be too low compared to the OST adTP of 2.18%. Studies revealed that OST access depended mainly on substitution treatment before imprisonment, short duration of imprisonment and co-morbidity such as infectious diseases [5, 42].

Although OST guidelines exist for Germany [54], this work shows that these guidelines are not consistently applied, and that intramural OST highly differs among the FS and prisons. This might be due to the lack of nationwide OST guidelines for prisons [35]. However, in the absence of prison-specific guidelines the existing national OST guidelines should be applied to prisoners as well.

Limitations

The following limitations have to be considered in the interpretation of the data.

The evaluation of pharmacy delivery data allows no statement about which and how many medicines actually reached the individual patient. This can potentially lead to an overestimation of the calculated DDD for all evaluated drugs because they can be ordered in advance. On the other hand, emergency or ad hoc-orders are taken over by local pharmacies not included in our analysis, leading to a potential underestimation of the data and the corresponding treatments. However, according to a prison-supplying pharmacy, emergency orders amount to less than 2% [55]. Furthermore, one drug package might be used for several patients. Usually, the pills are packaged according to the prescription per patient or per patient and day [56]. We tried to avoid a bias by calculating the treatment prevalence per day. Tablets are divided only in particular cases. However, this procedure can differ from prison to prison. In addition, there are differences in the treatment management and the supply of medication in case of transfers of prisoners. In some cases, medicines are completely provided by the previously responsible prison. In other cases, after the transfer to another prison, the medicines are provided by the new prison [56].

The treatment success and failure, including side effects and drug interactions, remain unknown. We had no knowledge of the treatment duration. Therefore we calculated the average treatment prevalence as point prevalence in percent at each single day of the whole study period. For OST we did not consider initial dosage or gradual reduction of OST, but assumed a steady dosage, so we might have underestimated the number of persons under OST medication.

Because of the missing pharmacy data of one sick ward in a prison in Mecklenburg-Western Pomerania with five beds and one correctional hospital in Lower Saxony with 52 beds, the data of Mecklenburg-Western Pomerania and Lower Saxony are not complete. Therefore the DDD and adTP in these FS might be underestimated.

Several co-operations exist among the FS limiting the representativeness of the data for the respective FS. For example, Saarland had a contract to transfer ill prisoners to Rhineland-Palatinate [36]. Schleswig-Holstein had a transfer co-operation with Hamburg [37]. Thuringia had co-operations with Saxony, Saxony-Anhalt and Hessen to transfer ill prisoners [38]. Therefore the DDD and adTP of Saarland, Schleswig-Holstein and Thuringia are potentially underestimated and of Hamburg, Saxony and Saxony-Anhalt are potentially overestimated.

A further limitation is the different temporal units of the pharmacy delivery data on the one hand (per quarter of a year) and the number of the prisoners on the other hand (four calendar months). The actual duration of imprisonment as well as the information on releases such as the day of the release and the number of released prisoners cannot be derived from the available data and remain unknown. Therefore we chose to account the DDD for each day in the study period.

Moreover, this paper describes merely the proportion of treated persons among all prisoners and not among infected prisoners. To evaluate our treatment prevalence, we compared it with the prevalence seen in previous studies.

Conclusions

This work is the first attempt to describe and assess the medical care of TB, blood-borne and sexually transmitted infections and OST in prison. The study indicates that treatment of TB, HCV, HIV and opioid dependence is carried out in German penal institutions, and that guideline-recommended substances and standard treatments are used. However, a high variation of treatment per prison

population was observed among the FS and among the respective diseases, which is not fully explained by the described transfer co-operations. Providing treatment of chronic infections and OST to prisoners seems to be dependent on structural and individual factors, e.g. the prison's medical service structure, the political attitude and the allocation of financial budget to medical treatment in the respective prison and in the FS. The WHO recommendations and the UN's Mandela Rules maintain that prisoner health care should be consistent with the community standards of care, and under the direction of the ministry of health [57]. According to our findings, prison health care and policy in Germany is not fully consistent with this, especially with regard to treatment of HCV and OST. Treatment rates for TB were consistent with the expected TB prevalence, at least in Berlin. Treatment for HIV seems to be the one that is offered to a more or less adequate proportion of estimated infected prisoners in the FS. In the view of the expected high HCV prevalence among prison populations and in comparison to HIV and opioid dependence treatment prevalence, the HCV treatment prevalence we observed was too low. HCV treatment with DAAs has improved remarkably since the study period and will hopefully have an impact on the treatment prevalence in prisons despite high costs. Despite a varying proportion of PWID among prisoners and limitations due to a purely secondary data analysis, the large differences among the FS regarding all infection treatments and OST point to inconsistent treatment practices although nationwide extramural treatment guidelines for Germany exist. It is alarming that some FS seem to provide OST at a very low level. However, in some FS our data suggest that a high proportion of prisoners is covered with OST.

Despite its challenges, the prison setting is an opportunity for prevention and treatment of TB, HIV, HCV and OST [18] which could be carried out at a greater extent and more consistently. The regulated environment offers good requirements for e.g. distribution of sterile injection utensils, supervised application, regularity of intake and the opportunity for restructuring of daily life. Prisons therefore provide both risks for the spread of diseases but also many opportunities for prevention of these infections [17]. Continuous analyses for longer periods are necessary in order to make further statements regarding the health care situation in German prisons. A monitoring and reporting system of infectious diseases among prisoners would help to ensure equal access to treatment and to harmonize strategies among FS. Finally, correctional facilities should consistently implement prevention and harm-reduction measures such as needle-exchange and condom distribution programs to avoid further spread of diseases [30].

Abbreviations

3TC: Lamivudine; adTP: Average daily treatment prevalence; ART: Antiretroviral therapy; ATC: Anatomical Therapeutic Chemical; BOC: Boceprevir; DAA: Direct-acting antiviral; DDD: Defined daily dose(s); DDD_{cum}: Cumulative number of DDD; DDD_d: Average daily number of DDD; E: Ethambutol; EI: Entry inhibitor; FS: Federal state(s); FTC: Emtricitabine; H: Isoniazid; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IDU: Intravenous drug use; INI: Integrase inhibitor; MDR-TB: Multidrug-resistant-TB; MoJ: Ministry of Justice; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside reverse transcriptase inhibitor; OST: Opioid substitution treatment; PEG-IFN α-2a: Peginterferon α-2a; PEG-IFN α-2b: Peginterferon α-2b; PEG-IFN: Peginterferon; PI: Protease inhibitor; Pto: Protionamide; PWID: People who inject drugs; PZN: Central pharmaceutical number; R: Rifampicin; RBV: Ribavirin; Rfb: Rifabutin; SGB: Social Act; SHI: Statutory health insurance; StVollzG: Prison Act; TB: Tuberculosis; TCM: Thiacytidine medication; Trd: Terizidone; TVR: Telaprevir; Z: Pyrazinamid

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Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].
The original datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JM contributed to the conception of the study and study design, managed the data collection, performed the data analysis, interpreted the data, and drafted the manuscript. DS supported JM in data analysis, interpretation and drafted the manuscript. CK devised the estimation approach, performed the data analysis and interpretation of the data and was responsible for database management. ML contributed to the conception of the study, supported the interpretation of the results, and revised the manuscript. VB was responsible for the study design and revised the manuscript. RZ was responsible for the conception of the study and the study design, managed the data use, and contributed to the interpretation of the results and the writing of the manuscript. All authors participated in the critical discussion of the results, and all read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

ML was involved in the procurement of medicines from pharmacies in the context of his duties. The other authors, JM, DS, CK, VB and RZ declare that they have no competing interests.

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Everything counts - a method to determine viral suppression among people living with HIV using longitudinal data for the HIV care continuum - results of two large, German, multi-center real-life cohort studies over 20 years (1999–2018)

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Abstract

Background: The aim of this study was to develop a standardized method to reconstruct persons' individual viral load (VL) courses to determine viral suppression and duration of viremia for the HIV care continuum in Germany using longitudinal cohort data.

Methods: We analyzed data from two large, multi-center German cohort studies under the direction of the Robert Koch Institute. We included data from 1999 to 2018 of all diagnosed people and of people who initiated antiretroviral treatment (ART). We developed a model generating virtual VL values and an individual VL course corresponding to real VL measurements with a maximum distance of 180 days, considering ART status and VL dynamics. If the distance between VL measurements was > 180 days, the time between was defined as gap time. Additionally, we considered blips, which we defined as a single detectable VL < 1000 copies/ml within 180 days.

Results: A total of 22,120 people (164,691 person-years, PY) after ART initiation were included in the analyses. The proportion of people with viral suppression (VL < 50 copies/ml) increased from 34% in 1999 to 93% in 2018. The proportion of people with VL < 200 copies/ml increased from 47% in 1999 to 96% in 2018. The proportion of people with viremia > 1000 copies/ml decreased from 37% in 1999 to 3% in 2018. The proportion of people with gap time fluctuated and ranged between 18 and 28%. An analysis of the first VL after gap time showed that 90% showed viral suppression, 5% VL between 50- < 1000 copies/ml and 5% VL > 1000 copies/ml.

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Conclusion: We provide a method for estimating viral suppression and duration of viremia using longitudinal VL data. We observed a continuous and remarkable increase of viral suppression. Furthermore, a notable proportion of those with viremia showed low-level viremia and were therefore unlikely to transmit HIV. Individual health risks and HIV drug resistance among those with low-level viremia are problematic, and viral suppression remains the goal. In 2018, 93 and 96% of people after ART initiation showed VL < 50 copies/ml and VL < 200 copies/ml, respectively. Therefore, using the threshold of VL < 200 copies/ml, Germany reached the UNAIDS 95 target of viral suppression since 2017.

Keywords: Viral suppression, HIV care continuum, Treatment success, HIV cascade

Background

The Joint United Nations Programme on HIV/AIDS (UNAIDS) targets to accelerate the fight against HIV and to end the AIDS epidemic by 2030 aim to increase the proportion of people living with HIV (PLHIV) knowing their diagnosis, of people with diagnosed HIV infection receiving antiretroviral treatment (ART) and of people receiving ART being virally suppressed to 90% by 2020 and to 95% by 2030 [1–3].

It is estimated that, in 2018, 37.9 million people were living with HIV worldwide, and 23.3 million people were accessing ART. Globally, in 2018, 79% of PLHIV knew their status. Among people who knew their HIV status, 78% were accessing treatment. Among those people, 86% were virally suppressed. This statistic is a considerable increase in recent years compared to 2010, when only 24% of all people living with HIV were accessing treatment. New HIV infections have declined by approximately 16% since 2010 to 1.7 million new infections in 2018. Since 2010, the number of people who have died from AIDS-related illnesses worldwide has decreased by 33% to 770,000 in 2018 [4]. However, there are large differences across regions and countries regarding the HIV care continuum, with less than 50% of all people living with HIV accessing ART in Eastern Europe, central Asia, the Middle East and North Africa, and new HIV infections and AIDS-related deaths are rising in these regions [4, 5]. Additionally, for the first time since 2000, less funding was available for AIDS response in low- and middle-income countries -- almost US$ 1 billion less than in 2017 [4]. In addition, challenges with data quality, appropriate data sources and the absence of standardized definitions could hamper comparisons across countries [6].

In Germany, an increasing number of PLHIV are receiving ART [7, 8], and it is estimated that, at the end of 2018, of all PLHIV in Germany, 88% were diagnosed, and 93% of diagnosed were under ART [8]. The Robert Koch Institute (RKI) reports numbers for the German HIV care continuum to national and international stakeholders using the different available data sources. However, there is no national database containing follow-up clinical or treatment data on PLHIV. HIV surveillance, in addition to reports on diagnosed HIV/AIDS cases, requires additional surveillance tools, which are implemented with longitudinal clinical cohort studies at the RKI [9, 10]. In a former study, the RKI working group developed a method to determine the number of PLHIV receiving ART in Germany using ART prescription data and national clinical cohort data from the Clinical Surveillance of HIV Disease (ClinSurv HIV) [7]. This method, which was selected for a compendium of good HIV practices in the WHO European Region [11], has been continuously used for the second stage of the German HIV care continuum in the annual national HIV estimates of the RKI [8]. However, consistent methods for all stages of a standardized HIV continuum of care for Germany, especially for the numbers and proportions of people and their person-time with viral suppression, have not yet been published.

The main goal of ART is sustained viral suppression, which subsequently leads to several benefits. These benefits include immune recovery and decreased immune activation [12], prevention of HIV-related morbidity and mortality [13–15], reduction in non-AIDS diseases, such as cancer or cardiovascular disease [16], prevention of HIV transmission [17, 18] and avoiding the development of HIV drug resistance [19]. In Germany, effective ART evidenced by viral suppression is required by reimbursement regulations for health insurance. Hence, it is usually monitored every three months by viral load (VL) testing. Longer periods without VL controls are critical because, in cases of viral failure, immediate action would be required to avoid evolution of viral resistance or clinical progression of HIV disease.

Viral suppression is commonly defined as a VL test result below the detection limit or a certain threshold at the most recent VL test in one year [20–22]. However, such an approach does not address the dynamics of VL progression over time and could lead to biased results when the last VL is not representative of the respective year. We therefore aimed to present an alternative approach using longitudinal data, including all available VL measurements and persons' individual ART histories.

With this study, we aimed to:

a) develop a model to determine the durations and proportions of viral suppression and viremia among PLHIV to be used for the HIV care continuum;
b) determine the numbers and proportions of PLHIV and of person-time with viral suppression and viremia between 1999 and 2018 using national clinical cohort data;
c) compare the results of the conventional method with those of our longitudinal model; and
d) evaluate the UNAIDS target of viral suppression for PLHIV in Germany.

Methods

HIV surveillance in Germany

National HIV/AIDS surveillance in Germany is regulated by the national Protection Against Infection Act and is based on mandatory reports of newly diagnosed cases of HIV infection and voluntary reporting of AIDS cases to the RKI, which is the federal institute of public health under the umbrella of the German Ministry of Health [23]. In addition, continuous monitoring of the course of HIV infection, including HIV treatment, is performed in HIV cohort studies at the RKI.

Study population and data

We analyzed data from two large German cohort studies, the Clinical Surveillance of HIV Disease (ClinSurv HIV) and the HIV-1 Seroconverter cohort; both studies are under the direction of the RKI. For this analysis, cohort data between 1999 and 2018 of people with at least two VL measurements were included.

The *ClinSurv HIV cohort* is the base for a nationwide, prospective, multi-center, open, long-term observational cohort study for the clinical surveillance of HIV in Germany. Data on demographics, detailed information on the initiation, composition and discontinuation of individuals' daily ART, laboratory parameters and clinical events are collected biannually in a standardized format. ClinSurv HIV is the largest available nationwide source of PLHIV in Germany. The study design is described in detail elsewhere [9].

The *HIV-1 Seroconverter cohort* is the basis for a nationwide, multi-center, open, long-term observational cohort study of HIV-1-positive people with a known or reliably estimated date of HIV-1 seroconversion. Sociodemographic and clinical data from each participant were collected at the time of enrollment and at yearly follow-ups. Detailed descriptions of the study methods can be found elsewhere [10, 24, 25].

Developing a model and method to determine viral suppression and viremia

We developed a model to reconstruct the individual VL course of people to estimate the duration and proportion of viral suppression and viremia using longitudinal data, including all available VL measurements, taking into account ART status and VL dynamics. In this model, we looked for real VL measurements with a maximum distance of 180 days. We then connected the measurements linearly and generated virtual VL values for every 10-day interval along the line. The 10-day interval was chosen because it offers sufficient accuracy with manageable data volumes. Additionally, we took into account the ART status of the people when we connected the real VL measurements. For example, if a person was coming from an ART naïve time into therapy, we did not connect the VL measurements linearly, assuming that the VL decrease started with ART initiation; therefore, a virtual VL value was generated according to the ART status, and a horizontal line was drawn from the higher VL measurement to the ART start, and then the line decreased to the lower VL measurement. Similarly, if a person's viral load increased and an interruption were documented in the ART history, we assumed that the increase did not necessarily occur from the previous VL measurement but rather stemmed from the ART interruption (see Fig. 1). VL measurements without a consecutive VL measurement within 180 days were assigned a lifetime of 30 days prior to and after the VL measurement. The remaining time not covered by our model was defined as a longer period without VL control or so-called *gap time*. Additionally, we considered blips, which we defined as a single detectable VL < 1000 copies/ml within 180 days with a subsequent undetectable VL.

VL was a priori stratified into the following groups: VL < 50 copies/ml, VL 50- < 200 copies/ml, VL 200- < 500 copies/ml, VL 500- < 1000 copies/ml, VL 1000- < 10,000 copies/ml, VL 10,000- < 100,000 copies/ml, VL 100,000- < 1000,000 copies/ml, and VL ≥1000,000 copies/ml.

We analyzed the proportion of person-time with viral suppression and viremia over time in the total study population, indicating that, at different points in time, different people can have the same proportion of person-time and viral suppression. We also report the number and proportion of people with viral suppression and viremia, the interquartile range (IQR) and median person-time with viral suppression and viremia, and the IQR and median proportion of viral suppression and viremia to the observation time on an individual level.

Furthermore, we analyzed the time with viral suppression and viremia on an individual level, such as the proportion of people with continuous viral suppression over a period of time.

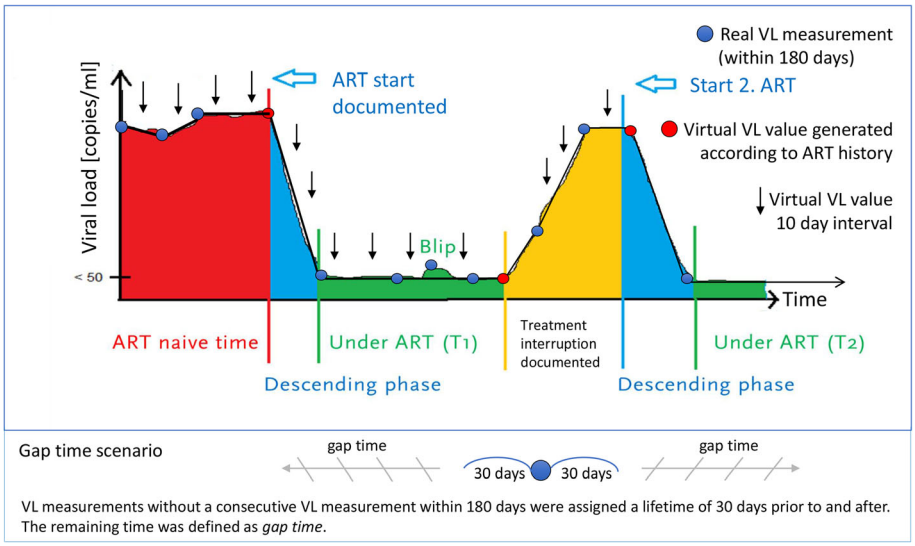


Fig. 1 Model to determine viral suppression and viremia using longitudinal data on VL and ART history

Viral suppression and viremia from 1999 to 2018

People observed between 1999 and 2018 with at least two VLs were included. We determined viral suppression and viremia over time: (i) among all PLHIV in the cohort studies regardless of their ART status, including ART-naïve and treated person-time; and (ii) among PLHIV after ART initiation regardless of whether they were continuously under ART, including person-time with documented interruptions or gaps in treatment. Viral suppression was defined as VL < 50 copies/ml according to the German-Austrian ART guidelines [26]. When evaluating the UNAIDS target of viral suppression for PLHIV, we also report the proportion of person-time with VL < 200 copies/ml for comparability. This threshold of < 200 copies/ml for population-level monitoring is consistent with the guidelines and recommendations of several institutions, such as the US Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control [20, 27].

We determined viral suppression and viremia over time among PLHIV after ART initiation with the conventional method, using the most recent VL in each year, and we compared the results with those of our longitudinal model.

To further investigate potential misclassification using the conventional method with a single VL during one year, we determined the number and proportion of PLHIV with continuous viral suppression over a year-long observation period on an individual level and compared it with the results of the conventional method using the most recent VL in one year.

The results on the proportion of people and person-time with viral suppression and viremia in the respective year are reported excluding gap time. The proportion of people with gap time is reported separately. Furthermore, we performed separate sensitivity analyses in the group of people with gap time to assess their VL status.

Analysis of people with longer periods without VL control (gap time)

We report the proportion of person-time with gap time on the total observation time in the study population, the number and proportion of people with gap time, the IQR and median gap time, and the IQR and median proportion of gap time to the observation time on an individual level.

In people with gap time, the last VL measurement before and the first VL measurement after having gap time were analyzed to approximate the VL status of the people during gap time. This approach is in accordance with methods used in other studies [28, 29]. The last and first VL before and after gap time were analyzed for the recent study period from 2015 to 2018. We determined the overall proportion of people with viral suppression at the last and first VL before and after gap time. Furthermore, the congruence of the last and first VL on an individual level was determined. For the analysis of the congruence between the last and first VL before and after gap time, the proportions of people with viral suppression at both VL measurements, both VL measurements 50- < 1000 copies/ml, both VL measurements > 1000 copies/ml, the proportion of people with a VL increase (last VL < first VL) and the proportion of people with a VL decrease (last VL > first VL) were determined. Among those with detectable VL, we also report the IQR and median VL in each group.

To approximate the impact of gap time on the overall viral suppression in people who initiated ART, we

calculated the resulting proportion of viral suppression after considering for viremic gap time. Therefore, we determined the proportion of viremia at the first VL measurement after gap time, determined the proportion of gap time among all people who initiated ART, then determined the resulting proportion of viremic gap time and viral suppression among all people who initiated ART.

Analysis of antiretroviral treatment regimens over time

The ART regimens were separated into mainly used regimens according to the German-Austrian ART guidelines [26], consisting of nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI). Further ART was classified into triple-class regimens, NRTI only, NRTI-sparing regimens, attachment inhibitor (AI) containing, salvage regimens (3 drug classes and AI or fusion inhibitor (FI) or 4 drug classes), study medication, ART interruption, not fully active ART and ART gap.

We created our analytic sample in SQL Server Management Studio software, version 17.4 (Microsoft Corporation Redmond, WA, USA), and conducted the statistical analysis in Stata software, version 15.1 (StataCorp., College Station, TX, USA). Figures were created using Microsoft Excel and Microsoft Power Point 2019.

Results

Study population

A total of 24,569 people with at least two documented VLs from the ClinSurv HIV and the HIV-1 Seroconverter cohorts were enrolled and followed for a median of 5.9 years (IQR 2.4–11), totaling 171,990 person-years (PY). The total number of real VL measurements was 570,753, the median number of VL measurements per person was 18 (IQR 7–35), and VL monitoring occurred at a median frequency of every 91 days (IQR 64–112). With the model, 4,541,141 virtual VL values were generated. The real VL measurement and the virtual VL value occurred on the same date in 69,297 cases.

The majority of people, 88.4% ($N = 21,716$), were enrolled in the ClinSurv HIV cohort, 9.2% ($N = 2264$) were enrolled in the HIV-1 Seroconverter cohort, and 2.4% ($N = 589$) were enrolled in both cohort studies. Of the 24,569 people, 22,120 initiated ART, and 2449 were ART naïve at the end of observation. The characteristics of the study population are summarized in Table 1.

On an individual level, a total of 88% (21,584/24,569) achieved viral suppression at any time, and 12% (2985/24,569) never achieved viral suppression. Of all subjects, 89% (21,967/24,569) showed viremia at any time, and 82% (20,249/24,569) showed viremia with VL > 1000 copies/ml. The total median observation time was 2180 days (interquartile range (IQR) 860–4020). The median person-time with viral suppression among all people was 930 days (IQR 190–2140). The resulting individual proportion of person-time with viral suppression to the observation time had a median of 52% (IQR: 18–77). Excluding gap time, the proportion of person-time with viral suppression to the observation time had a median of 75% (IQR: 37–92). The median person-time with viremia with VL > 1000 copies/ml was 120 days (IQR 40–420). The individual proportion of person-time with viremia with VL ≥1000 copies/ml to the observation time had a median of 8% (IQR: 1.8–24). Excluding gap time, the proportion of viremia with VL ≥1000 copies/ml to the observation time had a median of 12% (IQR: 2.3–40).

Viral suppression and viremia from 1999 to 2018

Among all diagnosed PLHIV

Based on the longitudinal model, the proportion of person-time with viral suppression (VL < 50 copies/ml) of the 24,569 people increased over time from 22.2% in 1999 to 92.3% in 2018. The proportion of person-time with VL < 200 copies/ml increased from 31.3% in 1999 to 95.6% in 2018. VLs of 50- < 200 copies/ml, 200- < 500 copies/ml and 500- < 1000 copies/ml were observed in 9.1, 7.4 and 4.8% of the people in 1999, respectively, and in 3.3, 0.8 and 0.4% of the people in 2018, respectively. The proportion of people with viremia > 1000 copies/ml therefore decreased from 56.4% in 1999 to 3.1% in 2018 (see Fig. 2 and Table 2 for detailed results).

People who initiated ART

A total of 22,120 people were included in the analysis with a total follow-up time of 164,691 PY, a median observation time of 6.5 years (IQR 2.8–11.5) and a median time under ART of 5.5 years (IQR 2.3–9.9). The total number of real VL measurements was 490,352, the median number of VL measurements per person was 17 (IQR 8–32), and VL monitoring occurred at a median frequency of every 91 days (IQR 70–112). With the model, 3,974,309 virtual VL values were generated. The real VL measurements and the virtual VL values occurred on the same date in 52,205 cases.

At 88.9% ($N = 19,663$), the majority were enrolled in ClinSurv HIV, 8.7% ($N = 1936$) were enrolled in the HIV-1 Seroconverter cohort, and 2.4% ($N = 521$) were enrolled in both cohort studies. The characteristics of the study population who ever initiated ART are summarized in Table 1.

On an individual level, a total of 94% (20,849/22,120) achieved viral suppression after ART initiation, and 6% (1271/22,120) never achieved viral suppression. Of all, 86% (19,076/22,120) showed viremia at any time, and

Table 1 Characteristics of the study population (1999-2018)

	Patients	Study population (all diagnosed PLHIV)		People who initiated ART	
		24,569	(100%)	22,120	(100%)
Observation time	Total PY	171,990		164,691	
Sex	Male	19,794	(81%)	17,794	(80%)
	Female	4775	(19%)	4326	(20%)
HIV transmission risk	Men who have sex with men (MSM)	13,006	(53%)	11,676	(53%)
	Heterosexual contacts	3227	(13%)	2954	(13%)
	High prevalence country	3200	(13%)	2958	(13%)
	People with injecting drug use	1612	(7%)	1411	(6%)
	Other	212	(1%)	203	(1%)
	Unknown	3312	(13%)	2918	(13%)
Region of origin	Germany	16,683	(68%)	15,065	(68%)
	Eastern Europe	682	(3%)	592	(3%)
	Central Europe	1129	(5%)	1021	(5%)
	Western Europe (excl. Germany)	949	(4%)	834	(4%)
	Africa	2998	(12%)	2749	(12%)
	Asia	686	(3%)	649	(3%)
	America	546	(2%)	491	(2%)
	Caribbean/Ozeania	107	(0%)	96	(0%)
	Unknown	789	(3%)	623	(3%)
Age at Enrolment (years)	Median (IQR)	37	(30-45)	37	(31-45)
Enrollment	1999–2001	3422	(14%)	3098	(14%)
	2002–2005	5454	(22%)	4834	(22%)
	2006–2009	5529	(23%)	4925	(22%)
	2010–2013	5343	(22%)	4819	(22%)
	2014–2018	4821	(20%)	4444	(20%)
Observation time (years)	Median (IQR)	5.9	(2.4-11)	6.5	(2.8-11.5)
Number of viral loads	Median (IQR)	18	(7-35)	17	(8-32)
Distance between viral loads (days)	Median (IQR)	91	(64–112)	91	(70–112)
Viral load baseline (copies/ml)	Median (IQR)	49,973	(9350–198,000)	55,544	(10,899–211,000)
CD4 cell count baseline (cells/μl)	Median (IQR)	349	(174–537)	328	(157–513)
Initiated ART	N (%)	22,120	(90%)		
ART start period	1999–2001			2416	(11%)
	2002–2005			3948	(18%)
	2006–2009			4833	(22%)
	2010–2013			5636	(25%)
	2014–2018			5287	(24%)
	not started ART			2449	(11%)
Age at ART start (years)	Median (IQR)			39	(32-46)
Time between enrollment and ART (days)	Mean (IQR)			321	(0–237)
Viral load ART start (copies/ml)	Median (IQR)			62,000	(12,300-212,604)
CD4 cell count ART start (cells/μl)	Median (IQR)			271	(133–429)
ART duration (years)	Median (IQR)			5.5	(2.3-9.9)

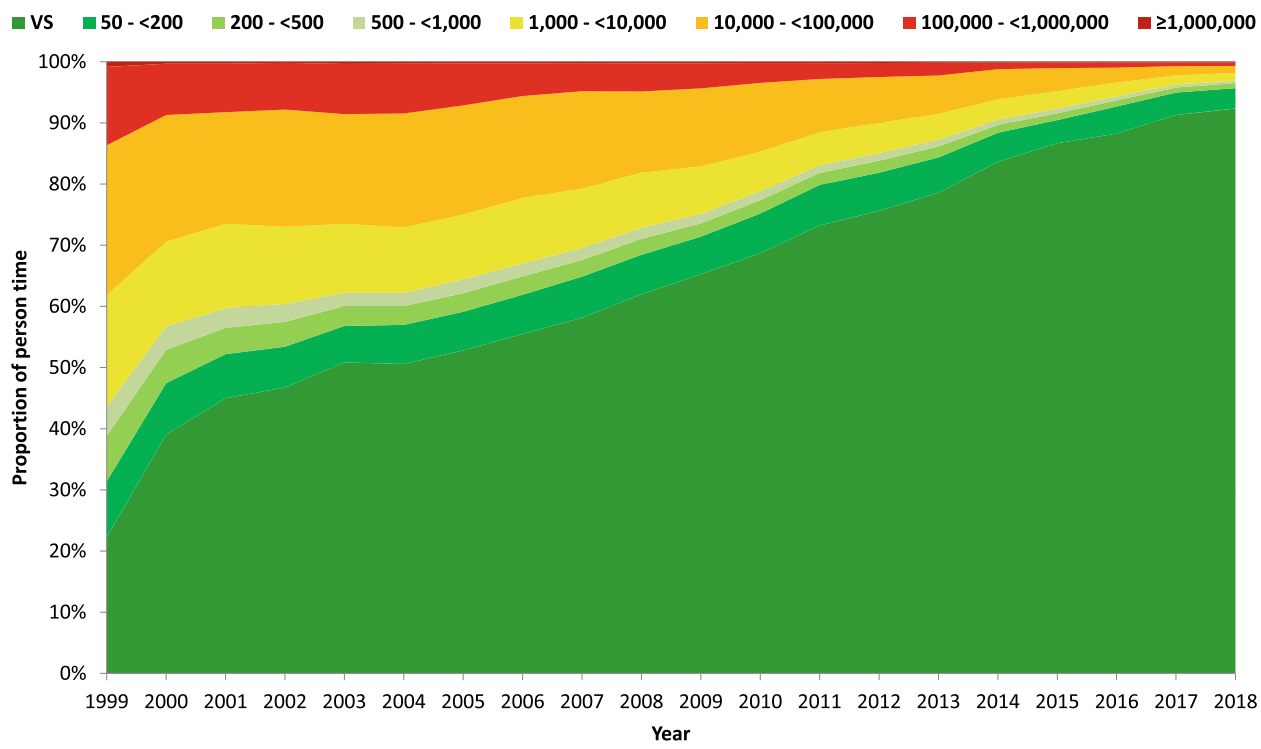


Fig. 2 Viral load levels of all diagnosed PLHIV in the study population from 1999 to 2018

77% (17,085/22,120) showed viremia with VL > 1000 copies/ml. The total median observation time was 2010 days (IQR 850–3620). The median person-time with viral suppression among all people was 1100 days (IQR 330–2310). The resulting individual proportion of person-time with viral suppression to the observation time had a median of 66% (IQR: 36–86). Excluding gap time, the proportion of person-time with viral suppression to the observation time had a median of 88% (IQR: 63–97). The median person-time with viremia with VL > 1000 copies/ml was 40 days (IQR 10–110). The individual proportion of person-time with viremia with VL ≥1000 copies/ml to the observation time had a median of 2.3% (IQR: 0.3–9). Excluding gap time, the proportion of viremia with VL ≥1000 copies/ml to the observation time had a median of 2.9% (IQR: 0.4–13).

Viral suppression and viremia from 1999 to 2018

Among PLHIV after ART initiation

Based on the longitudinal model, the proportion of person-time with viral suppression (VL < 50 copies/ml) of the 22,120 people who ever initiated any type of ART increased over time from 33.6% in 1999 to 93.0% in 2018. The proportion of person-time with VL < 200 copies/ml increased from 47.0% in 1999 to 96.3% in 2018. VLs of 50- < 200 copies/ml, 200- < 500 copies/ml and 500- < 1000 copies/ml were observed in 13.4, 10.5 and 5.2% of the people in 1999, respectively, and in 3.3, 0.8 and 0.3% of the people in 2018, respectively. The proportion of people with viremia > 1000 copies/ml therefore decreased from 37.3% in 1999 to 2.6% in 2018 (see Fig. 3 and Table 3a for detailed results).

Viral suppression and viremia from 1999 to 2018 using the most recent VL in each year

Among PLHIV after ART initiation

According to a conventional definition, viral suppression, as the last step of the HIV continuum of care, is defined as the number and percentage of people receiving medical care whose most recent HIV VL is suppressed. Following this definition and considering the last VL measurement in each year, the proportion of people with viral suppression among the 22,120 people who ever initiated ART and had a documented VL value increased over time from 51.7% in 1999 to 93.3% in 2018. The proportion of people with VL < 200 copies/ml increased from 61.1% in 1999 to 96.5% in 2018. VLs of 50- < 200 copies/ml, 200- < 500 copies/ml and 500- < 1000 copies/ml were observed in 9.4, 7.4 and 3.6% of the people in 1999, respectively, and in 3.2, 0.9 and 0.3% of the people in 2018, respectively. The proportion of people with viremia > 1000 copies/ml therefore decreased from 27.9% in 1999 to 2.3% in 2018 (see Table 3b for detailed results).

Table 2 Development of person-time with viral suppression and viremia among all diagnosed PLHIV in the cohorts, including ART-naïve and treated person-time between 1999 and 2018 based on our longitudinal model

All diagnosed people living with HIV								
Year	Viral suppression (< 50)	50 - < 200	200 - < 500	500 - < 1000	1000 - < 10,000	10,000 - < 100,000	100,000 - < 1.000000	> 1000,000
1999	22.2	9.1	7.4	4.8	18.2	24.5	12.8	0.8
2000	39.0	8.4	5.5	3.8	13.8	20.7	8.4	0.3
2001	45.0	7.2	4.3	3.2	13.8	18.2	7.9	0.3
2002	46.7	6.7	4.1	2.9	12.6	19.2	7.6	0.2
2003	50.8	6.0	3.2	2.2	11.3	17.9	8.2	0.4
2004	50.6	6.4	3.1	2.2	10.7	18.7	8.1	0.3
2005	52.8	6.3	3.0	2.3	10.6	17.9	6.9	0.3
2006	55.5	6.4	3.0	2.1	10.7	16.7	5.3	0.3
2007	58.1	6.7	2.7	2.0	9.7	15.9	4.5	0.3
2008	62.0	6.5	2.6	1.8	9.0	13.3	4.6	0.3
2009	65.3	6.2	2.2	1.6	7.7	12.8	4.1	0.3
2010	68.7	6.5	2.2	1.5	6.5	11.2	3.2	0.2
2011	73.2	6.6	2.0	1.3	5.4	8.7	2.6	0.2
2012	75.6	6.2	2.0	1.2	5.0	7.5	2.3	0.2
2013	78.6	5.8	1.8	1.1	4.2	6.3	2.1	0.2
2014	83.6	4.8	1.3	0.9	3.3	4.9	1.1	0.1
2015 [a]	86.7 [a]	3.8 [a]	1.1	0.8	2.8	3.8	0.9	0.1
2016	88.3	4.4	1.0	0.7	2.3	2.4	0.9	0.1
2017 [b]	91.3 [b]	3.7	0.8	0.5	1.5	1.5	0.6	0.1
2018	92.3	3.3	0.8	0.4	1.2	1.2	0.6	0.1

[a] The UNAIDS target of viral suppression with VL < 200 copies/ml has been met for all diagnosed PLHIV in the study population in Germany since 2015
[b] The UNAIDS target of viral suppression with VL < 50 copies/ml has been met for all diagnosed PLHIV in the study population in Germany since 2017

Continuous viral suppression over one year

A total of 11,837 people with 35,995 VL measurements were eligible for the analysis of continuous viral suppression over a one-year observation period on an individual level. In total, at the individual level, 88% (10,474/11,837) had no viral failure and showed continuous viral suppression with all VLs in 2018. The median number of VLs was 3 (IQR: 2–4), and 91% (10,792/11,837) had more than one VL. Categorizing those with 1 VL or more than 1 VL measurement, 81% (848/1045) and 89% (9626/10,792) showed continuous viral suppression, respectively. In comparison, using the last VL, 93% (11,044/11,837) showed viral suppression, which is 5% higher than the proportion with continuous viral suppression on the individual level. Using all of the available VL measurements, 93% (33,619/35,995) of the VL showed viral suppression.

Analysis of people with gap time (VL measurements > 180 days apart)

On an individual level of all 22,120 people who had ever initiated ART, 8023 (36%) had no gap time, and 14,097 (64%) had any gap time. The cumulative median gap time was 560 days (IQR: 260–1150), and the individual proportion of gap time to the observation time had a median of 27% (IQR: 12–47). The median number of gaps was 2 (IQR: 1–4), and the median gap time per gap was 223 days (IQR: 192–302).

A total of 8173 people with 15,892 VL measurements were eligible for the analysis of the last VL before and the first VL after gap time in the recent period from 2015 to 2018. Of all VL measurements, 90% (14,274/15,892) and 90% (14,293/15,892) showed viral suppression at last VL before and first VL after gap time, respectively. Furthermore, 4% (599/15,892) and 3% (531/15,892) had VL > 50- < 200 copies/ml, 1% (221/15,892) and 2% (227/15,892) had VL 200- < 1000 copies/ml, and 5% (798/15,892) and 5% (841/15,892) had VL ≥1000 copies/ml at the last VL before and the first VL after gap-time, respectively. Overall, among those with viremia, the median VL was 910 copies/ml (IQR: 104–25,700) and 1368 copies/ml (IQR: 118–31,853) for the last VL before and the first VL after gap-time, respectively.

On an individual level, of all last VLs before and first VLs after gap time, 86% were congruent with each other, with 84% showing viral suppression, 0.8% having VL 50-

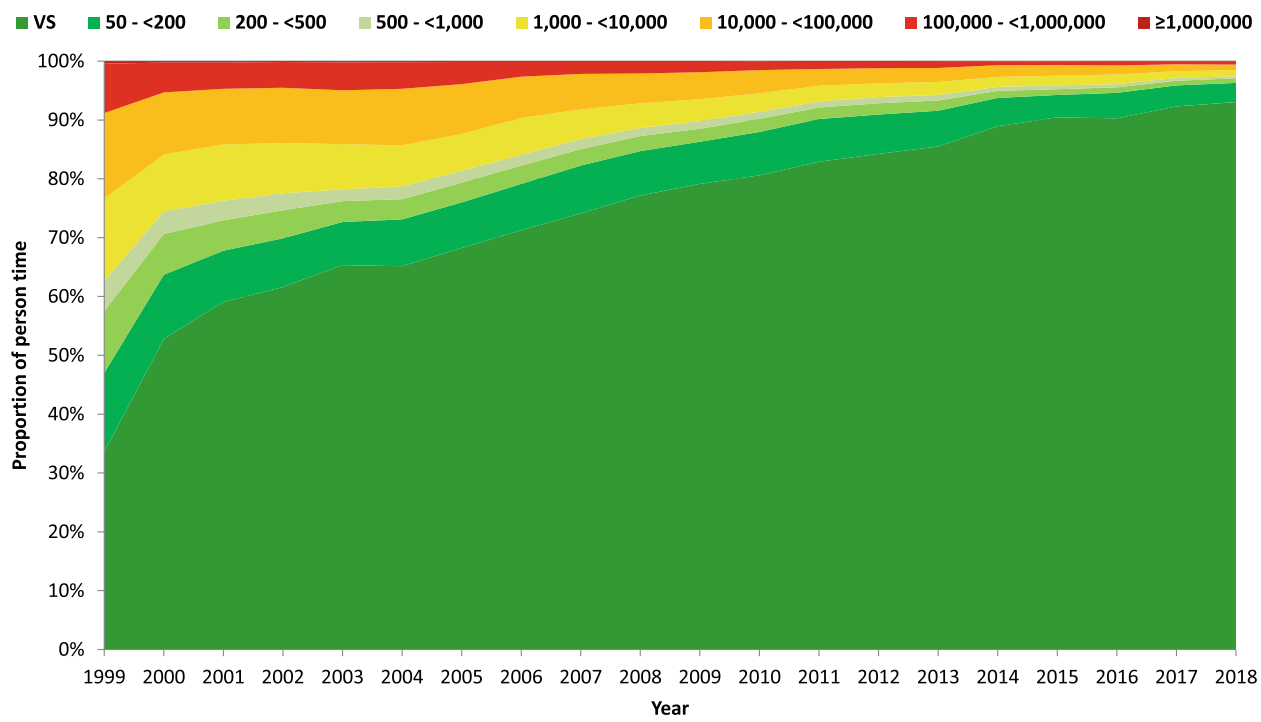


Fig. 3 Viral load levels of people who ever initiated any ART in the study population from 1999 to 2018

< 1000 copies/ml and 1.1% having VL ≥1000 copies/ml. A total of 14% were not congruent with another, with 7% having a VL increase and 7% with a VL decrease (Table 4).

To approximate the impact of gap time on the overall viral suppression in people who initiated ART, we calculated the resulting proportion of viral suppression after considering for viremic gap time. Figure 4 shows the proportion of viral suppression and viral load levels in people with gap time at their first VL measurement after gap time between 1999 and 2018. Additionally, it shows the proportion of gap time among all people who initiated ART, the proportion of viral suppression among all people who initiated ART and the resulting proportion of viral suppression among all people who initiated ART after considering for viremic gap time. The proportion of gap time was lowest in 1999 and 2018 at 18% and highest in 2003, 2005 and 2016 at 28%, and the mean and median gap time were both 24%. The proportion of viremic gap time ranged from approximately 12% between 1999 and 2005, then decreased constantly to 2% in 2018. The resulting proportion of viral suppression among all people who initiated ART after considering for viremic gap time increased from 21% in 1999 to 90% in 2018.

Analysis of antiretroviral treatment regimens over time

The exact composition of ART regimens in the cohort studies is shown in Fig. 5 and Table S1. Overall, NRTI/NNRTI regimens with 35% were most frequently used, followed by 32% NRTI/PI regimes and 16% NRTI/INSTI regimens. The remaining 17% were divided between less common or older regimens, and 5% had treatment interruptions. The composition of ART regimens in the cohort studies changed significantly over time. Between 1999 and 2014, NRTI/PI regimens were at approximately 35%, and this proportion decreased thereafter to 18% in 2018. NRTI/NNRTI regimens ranged from approximately 35 to 40% between 1999 and 2014 and then decreased to 25% in 2018. NRTI/INSTI regimens continuously increased after their market entry in 2006, reaching 3% in 2010 and 11% in 2013 and further increasing to 47% in 2018. In 1999, a proportion of 10% was NRTI-only regimens, and this proportion decreased from 2004 to 0.4% in 2018. NRTI sparing regimens continuously increased from 0.3% in 1999 to 4% in 2018. The proportion of not fully active ART was 6% in 1999 but continuously decreased over time to only 0.5% in 2018. Interruptions were highest in 2001 to 2006 at up to 13% and then decreased continuously from 2007 onward to 1% in 2018 (see Fig. 5 and Table S1).

Discussion

Summary

We developed a model to reconstruct the individual viral load course of people to estimate the durations and proportions of viral suppression and viremia using longitudinal clinical cohort data, including all available VL

Table 3 Development of person-time and PLHIV with viral suppression and viremia for PLHIV after ART initiation between 1999 and 2018, based on our longitudinal model (3a) and using the most recent VL in each year (3b)

People who ever initiated ART																		
Longitudinal model									Conventional method									
Year	Viral suppression (< 50)	50 - < 200	200 - < 500	500 - < 1000	1000 - < 10,000	10,000 - < 100,000	100,000 - < 1,000,000	> 1,000,000	Year	Viral suppression (< 50)	50 - < 200	200 - < 500	500 - < 1000	1000 - < 10,000	10,000 - < 100,000	100,000 - < 1,000,000	> 1,000,000	Difference in viral suppression between the methods
1999	33.6	13.4	10.5	5.2	14.0	14.5	8.4	0.4	1999	51.7	9.4	7.4	3.6	12.2	9.9	5.3	0.5	18.1
2000	52.8	10.9	6.9	3.9	9.7	10.5	5.1	0.2	2000	62.2	7.6	3.4	2.7	10.7	8.5	4.4	0.5	9.4
2001	59.1	8.7	5.2	3.3	9.5	9.5	4.4	0.3	2001	64.2	7.5	3.9	3.1	8.7	8.5	3.9	0.2	5.2
2002	61.6	8.3	4.8	2.9	8.6	9.4	4.4	0.2	2002	64.2	7.3	3.5	2.8	8.7	8.6	4.5	0.4	2.6
2003	65.3	7.3	3.5	2.0	7.7	9.1	4.7	0.2	2003	68.6	5.6	3.2	2.1	7.1	8.7	4.6	0.2	3.3
2004	65.2	7.9	3.5	2.2	7.0	9.6	4.5	0.2	2004	67.1	7.1	2.9	2.0	7.6	8.6	4.3	0.3	1.9
2005	68.2	7.7	3.4	2.0	6.3	8.4	3.8	0.1	2005	69.1	7.2	3.4	2.3	6.5	7.8	3.6	0.1	0.8
2006	71.3	7.9	3.1	1.8	6.2	7.0	2.5	0.2	2006	74.6	6.3	3.2	1.8	5.4	6.4	2.1	0.1	3.3
2007	74.1	8.1	2.8	1.7	5.1	6.1	2.0	0.1	2007	75.5	7.4	3.1	1.9	4.9	5.2	1.8	0.2	1.4
2008	77.2	7.6	2.6	1.4	4.2	5.0	2.0	0.1	2008	78.9	6.1	2.9	1.6	4.3	4.1	2.0	0.2	1.8
2009	79.1	7.2	2.2	1.3	3.7	4.6	1.7	0.1	2009	80.2	6.2	2.5	1.6	3.5	4.0	1.8	0.2	1.1
2010	80.6	7.4	2.2	1.2	3.1	4.0	1.4	0.1	2010	83.2	5.7	2.4	1.3	3.1	3.0	1.2	0.1	2.7
2011 [a]	82.9	7.3	1.9	1.1	2.6	2.8	1.2	0.1	2011	85.1	6.0	1.7	1.1	2.4	2.3	1.3	0.1	2.2
2012	84.3	6.7	1.9	1.0	2.4	2.6	1.0	0.1	2012	85.8	5.3	2.0	1.2	2.2	2.3	1.0	0.1	1.5
2013	85.5	6.1	1.7	1.0	2.2	2.4	1.0	0.1	2013	87.7	5.1	1.8	0.9	1.8	1.8	1.0	0.1	2.2
2014	88.9	4.8	1.2	0.7	1.7	2.0	0.6	0.1	2014	90.7	3.7	1.2	0.6	1.4	1.7	0.6	0.1	1.8
2015 [b]	90.4	3.8	1.0	0.6	1.7	1.8	0.6	0.1	2015	91.9	3.2	0.9	0.6	1.3	1.4	0.6	0.1	1.4
2016	90.3	4.3	0.9	0.6	1.6	1.6	0.6	0.1	2016	91.6	3.6	0.9	0.4	1.2	1.5	0.5	0.1	1.3
2017	92.3	3.6	0.8	0.5	1.2	1.1	0.5	0.1	2017	93.0	3.2	0.8	0.4	1.0	0.9	0.5	0.1	0.7
2018	93.0	3.3	0.8	0.3	1.1	0.9	0.5	0.1	2018	93.3	3.2	0.9	0.3	0.9	0.9	0.4	0.1	0.3

[a] The UNAIDS target of viral suppression using the longitudinal model with VL < 200 copies/ml has been met for PLHIV after ART initiation in the study population in Germany since 2011
[b] The UNAIDS target of viral suppression using the longitudinal model with VL < 50 copies/ml has been met for PLHIV after ART initiation in the study population in Germany since 2015

Table 4 Congruence of last VL before and first VL after gap time, viral suppression (VS) and median VL for each group and overall between 2015-2018

Congruence	N	(%)	Last VL before gap time				First VL after gap time			
			N no VS	(%) no VS	Median	(IQR)	N no VS	(%) no VS	Median	(IQR)
Congruent VS	13,407	84.4	–		–	–	–		–	–
Congruent 50- < 1000	134	0.8	134	100	88	(66–160)	134	100	93	(66–149)
Congruent > =1000	170	1.1	170	100	33,180	(7200-83,550)	170	100	33,180	(8900–73,827)
VL decrease last VL > first VL	1051	6.6	1051	100	1162	(101–31,300)	165	16	278	(101–1820)
VL increase last VL < first VL	1130	7.1	263	23	326	(114–2555)	1130	100	1667	(135–33,824)
Total	15,892	100.0	1618	10	910	(104–25,700)	1599	10	1368	(118–31,853)

measurements, additionally taking into account ART status and VL dynamics. The method provides a nationwide estimate and a useful method for calculating the number and proportion of PLHIV and of person-time with viral suppression for the HIV care continuum to evaluate the UNAIDS target of viral suppression for Germany. This model additionally allows for the determination and further analyses of people with longer periods without observation or missing VL control, defined as gap time. We determined the proportion of person-time and PLHIV with viral suppression and gap time between 1999 and 2018 using longitudinal national cohort data. We observed a continuous and remarkable increase in the proportion of person-time and of PLHIV being virally suppressed in both the whole study population and in PLHIV after ART initiation. The 90% UNAIDS target of viral suppression has been met in the whole study population of all diagnosed PLHIV since 2017 due to earlier and widespread use of ART and in PLHIV after ART initiation since 2015, respectively. Using the international comparable threshold of 200 copies/ml, the target was reached since 2015 and 2011, respectively. In 2018, 93% of PLHIV after ART initiation were virally suppressed with VL < 50 copies/ml, and 96% had VL < 200 copies/ml. Furthermore, we compared the results of the conventional method with those of our longitudinal method, showing potential misclassification of viral suppression when using only the last VL in a year. We observed a constant high proportion of gap time in these real-life cohort studies. We further analyzed people with

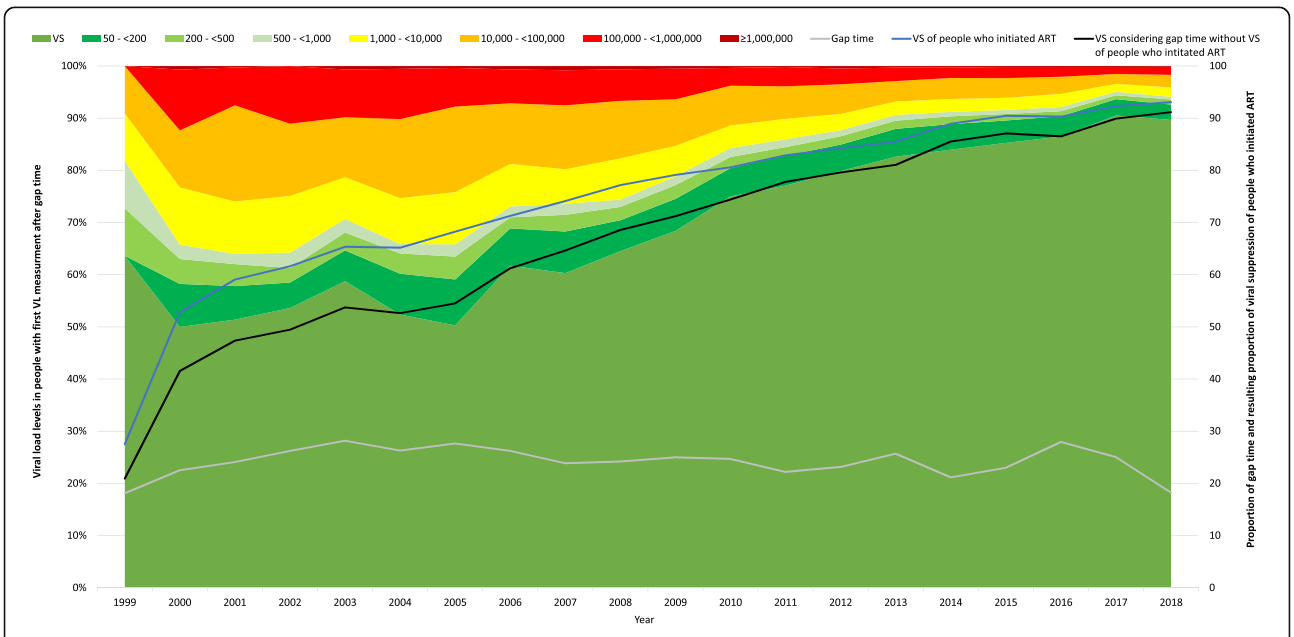
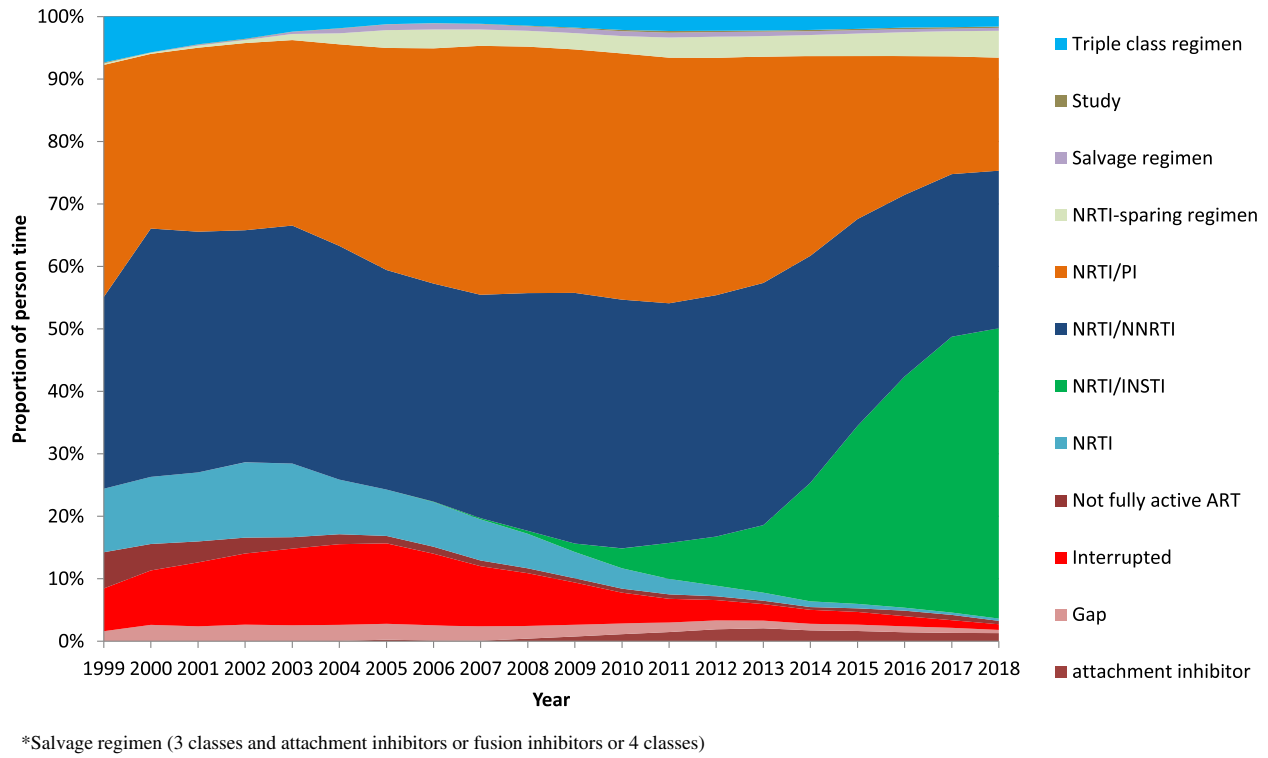


Fig. 4 Proportion of viral suppression and viral load levels in people with gap time at their first VL measurement after gap time between 1999 and 2018. Additionally, the proportion of gap time among all people who initiated ART (grey line), the proportion of viral suppression among all people who initiated ART (blue line) and the resulting proportion of viral suppression among all people who initiated ART after considering for viremic gap time (black line) is shown



*Salvage regimen (3 classes and attachment inhibitors or fusion inhibitors or 4 classes)

Fig. 5 Composition of ART regimens by drug classes in the cohort studies from 1999 to 2018

gap time, aiming to approximate their viral load status, and we showed that, in recent years, only a slightly lower proportion of viral suppression was associated with gap time.

Longitudinal model and comparison with the conventional method

Viral suppression is conventionally determined based on the most recent HIV viral load below a certain threshold, often < 200 copies/ml for comparability across studies and different settings and because this threshold was shown to be sufficient to avoid HIV transmission [17, 18, 30]. However, such a cross-sectional approach does not address the timeliness of either reaching or the time spent at each level [6] and person-time with viral suppression and viremia. Using a single VL measurement can lead to an overestimation of durable viral suppression [6, 22]. In our approach, instead of considering only the last VL measurement in a respective year, we examined the total observation time with all available VL measurements and additionally created virtual VL values taking into account ART status and VL dynamics to reconstruct persons' individual viral load courses. We believe that this approach provides a more accurate picture of the VL status of the study population and might be especially useful when the study population and sample size are smaller and therefore less robust. When examining a large number of people cross-sectionally, it is likely that, at each point in time, a certain more or less stable proportion of people shows viral suppression. In this study, the proportion of people with viral suppression in recent years using the conventional approach with the last VL per year was ~ 2% higher than in our longitudinal model. Although this difference is small, it might be due to the large numbers of people and measurements included, which could reflect an overestimation of durable viral suppression and could be different in smaller studies or other settings. From 1999 to 2001, when the study size was smaller, the difference was ~ 11%. Furthermore, the comparison of the conventional cross-sectional approach with the analysis of continuous viral suppression in one year on an individual level showed a notable difference of 5%. Recent studies have also demonstrated that simple, cross-sectional measures of viral suppression are prone to misclassification [31]. Viral suppression is not constant once achieved, and people often transition between suppressed and unsuppressed states, even over periods as short as one year [21]. Therefore, in agreement with the results of other studies, we believe that the dynamics of VL progression are easily overlooked with a cross-sectional assessment of the last VL measure, and longitudinal measures of VL dynamics provide more granular data with implications for HIV treatment and prevention [21, 22, 31]. Additionally,

with our model, it is possible to assign, quantify and further investigate longer periods without observation or VL control. For the reasons described, we believe that our method is superior when examining trends over time in longitudinal long-term cohorts with potential observation gaps and viral load changes. In addition, it should be emphasized that this advantage can be achieved on the basis of already established standards of therapy monitoring and thus with reasonable effort.

Gap time and retention in care

In our study, we defined longer periods without viral load control of more than 180 days between VL measurements as gap time. A notable proportion of 24% gap time was observed in these real-life cohort studies. The question of whether these people are considered successfully treated or whether having viremia is a factor of uncertainty in our analysis. However, following an approach using the last VL measure for viral suppression would not consider this proportion at all. Aiming to approximate the status of the people during gap time, we analyzed the last and first VL measurements before and after gap time. On an individual level, 84% of the people came back into observation with the same VL with which they left showing viral suppression. The overall proportion of virally suppressed before and after gap time in recent years was 90%, which is only slightly (3%) less than using our longitudinal model excluding gap time. In our opinion, it is therefore very unlikely to assume that the people had high VL only during their gap time, and we believe that the VL measurements before and after gap time are good proxies. Furthermore, the median VL of the 10% with viremia before and after gap time decreased remarkably over time. Finally, we calculated the resulting proportion of viral suppression after considering for viremic gap time and showed that this would decrease the overall viral suppression by only 2% among all people who initiated ART in 2018. One reason for viral suppression or low viremia during gap time can be that people were receiving care in non-cohort centers rather than being lost to care entirely. It is important to note again that these nationwide studies are real-life observational cohorts that reflect clinical practice. People might switch doctors or leave the country or region for a certain time and then return, or it is also possible that the gaps in observation and longer periods without VL controls are in fact gaps in documentation. These might be reasons for the constant high proportion of gap time in the studies. However, VL can be very dynamic, and after ART interruption, even in selected cases with long-term viral suppression, in the absence of plasma residual viremia and low HIV-DNA or people treated in Fiebig I acute infection, viral rebound occurred rapidly at a median time of 21 or 26 days, respectively [32, 33]. Longer periods without VL control are therefore problematic. Potentially, even the quarterly reimbursed VL testing in Germany would not be sufficient to detect every single VL even if counting them as blips, and from a researcher's perspective, we might wish to have information about the VL status of each person for every day. However, evidence has shown that quarterly VL testing is sufficient to determine treatment success, which is reflected in guidelines [26] and reimbursement regulations. Nonetheless, at least all of the available VLs should be used to determine the proportion of virally suppressed people in one year, instead of reducing the available data to only one VL per year. In our model, we use all available VLs, additionally taking into account the ART status and VL dynamics of the people to generate virtual VL values along a line, enabling us to assign a VL status at any point in observational time. We confirmed that VL testing occurred every 91 days in our cohorts, showing again that ART in Germany is performed by highly specialized practitioners in accordance with the guidelines [26]. Conversely, we also observed a constant high proportion of 24% gap time in the cohort studies, with a slightly higher likelihood of showing viremia. Retention in care is crucial for successful treatment, and we recommend maintaining engagement and retention in care and adherence to ART, accompanied, guided and monitored by regular VL testing. We also recommend further analysis among people with gap time, which we have planned. However, the achieved improvements in HIV care and treatment by highly specialized doctors are not doubted and can be seen in the composition of ART regimens over time and not least in the remarkable increase in viral suppression over time.

Trends of viral suppression between 1999 and 2018

Between 1999 and 2018, after ART initiation, the proportions of person-time and of PLHIV with viral suppression increased from 34 to 93%. With the threshold of VL < 200 copies/ml between 1999 and 2018, the proportion of person-time and PLHIV after ART initiation increased from 47 to 96%. A remarkable increase in viral suppression has also been observed in many other studies and countries [4, 5, 34–38]. These findings are likely explained by improvements in clinical care, treatment options and ART adherence [13, 35, 38]. Although not all regimens or drugs are still being equally used, treatment options have remarkably increased since the early era after the introduction of highly active, combined ART. Not fully active ART was at 6% in 1999 but soon continuously decreased to only 0.5% in 2018. The experience of practitioners and people in using ART and the importance of adherence have improved tremendously. Resistance test-guided therapy is now the

standard [26]. Much has been learned with regard to treatment interruptions, and at least since the results of the SMART study in 2006, interruptions are no longer recommended [39]. This learning can very well be seen in the proportion of interruptions in the RKI cohorts. Treatment interruptions in our study were highest at 13% in 2004 and 2005 and subsequently decreased to less than 1% in 2018. During 2015–2018 in our study population, ART interruptions still occurred in 1–2% of the people. Since ART is lifelong, we included all people who ever initiated ART even if treatment was interrupted, indicating that the proportion of viral suppression would be even higher if we restricted them to those under continuous ART. We also assessed the VL in the whole study population regardless of ART initiation, including ART-naïve people and person-time. An impressive increase was observed for all diagnosed PLHIV, which, as the results of the ClinSurv HIV and HIV-1 Seroconverter cohort showed [40], was connected with the widespread and earlier use of ART as recommended in the guidelines [26]. This achievement is a great one in terms of treatment as prevention (TasP), showing that, since early ART is common, the population of diagnosed PLHIV is not substantially contributing to HIV transmission in Germany. This fact shows that diagnosis is key to prevention. With regard to the whole HIV care continuum, we know that the potential for improvement is mostly seen at this first stage of the HIV care continuum -- the only stage for which Germany has not yet met the UNAIDS target of 90% [8]. Therefore, tailored HIV testing campaigns and enhanced access to HIV testing, including self-testing, should be further strengthened. For PLHIV after ART initiation, we recommend avoiding treatment interruptions and emphasizing adherence to ART.

Evaluation of the UNAIDS 90 target of viral suppression

The UNAIDS target of 90% viral suppression has been met among PLHIV who ever initiated ART since 2015 in these nationwide German cohort studies of PLHIV. The international comparable threshold of VL < 200 copies/ml has been met among PLHIV who ever initiated ART since 2011. In 2018, 93% of PLHIV after ART initiation were virally suppressed with VL < 50 copies/ml, and 96% had VL < 200 copies/ml. Therefore, when using the threshold of VL < 200 copies/ml, Germany reached the UNAIDS 95 target of viral suppression since 2017. On a population basis in light of the HIV transmission risk, studies have suggested that a VL up to 400 copies/ml might still be uncritical [41]. A notable proportion of our study population with viremia showed low-level viremia < 1000 copies/ml with a likely low risk of transmitting HIV [30]. However, individual health risks [42], the development of HIV drug resistance [43–45] and increased risk of viral rebound [46–48] among people with low-level viremia are problematic, and viral suppression remains the goal [49]. Therefore, further analysis of people with viral failure is essential.

Limitations

Assessing stages of the HIV continuum of care using cohorts can introduce bias since they might not be representative of all diagnosed PLHIV in a country. To estimate representativeness, we compared the demographic characteristics of our study population with all PLHIV in Germany and found them to be similar. The study population represents more than 20% of all PLHIV in Germany. ClinSurv HIV is the largest nationwide long-term cohort of HIV-positive people and the least biased source available. In a study by Gourlay et al., the authors also used country-specific cohort data to derive stages of the HIV care continuum in European Union countries [6]. Germany delivered data from ClinSurv HIV for this study and was assumed to be fairly representative of HIV people in care [6, 50, 51]. People outside of medical care, e.g., without health insurance, are not represented in ClinSurv. The HIV-1 Seroconverter cohort is assumed to be representative of men who have sex with men (MSM) in Germany [52] and therefore covers one specific group within the population of PLHIV. However, MSM is the largest group and is mainly affected by HIV; furthermore, ClinSurv HIV accounts for more than 90% of the study population in our analytic sample. In this respect, we believe that the representativeness of ClinSurv HIV applies, and following the results of Gourlay et al., our sample is fairly representative of HIV people in care in Germany. However, we cannot exclude that these studies are not representative.

As discussed, gap time is a factor of uncertainty, and although we believe that our sensitivity analysis of the last and first VL before and after gap time is a reasonable approximation, viral suppression was slightly lower, indicating that further analyses of people with gap time would be useful. Furthermore, in real-life studies, misclassification, loss to follow-up, lab-related issues and gaps in documentation can occur and influence gap time.

Conclusions

This report describes a model to estimating the number and proportion of PLHIV and person-time with viral suppression. The study provides a possible approach for estimating the number of people receiving continuously specialized HIV medical care in Germany and those with gaps in observation or VL control. With this study, we provide a nationwide estimate and a useful tool for calculating the number and proportion of PLHIV and of

person-time with viral suppression and with gap time as well as trends of viral suppression and gap time between 1999 and 2018 in Germany. We observed an increase in the proportion of person-time and of diagnosed PLHIV with viral suppression. The UNAIDS 90 target of viral suppression has been met in these nationwide German cohort studies since 2015 and, when using the international comparable threshold of < 200 copies/ml, since 2011. In 2018, 93% of PLHIV after ART initiation were virally suppressed with VL < 50 copies/ml, and 96% had VL < 200 copies/ml. Germany reached the UNAIDS 95 target of viral suppression since 2017 when using the threshold of VL < 200 copies/ml. Our results suggest that the population of diagnosed PLHIV is not substantially contributing to HIV transmission in Germany. Continuous efforts toward tailored HIV testing campaigns and enhanced access to HIV testing, including self-testing, are recommended.

We also recommend regular VL testing and engagement and retention in care as well as adherence to continuous ART. Further analysis of people with viral failure is essential to understand and determine risk factors for viral failure in times of highly effective and mostly successful ART.

This approach and model to reconstruct persons' individual viral load course can be useful for estimating the number and proportion of PLHIV with viral suppression in other countries, provided that the required resources are available. The described methodology could be used and adapted for different investigations or parameters in the future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-020-10088-7.

Additional file 1.

Abbreviations

AI: Attachment inhibitor; ART: Antiretroviral treatment; ClinSurv HIV: Clinical Surveillance of HIV Disease; FI: Fusion inhibitor; INSTI: Integrase strand transfer inhibitor; IQR: Interquartile range; MSM: Men who have sex with men; NRTI: Nucleoside reverse transcriptase inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; PLHIV: People living with HIV (PLHIV) ; PY: Person-years; RKI: Robert Koch Institute; UNAIDS: Joint United Nations Programme on HIV/AIDS; VL: Viral load

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Authors' contributions
DS was responsible for the study design, devised the estimation approach, performed the data analysis and statistical analysis, interpreted the data and drafted the manuscript. CK was responsible for the study design, devised the estimation approach, was responsible for database management, supported the data analysis and interpretation of the data and helped to draft the manuscript. MS is site principal investigator, contributed data, supported the interpretation of the data and helped to draft the manuscript. OH was responsible for the design and implementation of the HIV-1 Seroconverter and the ClinSurv HIV cohort and supported the writing of the manuscript. BB supported the management and coordination of the study, served as the ClinSurv HIV study coordinator, contributed to improving the data quality and coverage and helped to draft the manuscript. VB supported the management and coordination of the study and helped to draft the manuscript. TK supported the data analysis and interpretation of the data and helped to draft the manuscript. All of the authors participated in the critical discussion of the results, and all of them read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to data protection and confidentiality but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The RKI is the German national public health institute, therefore the Federal Commissioner for Data Protection is the responsible entity for studies which are conducted by the RKI. Information on HIV infection collected in ClinSurv HIV corresponds to the data reported to the RKI according to legal requirements implemented by the national Protection against Infection act (IfSG) of 2001. All patient data collected in ClinSurv HIV are generated during routine care. The German Federal Commissioner for Data Protection therefore waived the need for ethical approval for the ClinSurv HIV study. The study protocol for the HIV-1 Seroconverter cohort was initially approved in 2005 by the Ethics Committee of the Charité, University Medicine Berlin (EA2/105/05), with approval amended and confirmed in 2013. Participants provide their written informed consent to participate in this study. The ethics committee approved this consent procedure.

Consent for publication
Not applicable.

Competing interests
DS, BGB, VB, OH and MS declare that they have no competing interests. CK is small shareholder in companies manufacturing antiretroviral drugs. TK reports outside of the submitted work to have received honoraria from Eli Lilly, Newsenselab, and Total for providing methodological advice, and from the BMJ for editorial services.

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Publisher's Note

5 Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

6 Publikationsliste

6.1 Publikationen in wissenschaftlichen Zeitschriften mit Peer-Review

- **Schmidt D**, Kollan C, Stoll M, Hamouda O, Bremer V, Kurth T, Bartmeyer B, the HIV-1 Seroconverter cohort, the ClinSurv HIV cohort. Everything counts - a method to determine viral suppression among people living with HIV using longitudinal data for the HIV care continuum - results of two large, German, multi-center real-life cohort studies over 20 years (1999–2018). BMC Public Health 21, 200 (2021). https://doi.org/10.1186/s12889-020-10088-7
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- **Schmidt D**, Merbach M, Friebe M, Hanhoff N, Rüsenberg R, Schewe K. Wissenschaftliche Begleitung und Evaluation der HIV-Präexpositionsprophylaxe (PrEP) als Leistung der gesetzlichen Krankenversicherung – das Projekt EvE-PrEP in Zeiten der SARS-CoV-2-Pandemie. Epid Bull 2021;6:3 -12 | DOI 10.25646/7973

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- an der Heiden M, Marcus U, Kollan C, **Schmidt D**, Gunsenheimer-Bartmeyer B, Bremer V: Schätzung der Zahl der HIV-Neuinfektionen und der Gesamtzahl von Menschen mit HIV in Deutschland, Stand Ende 2019. Epid Bull 2020; 48:3–16 | DOI 10.25646/7213

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