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Usage of Antivirals and the Occurrence of Antiviral Resistance in Norway 2022

RAVN

Resistensovervåking av virus i Norge

Resistance against Antivirals in Norway

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Introduction

It is a pleasure to present the tenth report from the surveillance system for Resistance against Antivirals in Norway (RAVN). In this report, we present data for 2022 on resistance against antivirals for treatment of influenza, HIV-1 infection, hepatitis B virus infection (HBV), hepatitis C virus infection (HCV), human herpes virus infections, and SARS-CoV-2, as well as data from The Norwegian Drug Wholesales Statistics Database showing the usage of antiviral drugs in Norway in 2022.

In addition to the surveillance data, we have selected relevant topics that are given special attention in the report. The first is related to the ongoing conflict in Ukraine. We have chosen to include a chapter addressing drug resistance in Eastern Europe, and how the increased migration related to the humanitarian challenges in Ukraine might affect the prevalence of antiviral resistance in Norway.

Another topic we have focused on in this report, is HIV drug resistance after six years with fully reimbursed pre-exposure prophylaxis (PrEP) in Norway. We present data on key drug resistance mutations associated with reduced susceptibility to the drugs used for PrEP, detected in Norway during the last 10 years.

Furthermore, we include a chapter describing a new antiviral that has recently received conditional approvement for treatment of infection with hepatitis D virus (HDV). Treatment of HDV infection is discussed, along with the potential risk for antiviral drug resistance.

Antimicrobial resistance is considered one of the greatest threats to global health. Better knowledge and increased awareness are essential to be able to control emerging antiviral drug resistance, and surveillance will be a key tool for management. It is our hope that the report contains valuable data and interesting perspectives for all colleagues with an interest in the field of infectious diseases, and for those developing guidelines and strategies to prevent transmission of viral infections.

RAVN would like to thank those who contributed with data and writing this report, for excellent work.

Enjoy!

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Abbreviations

ART	Antiretroviral therapy
CMV	Cytomegalovirus
CRF	Circulating recombinant form
DAA	Direct-acting antiviral
DDD	Defined daily dose
FTC/TDF	Emtricitabine and tenofovir disoproxil fumarate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus-1
HSV	Herpes simplex virus
INSTI	Integrase strand transfer inhibitors
MSIS	Norwegian Surveillance System for Communicable Diseases
MSM	Men who have sex with men
NA	Nucleoside/nucleotide analogue
NIPH	Norwegian Institute of Public Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PEP	Post exposure prophylaxis
PrEP	Pre-exposure prophylaxis
RAS	Resistance-associated substitution
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDRM	Surveillance drug-resistance mutation
SVR	Sustained virological response
TAF	Tenofovir alafenamide fumarate
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

Sammendrag

Bruk av antivirale midler

Både nasjonale retningslinjer for behandling og anbudsordninger for innkjøp spiller en betydelig rolle i valg av legemidler for flere virusinfeksjoner. Ifølge data fra Legemiddelregisteret, var det en nedgang i salget av antivirale legemidler målt i definerte døgndoser både i 2020 og 2021, etter flere år med økning. Denne nedgangen skyldtes hovedsakelig reduksjon i salget av antivirale legemidler mot hiv som utgjør en stor andel. Nedgangen kommer til tross for en økning i antall behandlede pasienter, og kan forklares med at stadig flere behandles med enkelttablettregimer.

Antallet personer behandlet for HCV-infeksjon har gått ned etter 2018, og kombinasjonspreparater har i stor grad erstattet enkeltmidler. Det har vært en liten økning i antall personer behandlet for hepatitt B. Antivirale midler mot herpesvirus fortsetter å være den mest brukte gruppen av antivirale midler målt etter antall brukere. Bruken av neuraminidasehemmere mot influensa varierer basert på variasjoner mellom sesonger og vaksinenes treffsikkerhet. For SARS-CoV-2 har nirmatrelvir/ritonavir gjennom 2022 vært tilgjengelig for poliklinisk behandling av definerte risikogrupper, men bare 614 personer fikk utskrevet resept i 2022. Intravenøs behandling av COVID-19 i Norge er kun for sykehusbruk, der data for faktisk bruk ikke er tilgjengelig.

Influensavirus

Influensasesongen 2022/23 startet tidlig med høye positivitetsrater mot slutten av desember. Influensa A(H1N1) dominerte innledningsvis, etterfulgt av influensa B/Victoria. I alt 1133 prøver ble undersøkt for antiviral resistens, hvorav det ble påvist ett tilfelle av resistens mot neuraminidasehemmere etter behandling. Alle andre testede virus var følsomme for både oseltamivir og baloxavir marboxil.

Humant immunsviktvirus-1

I 2022 ble det analysert i alt 106 prøver fra nydiagnostiserte tilfeller av hiv-infeksjon i Norge. Dette utgjør 43 % av antall tilfeller rapportert til MSIS samme år. Dekningen av resistenstesting var høyere blant pasienter smittet i Norge (nesten fullstendig) sammenlignet med smittede i utlandet (37 %), noe som tyder på gode nasjonale rutiner for å inkludere nydiagnostiserte pasienter i resistensovervåkingen. Blant de som er smittet i utlandet, er det mange som allerede står på behandling og som derfor ikke kan resistenstestes.

I 2022 ble resistensmutasjoner påvist i 9,4 % av prøvene, omtrent på samme nivå som tidligere år. Det er fortrinnsvis påvist mutasjoner som påvirker følsomheten for revers transkriptasehemmere, og i mindre grad proteasehemmere. Det finnes flere tilgjengelige behandlingsalternativer for pasienter med påviste resistensmutasjoner.

Ingen av de påviste mutasjonene er assosiert med redusert effekt av medikamentene som brukes forebyggende (PrEP). Det er fortsatt lav forekomst av smitte med resistente varianter i Norge og de fleste resistensmutasjonene er funnet hos pasienter smittet i utlandet. Fortsatt overvåking av antiretroviral resistens, er viktig spesielt relatert til PrEP.

Hepatitt B-virus

I 2022 ble totalt 156 prøver med hepatitt B virus (HBV) analysert med tanke på resistensmutasjoner. De fleste av disse prøvene (n=138) var sendt inn til referanselaboratoriet for genotyping før behandling. Disse prøvene utgjør den norske overvåkingen av primærresistens. De resterende 18 prøvene var fra pasienter med pågående antiviral behandling og ble sendt inn for undersøkelse av resistens som mulig årsak til behandlingssvikt. Det ble funnet relevante resistensmutasjoner i fire av de 18 prøvene fra pasienter med behandlingssvikt. Ingen resistensmutasjoner ble funnet i noen av overvåkingsprøvene.

Humane herpesvirus: Cytomegalovirus

I 2022 ble det funnet relevante resistensmutasjoner i fem av totalt 24 pasientprøver analysert for resistens hos cytomegalovirus (CMV). Mutasjonene som ble påvist, påvirker særlig følsomhet for ganciclovir og er alle lokalisert i en liten region av UL97-genet. Disse mutasjonene gir lav til moderat resistens, men kan være av klinisk betydning hos immunsupprimerte pasienter. Tidlig påvisning er avgjørende hos immunsupprimerte pasienter, så klinikere og laboratorier oppfordres til å vurdere resistensundersøkelse ved mistenkt behandlingssvikt.

Humane herpesvirus: Herpes simplex-virus

Kun tre prøver fra Norge ble sendt for resistensundersøkelse av herpes simplex-virus (HSV) i 2022. Det ble ikke funnet noen resistensmutasjoner. Det er ingen systematisk resistensovervåking av HSV. Antall prøver som er sendt inn for HSV-resistens i løpet av de siste fem årene har vært svært lavt tatt i betraktning det høye forbruket av HSV-antivirale midler.

Hepatitt C-Virus

Et system for nasjonal resistensovervåkning av hepatitt C-virus (HCV) ble lansert i mai 2022. I 2022 ble totalt 133 prøver analysert for HCV-resistens. Resistensassosierte substitusjoner (RAS) ble påvist i 106 av de analyserte prøvene. Resistensdata er koblet sammen med epidemiologiske data fra MSIS for å muliggjøre sammenligninger av ulike undergrupper. De kliniske konsekvensene av tilstedeværelsen av RAS før behandling er usikre, men man kan anta at tilstedeværelsen av enkelte RAS kan begrense effektiviteten av antiviral behandling.

SARS-CoV-2

Overvåkingen av antiviral resistens hos SARS-CoV-2 er basert på samme sekvensdata som utgjør den nasjonale overvåkingen av SARS-CoV-2-varianter. Data fra januar til mars 2023 er inkludert i overvåkingen. Totalt ble 2095 prøver analysert. Mutasjoner assosiert med noe redusert følsomhet for nirmatrelvir ble funnet i totalt 12 prøver, men alle de påviste mutasjonene gir under 10 ganger redusert følsomhet og er sannsynligvis ikke av klinisk betydning for behandlingsrespons. Ingen av sekvensene inneholdt noen av mutasjonene som er kjent for å gi delvis eller fullstendig resistens mot nirmatrelvir.

Summary

The usage of antivirals

National treatment guidelines and procurement recommendations play a significant role in drug choices for various infections. According to The Norwegian Drug Wholesales Statistics Database, the sales of antiviral drugs measured in defined daily doses (DDDs) increased from 2018 to 2022, with a temporary decrease in 2020 and 2021. Antivirals against HIV constitute a significant portion of antiviral drug sales, and the observed reduction in sales despite an increase in number of users, is explained by a transition to treatment with single tablet regimens. The number of individuals treated for HCV decreased after 2018, with fixed combinations replacing single component drugs. There has been a small increase in the number of individuals treated for hepatitis B.

Antivirals against herpesviruses continue to be the most commonly used antivirals when measured by the number of users. Usage of neuraminidase inhibitors for influenza treatment fluctuates based on seasonal outbreaks and vaccine efficacy. For SARS-CoV-2, nirmatrelvir/ritonavir is available for out-patient treatment for defined risk groups, but only 614 individuals received a prescription in 2022. Intravenous antiviral treatment of COVID-19 in Norway is only for hospital use, and records of actual use in hospitals are not available.

Influenza virus

The 2022/23 influenza season in Norway started early, with high positivity rates peaking late December. Influenza A(H1N1) dominated initially before influenza B/Victoria lineage viruses took over. Antiviral resistance testing showed only one case with treatment related resistance to neuraminidase inhibitors out of the 1133 analysed samples. All other tested viruses were sensitive to both oseltamivir and baloxavir marboxil.

Human immunodeficiency virus-1

In 2022, 106 samples from newly diagnosed HIV-1 cases were analysed, covering 43% of the cases reported to MSIS. Coverage of resistance testing was higher among patients infected in Norway (nearly complete) compared to those infected abroad, indicating that that national routines for follow-up of newly diagnosed patients regarding antiviral resistance are good. Many of the patients infected abroad are already receiving treatment and are not eligible for resistance testing due to suppressed viremia.

In 2022, surveillance drug resistance mutations (SDRMs) were detected in 9.4% of the samples, which is similar to previous years. The majority of the detected mutations affects the susceptibilty to reverse transcriptase inhibitors, and to a lesser extent protease inhibitors. There are many available treatment options for patients with detected mutations.

No mutations reducing PrEP effectiveness were found. The prevalence of transmitted drug resistance in Norway remains low, with most drug resistance mutations detected in patients infected abroad. Continued monitoring of drug resistance, especially related to PrEP, is essential.

Hepatitis B virus

In 2022, a total of 156 samples were analysed for HBV drug resistance mutations. Most of these samples (n=138) had been submitted to the reference laboratory for genotyping prior to treatment. These samples constitute the Norwegian surveillance of primary resistance. The remaining 18 samples were from patients with ongoing antiviral treatment and were submitted for investigation of resistance as a possible cause of suspected treatment failure. Relevant resistance mutations were found in four of the 18 samples from patients with treatment failure. No resistance mutations were found in any of the surveillance samples.

Human herpes viruses: Cytomegalovirus

In 2022, relevant resistance mutations to CMV drugs were found in five out of 24 patient samples analysed. These mutations mostly affect ganciclovir susceptibility and are clustered within a small region of the UL97 gene. While these mutations confer low to moderate resistance, they can be clinically significant in immunosuppressed patients. Early detection is crucial in immunosuppressed patients, so clinicians and labs are encouraged to consider drug resistance testing in cases of treatment failure.

Human herpes viruses: Herpes simplex virus

Only three samples from Norway were submitted for herpes simplex virus (HSV) drug resistance analysis in 2022. No resistance mutations were found. There is no systematic surveillance of drug resistant HSV. The number of samples submitted for HSV drug resistance during the past five years has been very low considering the high consumption of HSV antivirals.

Hepatitis C virus

A surveillance system for newly diagnosed HCV infections was launched in May 2022. In 2022, a total of 133 samples were analysed for HCV drug resistance. Resistance-associated substitutions (RASs) were detected in 106 of the analysed samples. Drug resistance data was cross-referenced with epidemiological data from MSIS to enable comparisons of different subgroups. The clinical consequences of the presence of RAS pretreatment are uncertain, but the occurrence of some RAS may limit the efficiency of antiviral treatment.

SARS-CoV-2

The surveillance of drug resistance is based on the same sequence data that is part of the national monitoring of SARS-CoV-2 variants. For the 2022/23 SARS-CoV-2 season, data from January to March 2023 is included in the surveillance. A total of 2095 samples were analysed. Mutations associated with slightly reduced susceptibility to nirmatrelvir were found in a total of 12 samples, but all the detected mutations were below 10-fold reduced susceptibility. None of the sequences harboured any of the mutations known to confer partial or complete resistance to nirmatrelvir

1 Antivirals and development of drug resistance

Antiviral drugs act by inhibiting propagation and spread of virus, usually by interfering directly with one or more specific steps in the virus' replication cycle. Most antiviral drugs are effective only against one particular virus or a group of viruses, and specific antiviral therapy is available only for a few viral infections. In principle, drugs may be designed to inhibit any step in the replication cycle of a virus, including entry to host cells, replication of the genome, viral protein production, and particle assembly or release as shown in Figure 1.1 (1). Most of the antivirals currently available, work by inhibiting viral DNA- or RNA-synthesis, or by direct inhibition of other essential viral enzymes (2). Recently, therapeutic use of monoclonal antibodies directed against specific viral proteins has increased. Although traditionally thought of as passive immunization, monoclonal antibodies can also be classified as antiviral agents, as they directly interfere with binding of the virus to the host cell, they are used in treatment of established viral infections, and they are subject to resistance.

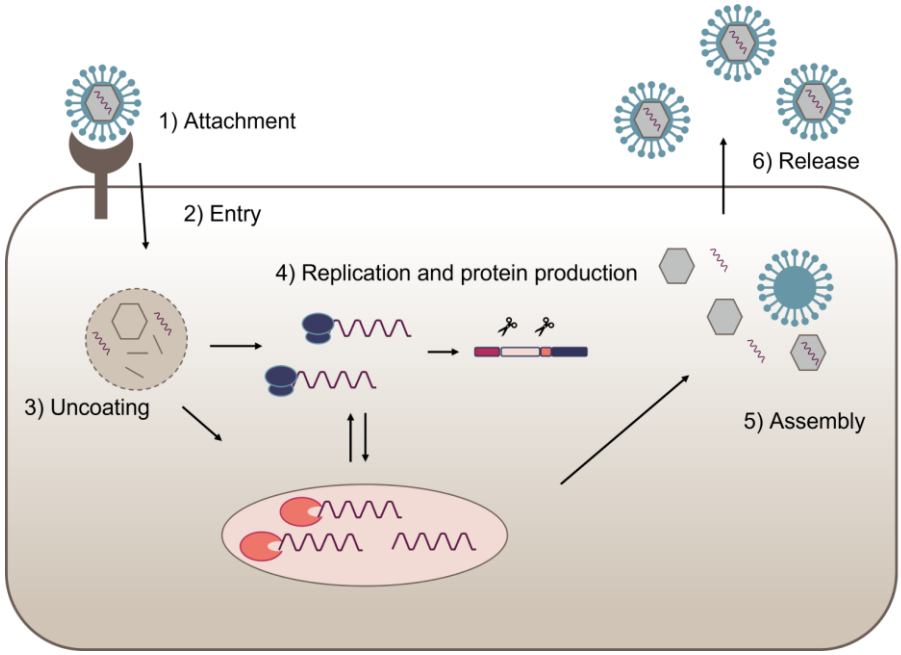

Figure 1.1. Generalized depiction of the viral replication cycle showing the major steps in replication.

Antivirals inhibit the propagation of virus by inhibiting one or more of the steps in the replication cycle, such as 1) attachment of the virus to the host cell, 2) entry into host cell, 3) uncoating of the viral capsid and release of the viral genome and proteins, 4) replication of viral DNA/RNA and protein production including cleavage of viral polyproteins by proteases, 5) assembly of viral proteins and viral genome into new virions, and 6) release of viral particles. The replication cycle of different viruses may vary considerably, including variations in the sequential order of replication of the genome and translation of viral proteins.

Drug resistance against antivirals is caused by changes in the viral genome (mutations) leading to amino acid alterations (substitutions, insertions or deletions) in the protein targeted by the drug, thereby affecting the activity of the drug. Recombination or exchange of genetic material may also occur for certain viruses, which may introduce resistance into a new biological context. For example, antigenic shift in influenza transferred adamantane resistance from avian to human populations (3). Genetic alteration at a key site of the viral genome is usually a disadvantage for the virus, as most resistance mutations impair viral fitness. However, in the presence of antiviral drugs, resistant variants will have a fitness

advantage over wild type virus. Resistant virus variants are therefore selected and may continue replication under these conditions. In addition, compensatory mutations that restore viral fitness of the resistant variants, may then be selected by similar mechanisms. This may ultimately lead to the expansion of resistant variants even in the absence of antiviral drugs.
The risk of developing drug resistance varies significantly between different viruses, depending on factors such as mutation frequency and replication accuracy of the virus, viral load, turnover, fitness of mutated virus variants, and the duration of both infection and treatment. Immunocompromised patients are at particular risk for development of antiviral drug resistance. Furthermore, the genetic barrier for development of resistance is different for different drugs.

Antivirals against influenza

Three classes of antiviral drugs against influenza are approved in Europe, targeting entry, replication and release:

- Entry: M2-inhibitors block the M2 ion channel of influenza A virus, thereby inhibiting escape to the cytoplasm from endocytic vesicles. Influenza B is inherently resistant. Examples: amantadine and rimantadine.
- Release: Neuraminidase inhibitors bind to neuraminidase on the surface of influenza virus A and B, preventing cleavage of sialic acid. Neuraminidase inhibitors thereby prevent release of the virus from the surface of the host cell and may possibly also affect viral entry by inhibiting viral penetration of mucus. Examples: oseltamivir and zanamivir (4;5).
- Replication: The polymerase inhibitor baloxavir marboxil was recently approved in Europe and is now available in Norway. The drug targets the endonuclease function of influenza RNA polymerase and inhibits transcription of viral mRNA by preventing the cap-snatching activity of the endonuclease.

Since 2016, oseltamivir has been the only antiviral drug against influenza on the market in Norway, until baloxavir marboxil was recently approved. Zanamivir is still registered but was withdrawn from the market in 2016 due to limited use. Since 2009, all circulating influenza viruses have been resistant to the two M2-inhibitors, and these drugs are not presently in use for treatment of influenza. Other neuraminidase inhibitors have been developed and are in use in the USA (peramivir) and Japan (peramivir, laninamivir).

Drug resistant influenza

As mentioned earlier, drug resistant virus variants may propagate in the absence of antiviral agents as long as the mutation that confers resistance does not cause significant selective disadvantage for the virus. This is particularly evident for influenza virus. The largest outbreak of such a virus occurred in 2007, when an oseltamivir resistant H1N1 virus completely replaced the sensitive wildtype virus within one year after its first occurrence, before disappearing completely within the following two years. Resistance may 'hitch-hike' on another advantageous feature that promotes one virus strain over others, such as immune-escape mutations or fitness-enhancing mutations at other genomic sites (6). Furthermore, reassortment of the segmented genome may rapidly lead to major genetic changes that could involve domains of importance for drug resistance characteristics.

Antivirals against human immunodeficiency virus

The different classes of antiretroviral drugs used in the treatment of human immunodeficiency virus (HIV) infection target different stages in the HIV replication cycle (HIV entry, replication and protein production):

- Attachment and entry: Attachment and entry inhibitors comprise four subclasses:
    - CCR5 antagonists block the binding between viral gp120 and the chemokine receptor CCR5 (example: maraviroc).
    - Attachment inhibitors bind to and inhibit the CD4-binding activity of gp120 (example: fostemsavir).
    - The post-attachment inhibitor, ibalizumab, is a monoclonal antibody directed against CD4 which inhibits viral entry but not attachment.
    - Fusion inhibitors, preventing gp41-mediated fusion of the viral envelope with the cell membrane (example: enfuvirtide), are no longer registered.
- Replication:
    - Nucleoside reverse transcriptase inhibitors (NRTIs) are analogues of naturally occurring deoxynucleotides that are incorporated into the viral DNA chain in competition with the natural substrate. When incorporated, the drug stops further elongation of the viral DNA chain (chain termination), thereby inhibiting transcription of RNA into DNA by the reverse transcriptase. Examples: abacavir, lamivudine, emtricitabine, tenofovir, and zidovudine.
    - Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to the reverse transcriptase at a site distant to the nucleotide binding site inducing a conformational change, thereby inhibiting transcription of RNA into DNA. Examples: rilpivirine, etravirine, nevirapine, efavirenz, and doravirine.
    - Integrase strand transfer inhibitors prevent integration of pro-viral DNA into the host cell DNA. Examples: dolutegravir, raltegravir, elvitegravir, and bictegravir.
- Protein production: Protease inhibitors bind to the HIV protease and prevent the cleavage of polyproteins in the maturing virus particle. Examples: darunavir, atazanavir, and lopinavir. The effect is improved by addition of a pharmacokinetic enhancer (ritonavir or cobicistat).

In antiretroviral therapy (ART) for HIV-1, combinations of at least two drugs from different classes are used in order to achieve suppression of viral replication and reduce the risk of drug resistance. Currently recommended first line regimens consist of an integrase inhibitor in combination with one or two NRTIs (7). Alternatively, a boosted protease inhibitor or an NNRTI may replace the integrase inhibitor. These drugs need to be combined with two NRTIs. Single-pill regimens with fixed-dose combinations are widely available.

Drug resistant HIV

HIV has a very high mutation rate and high turnover, resulting in a considerable risk for development of resistant variants, mainly due to inaccuracy in viral replication and the lack of proofreading. There is vast genetic variation in the HIV-1 genome, and each patient harbours a mixture of coexisting genetic variants. This genetic variation increases during the course of infection. Drug resistant viruses may evolve from wild-type viruses if viral replication persists during antiretroviral treatment. Because most drug resistance mutations impair viral fitness, wild type virus often rapidly reemerges when treatment is interrupted. Drug resistance rarely occurs without previous drug exposure, but individuals carrying virus with resistance mutations may transmit this virus to others. Drug resistance emerging during antiviral treatment is called acquired drug resistance. Drug resistance detected in previously untreated persons is usually transmitted from a person with acquired drug resistance and may subsequently spread to others. The term transmitted drug resistance is used when previously uninfected individuals are infected with a virus that has drug resistance mutations (8).

Antivirals against hepatitis B virus

Only one class of antivirals, targeting HBV genome replication, is used for treating chronic hepatitis B virus (HBV) infection:

- Replication: Nucleoside/nucleotide analogues are analogues of naturally occurring deoxynucleotides that are incorporated into the viral DNA chain in competition with the natural substrate. When incorporated, the drug stops further elongation of the viral DNA chain (chain termination), thereby inhibiting transcription of RNA into DNA by the HBV polymerase. Nucleotide analogues may be directly incorporated into the DNA chain, whereas nucleoside analogues need to be phosphorylated prior to incorporation. Examples: entecavir, tenofovir disoproxil, and tenofovir alafenamide.

The activity of the HBV polymerase is similar to that of HIV reverse transcriptase, and several of the nucleoside/nucleotide analogues have activity against both viruses. Currently, monotherapy with entecavir or tenofovir is recommended as first-line treatment, given their antiviral potency and favorable resistance profile (9). Another treatment option is interferon therapy, which works by several mechanisms, including enhancement and regulation of the host's immune response. Although interferon-based treatment strategies offer an opportunity for seroconversion, current use in treatment is limited, mainly due to considerable side effects. Until recently, interferon therapy has been the only treatment option for HBV/HDV coinfection. In 2020, the entry inhibitor Bulevirtide was approved for the treatment of HDV by the European Medicines Agency.

Drug resistant HBV

The mutations associated with HBV drug-resistance are located in the reverse transcriptase domain of the HBV polymerase, and lead to reduced inhibitory effect of the drug on the viral polymerase. Aside from reducing the sensitivity of the virus to the drug, primary mutations often simultaneously reduce viral fitness. Compensatory resistance mutations restoring replication capacity, and secondary resistance mutations increasing drug resistance, may arise after the emergence of primary resistance mutations. Drug resistant HBV may develop under antiviral treatment but is rarely transmitted. Reported resistance in HBV is mainly towards the less potent drugs lamivudine and adefovir, which have a low genetic barrier to resistance compared to tenofovir and entecavir. For

entecavir, several mutations are required to confer drug resistance. Resistance to entecavir may still occur, but it is rare. For tenofovir, only a few cases of clinically significant drug resistance are described worldwide, all of them as part of multidrug resistance (10). Because of the rarity of resistant cases, the relevant mutation sites for tenofovir-resistance are not fully confirmed.

Antivirals against cytomegalovirus

There are three classes of antivirals used for treating cytomegalovirus (CMV) infection, targeting different stages of the CMV replication cycle:

- Replication: Analogues of naturally occurring deoxynucleotides that are incorporated into the growing strand of viral DNA by CMV polymerase (UL54), causing termination of the growing viral DNA strand (chain termination). Examples: Ganciclovir, valganciclovir, cidofovir, foscarnet.
- Assembly: DNA terminase complex inhibitors bind to and inhibit the CMV-DNA terminase complex which is involved in cleaving and packaging of CMV-DNA genome into the capsid. The drug is approved for prophylactic use after stem cell transplantation. Example: letermovir.
- Multiple stages: Inhibition of UL-97-kinase leading to reduced phosphorylation of viral and host proteins (multiple effects) and nucleotides for DNA replication. Example: maribavir

Ganciclovir and its prodrug valganciclovir are the drugs of choice since they are effective in inhibiting virus replication and have few side effects. To become active, ganciclovir is monophosphorylated by the CMV UL97 kinase and then di- and tri-phosphorylated by cellular kinases. Cidofovir and foscarnet are also incorporated by the DNA polymerase, but do not require activation by CMV viral kinase and thus their action is not limited to infected cells. These drugs have more side-effects and are used only in special situations such as ganciclovir resistance, CMV retinitis, or retinal necrosis.

Maribavir, a UL97-kinase inhibitor, was appoved by the European Medicines Agency in November 2022 for treatment of post-transplant CMV infection that does not respond to other CMV antivirals. Unsurprisingly, maribavir antagonises ganciclovir, since the UL97-kinase is required for activation of ganciclovir, and the two drugs should not be used in combination. The drug is normally well tolerated; the main adverse effects are gastrointestinal, with dysgeusia being the most frequent. Maribavir and letermovir have not been found to induce myelosuppression, which is a main side-effect of ganciclovir.

Letermovir has been approved for CMV prophylaxis in CMV seropositive stem cell recipients in Norway since 2019. Letermovir has a completely different target from the other established drugs, as it targets the CMV terminase complex. The terminase complex is responsible for cleavage of freshly replicated viral DNA into individual viral subunits and packaging them into the developing viral capsids. When this cleavage is inhibited, the result is long noninfectious DNA particles. The genes UL56, UL89 and UL51 code for the three parts that comprise the terminase complex. Resistance is mainly conferred by mutations in the UL56 gene. As letermovir has a different target, there is no cross resistance with the other CMV antivirals.

Drug resistant CMV

During ganciclovir anti-CMV therapy, resistance mutations usually develop after a cumulative exposure of six weeks or more. Resistance mutations are usually first seen in the UL97 kinase gene. The UL54 (DNA-polymerase) mutations tend to emerge later and add to the level of resistance conferred by preexisting UL97 mutations. UL54 resistance mutations in the absence of UL97 mutations are uncommon.
There is little experience with Maribavir and Letermovir resistance in Norway as the use of the drugs has been very limited.

Antivirals against herpes simplex virus

Only one class of antivirals, targeting replication, is used for treating herpes simplex virus (HSV) infection:

- Replication: Analogues of naturally occurring guanosine that are incorporated into the growing strand of viral DNA by HSV DNA polymerase (UL30), causing termination of the growing viral DNA strand (chain termination). Examples: guanosine analogues aciclovir, penciclovir and their prodrugs

To be effective, aciclovir has to be triphosphorylated, first by a viral thymidine kinase and then by the cellular kinases to the active aciclovir-triphosphate. Aciclovir and valaciclovir are effective against both HSV-1 and HSV-2, as well as varicella zoster virus. Penciclovir is available as ointment for topical treatment of herpes labialis. Second line drugs include foscarnet and cidofovir.

Helicase-primase inhibitors, also targeting viral genome replication, are in development for treatment of HSV and VZV (pritelivir and amenamevir) (11).

Drug resistant HSV

Resistance to aciclovir develops by mutations of either the HSV-thymidine kinase or HSV DNA polymerase gene. Mutations in HSV- thymidine kinase are by far the most common, and about 95% of the resistance mutations are localized in the thymidine-kinase gene (UL23) whereas 5% are localized in the DNA-polymerase gene (UL30) (12).

Aciclovir resistance is frequently associated with cross-resistance to other HSV- thymidine kinase dependent nucleoside analogues (13). Cidofovir and foscarnet are independent of HSV- thymidine kinase and thus active against most of the strains that are resistant to aciclovir. Cross-resistance between foscarnet and aciclovir is rare (13). Although the prevalence of HSV resistance mutations is reported to be 0.1% -0.7% in immunocompetent patients and 3.5% to 10% in immunocompromised patients, treatment failures are relatively rare (12).

Antivirals against hepatitis C virus

There has been a rapid development of new and better drugs against hepatitis C virus (HCV) over the last years, replacing the early generations of direct-acting antivirals. There are now several pangenotypic combination tablets available, with high genetic barriers to resistance and excellent treatment responses. The goal of HCV therapy is to cure the infection. Treatment is usually given over 8-12 weeks, and most patients obtain sustained virological response (defined as absence of viremia 12 or 24 weeks after completion of treatment) (14).

There are currently three groups of direct-acting antivirals (DAAs) targeting HCV genome replication/transcription, protein production or multiple stages simultaneously (15):

- Replication: NS5B inhibitors.
    - Nucleoside analogue polymerase inhibitors: Compete with nucleosides for the active site of the HCV RNA dependent RNA polymerase (NS5B). Example: sofosbuvir.
    - Non-nucleoside analogue polymerase inhibitors: Alter the shape of the polymerase and thus inhibit replication of HCV. Example: dasabuvir.
- Protein production: NS3/4A protease inhibitors target the active site of the protease enzyme, NS3/4A, inhibiting proteolysis of the HCV polyprotein. Genotype specific. Example: voxilaprevir, grazoprevir.
- Multiple stages: NS5A inhibitors target the multifunctional NS5A protein, thereby affecting the replication, assembly and release of the virus. Examples: velpatasvir, ledipasvir.

Drug resistant HCV

Similar to HIV, HCV exhibits considerable genetic variation. The HCV RNA polymerase is relatively inaccurate and lacks proofreading, leading to a high mutation rate. As a result, a single infected person may harbour a vast population of variants, or quasispecies, dominated by the variants with the best viral fitness. Some of these random mutations may lead to amino acid substitutions associated with reduced susceptibility to antiviral drugs, called resistance-associated substitution (RAS). The RASs can be present prior to treatment, or they may develop during treatment. Continued replication under antiviral pressure increases selection of viruses with RASs. The clinical significance of the different RASs is variable, and the presence of a RAS does not necessarily predict treatment failure. After interruption of treatment, most RASs are reversed. However, some RASs may persist also in the absence of antiviral drugs, affecting future treatment options.

Antivirals against severe acute respiratory syndrome coronavirus 2

There are now several options with documented effect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) targeting entry, genome replication/transcription and protein production.

- Replication: Analogues of naturally occurring deoxynucleotides which are incorporated by the RNA-dependent RNA polymerase (RdRp) into the growing RNA product and inhibit RNA synthesis. Example: remdesivir.

- Protein production: Protease inhibitors block the activity of the main protease (Mpro) involved in cleaving the viral polyproteins. Example: nirmatrelvir/ritonavir.
- Attachment and entry: Monoclonal antibodies specifically directed against the spike protein of SARS-CoV-2, thereby blocking the virus' attachment and entry into human cells. Examples: sotrovimab, casirivimab/imdevimab, cilgavimab/tiksagevimab.

In addition, the peroral ribonucleoside analogoue molnupiravir, a drug that inhibits SARS-CoV-2 replication by viral mutagenesis, showed promising results in early clinical trials. However, the results could not be reproduced, the FDA emergency use authorization was withdrawn, and in June 2023, the company withdrew its application for a marketing authorization (16). Additional antivirals from new drug classes are under development, and some are in clinical trials.

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2 The usage of antivirals in Norway

Many new direct acting antivirals (DAAs), especially against HIV and HCV, have been developed during the last decades, but in recent years new drugs introduced have mostly been fixed combinations of already established drugs. The sales for the different ATC subgroups of DAAs over time are shown in Figure 2.1. The sales of DAAs, measured both in defined daily doses (DDDs) and in number of patients treated, have increased from 2018 to 2022 although the sales measured in number of DDDs was slightly reduced in 2020 and 2021. The number of users has increased from 59796 in 2018 to 75 489 in 2022 (Figure 2.1 and Figure 2.2, respectively). Drugs used for treatment of HIV-infection make up a large proportion of the total of antiviral drugs sold in Norway, measured in DDDs (1). Because a growing proportion of patients is treated with single tablet regimens, the number of drugs sold is reduced despite an increase in number of users. In 2018, price reduction for some of the drugs used in treatment of HIV and HCV resulted in reduced costs despite continued increase in sales. In 2022 the total cost of the DAAs had fallen by almost 38% since 2018.

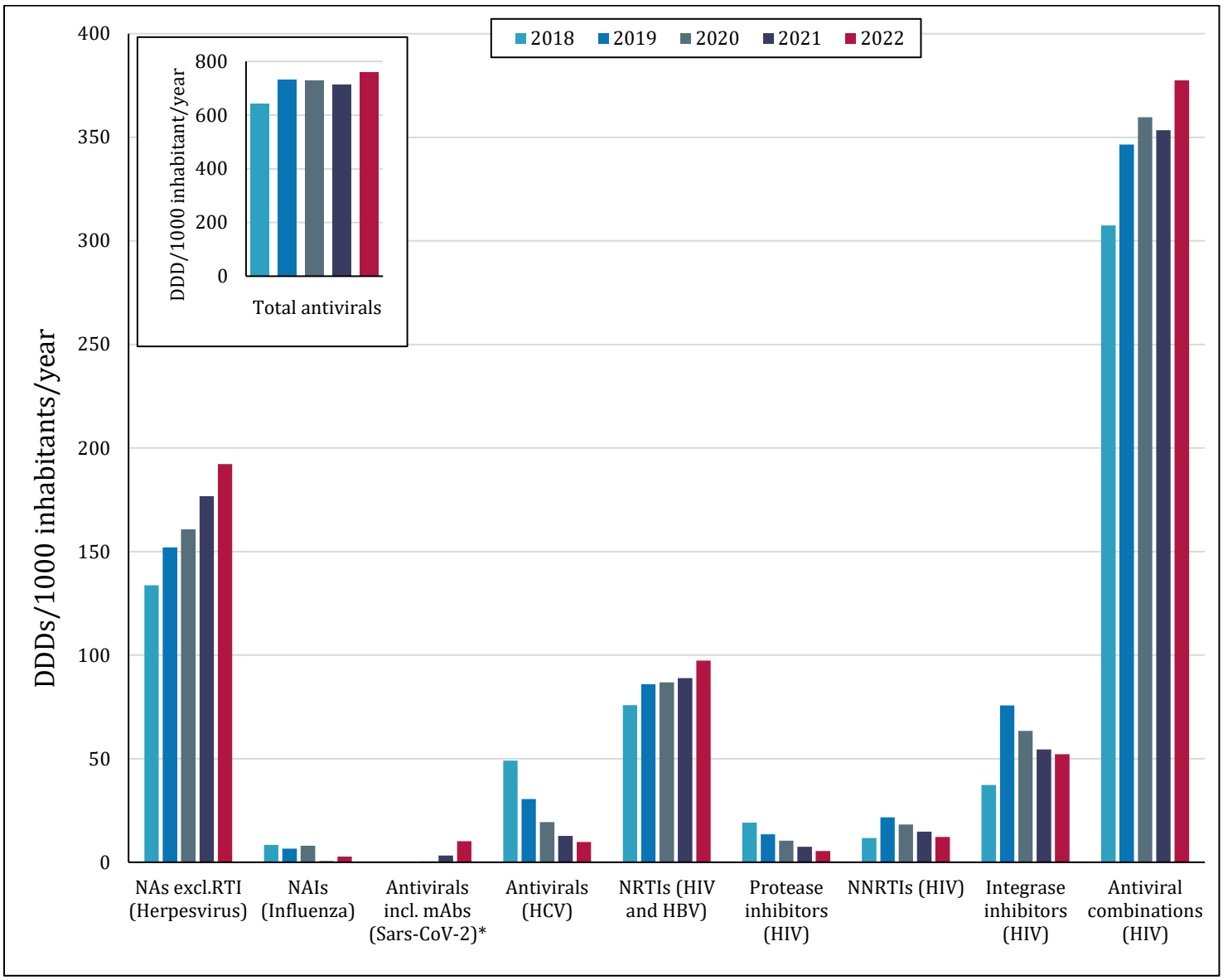

Figure 2.1 Sales of direct acting antiviral drugs for systemic use (ATC group J05A) for 2018-2022.

The figure shows the sales of direct acting antiviral groups over time according to the Norwegian drug wholesales statistics database. The numbers are given as defined daily doses (DDDs) per 1000 inhabitants per year. NAs excl. RTI: Nucleo(s/t)ide-analogues excluding reverse transcriptase inhibitors (J05AB); NAIs: Neuraminidase inhibitors (J05AH); Antivirals including monoclonal antibodies used in Sars-CoV-2 treatment/ prophylaxis: Remdesivir, Favipiravir, Molnupiravir, Nirmatrelvir and ritonavir, Sotrovimab, Tixagevimab and cilgavimab, Casirivimab and imdevimab(J05B, J05AE, J05AX and J06BD); Antivirals for treatment of HCV infections (J05AP); NRTIs: Nucleo(s/t)ide-analogue reverse transcriptase inhibitors (J05AF); Protease inhibitors (J05AE); NNRTIs: Non- nucleo(s/t)ide-analogue reverse transcriptase inhibitors (J05AG); Integrase inhibitors (J05AJ); Antiviral combinations, HIV: Antivirals for treatment of HIV infections, combinations (J05AR). The insert is a plot illustrating the total sales of antivirals in ATC group J05A in Norway. Antivirals reported from wholesales have not necessarily been used in 2022 but could be stored in pharmacies or in hospitals. * DDDs are not defined for tablets sold in packages.

The number of individuals treated with DAAs for HIV, HBV and herpes has increased since 2018, while the number of individuals treated for HCV has decreased. The use of DAAs against influenza varies from year to year and is usually closely connected to the magnitude of the seasonal influenza outbreaks. The number treated for influenza were extremely low in 2021, but in 2022, individuals treated increased, although the number is still lower than previous years (Figure 2.2). The number treated for cytomegalovirus infection is relatively stable, but slowly increasing.

Antivirals used for treatment of HIV dominate when sales are measured in number of DDDs (Fig. 2.1), while DAAs against herpesviruses are by far the most commonly used antivirals when measured in number of users (Figure 2.2). The high number of DDDs for HIV drugs reflects the long-term chronic treatment, while antivirals against herpes infections are given in short courses. For DAAs against herpesvirus, the use of topical agents (creams and ointments) is not included in the measurement of DDD.

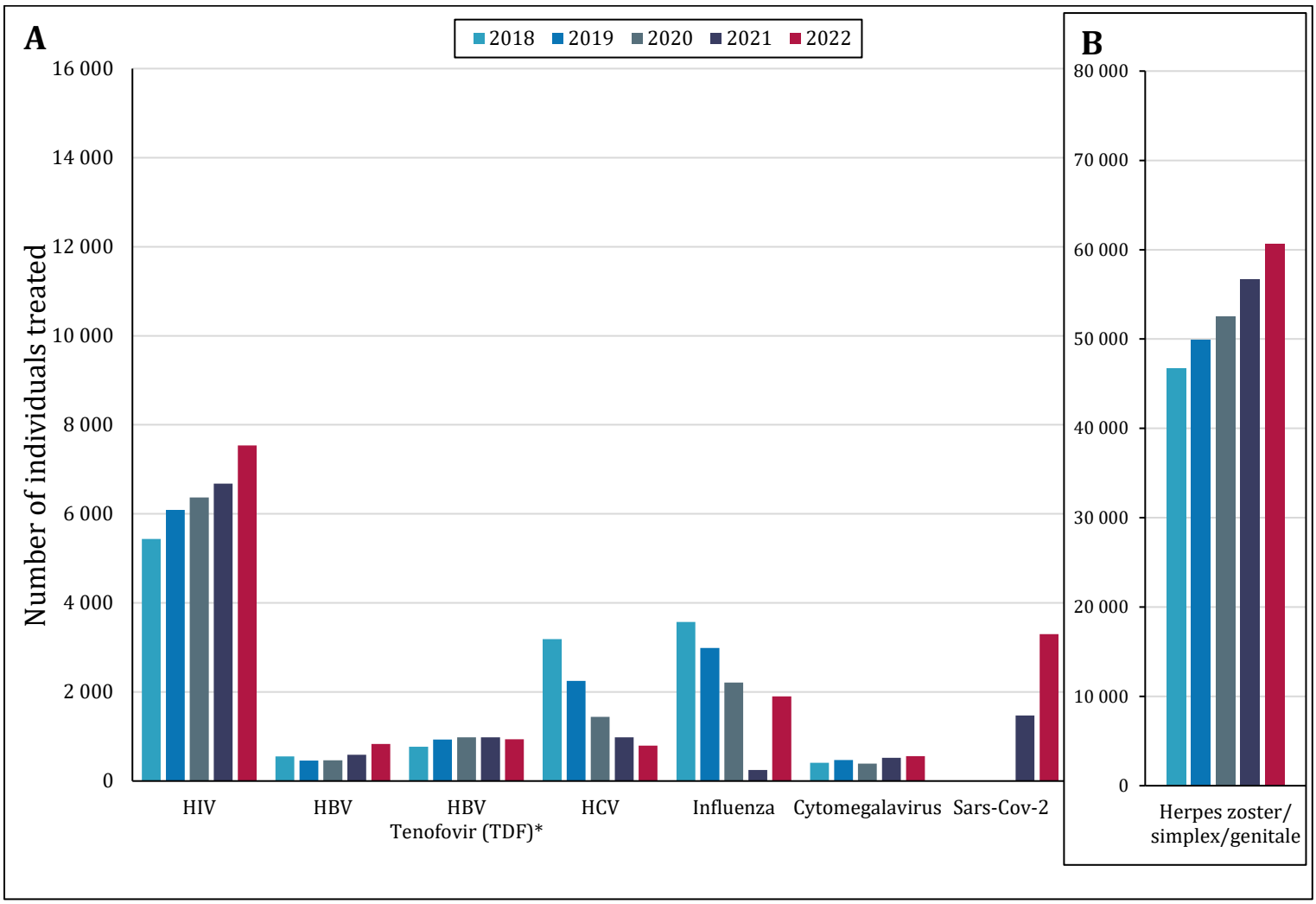

Figure 2.2 Trends in the use of direct acting antiviral drugs for systemic use (ATC group J05A) grouped by virus for 2018-2022 (2).

The figure shows the number of individuals treated for different viruses with systemic direct acting antivirals over time. The number of persons treated is based on the number of patients given at least one prescription per year. Panel A: HIV: All HIV pharmaceuticals incl. Epivir® (lamivudine); HBV: All HBV pharmaceuticals incl.Zeffix®(lamivudine), excl. Tenofovir (TDF); HBV (Tenofovir (TDF));HCV antivirals; Influenza: Neuraminidase inhibitors; Sars-Cov-2: nirmatrelvir and ritonavir and favipiravir; Cytomegalovirus: ganciclovir, cidofovir, foscarnet and letermovir. Panel B: Herpes zoster/genitale/simplex: aciclovir, valaciclovir and famciclovir. Data from the Norwegian prescription database (NorPD). * Tenofovir (TDF) is approved for use against both HIV and HBV, but as a single component drug it is mostly used to treat HBV. Other single component drugs approved for both HBV and HIV are included in the HBV numbers only.

Influenza virus

The usage of the neuraminidase inhibitors, antivirals for the treatment of influenza (ATC group J05AH), is shown in Table 2.1. The variation in the number of users of DAAs for treatment of influenza is probably related to the size and intensity of the seasonal influenza epidemic each year, the accuracy of the yearly influenza vaccine, and the proportion of the population vaccinated. It should be noted that the data on antiviral usage is collected per calendar year, which includes the end of one influenza season and the beginning of the next. The low number of users of antivirals against influenza in 2021 coincides with the low number of reported influenza cases in the seasonal influenza epidemics in 2021. Due to limited use, zanamivir was withdrawn from the market in 2016; consequently, oseltamivir is now the only neuraminidase inhibitor available for treatment of influenza in Norway.

Table 2.1 Number of individuals with at least one prescription of neuraminidase inhibitor per year (2).

	2018	2019	2020	2021	2022
Oseltamivir (J05AH02)	3571	2987	2214	248	1898

Human immunodeficiency virus

There are currently 34 drugs or combination drugs in Norway that are used solely for treatment of HIV. The use of the different drugs has shifted in the last five-year period. The number of patients retrieving at least one prescription of these drugs has increased by almost 39% from 2018 to 2022, partly attributable to the concurrent increase in the number of persons receiving pre-exposure prophylaxis (PrEP). During the whole period, nearly 99% of persons treated, received combination drugs containing more than one active substance. Some of these combination drugs contain complete combination ART (single-pill regimens). Figure 2.3 shows the trends in use of antiviral drugs for treatment of HIV, measured in number of persons treated. The figure shows single tablet regimens; fixed dose combination drugs, which contain combinations of two substances, typically two NRTIs that are commonly combined; and single substance drugs that are given in addition to the fixed combinations in order to obtain complete ART. Tenofovir disoproxil (TDF), adefovir dipivoxil and emtricitabine are approved for treatment of both HIV and HBV infections. However, since these single substance drugs are rarely used for HIV therapy, the users of these drugs are neither included in the total number of users of HIV treatment nor in the different groups in Figure 2.3. The sum of the patients using the different drugs is higher than the total number of patients treated with HIV drugs in Figure 2.2. This is because some patients receive more than one drug or may change treatment regimens during a year. The fixed combination of emtricitabine and tenofovir disoproxil (FTC/TDF) has been the most commonly used combination drug in recent years. It is usually used in treatment regimens together with either an integrase inhibitor, boosted protease inhibitor, or an NNRTI. For post exposure prophylaxis (PEP), the recommendation is to use FTC/TDF in combination with the integrase inhibitor raltegravir. In 2016, FTC/TDF was approved as PrEP to reduce the risk of sexually acquired HIV-1 infection in adults at high risk, with full reimbursement of the costs. PrEP is most likely the main reason for the observed yearly increase in the use of FTC/TDF since 2016. The number of patients receiving FTC/TDF in 2022 was 3722. The use of FTC/TDF increased almost 47% from 2018 to 2019, while the increase was only one percent from 2019 to 2020, two percent from 2020 to 2021 and 16% from 2021-2022. It is not unlikely that the extensive infection control measures applied in connection with the COVID-19 pandemic in 2020 and 2021 may have reduced the demand for PrEP, thereby contributing to the stagnation in 2020-21. However, from the drug statistics, it is not possible to separate the proportion of PrEP nor PEP from the total use of these drugs, and the changes in the use of FTC/TDF seen the latest few years might also have additional explanations. The prodrug of tenofovir, tenofovir alafenamide (TAF), is given in lower doses, and has a greater bioavailability in relevant body tissues than TDF. TAF is available in various fixed dose combinations with emtricitabine, both as duo-ingredient drug, and in combinations with substances from other drug classes as single-teblet complete treatment regimens (3). The combination drug FTC/TAF 25mg is approved as an alternative in continuous PrEP in persons with contraindications for FTC/TDF.

When looking at complete treatment regimens, combinations containing integrase inhibitors are widely used, which is also in accordance with the Norwegian guidelines (3). This is illustrated in Figure 2.3, which shows that many combination drugs containing integrase inhibitors are among the most sold drugs the latest years, measured in number of users. The recommendations from The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF) which negotiate prices and indicates the drugs of preference when it comes to reimbursement, have a great impact on the choice of drugs for treatment of HIV (4). The injection combination of the two single ingredients cabotegravir and rilpivirin,

was approved as complete dual therapy in December 2020. The sales of these injections were very limited in 2021 but increased markedly in 2022.

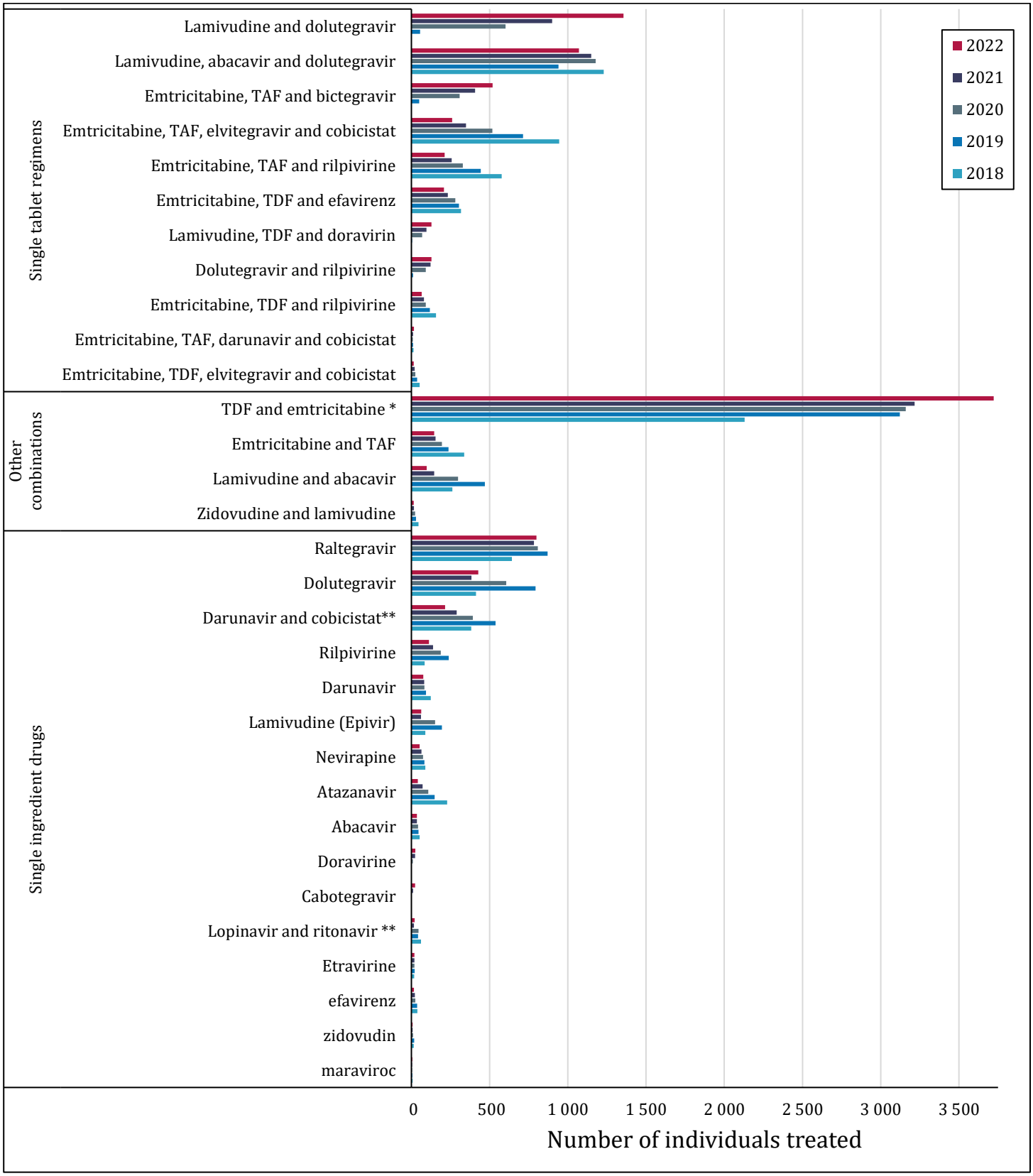

Figure 2.3 Trends in the use of antiviral drugs for treatment of HIV in the periods 2018-2022 (2).

The figure shows the number of individuals given at least one prescription per year. Complete single tablet regimens, other fixed dose combination drugs, and single ingredient drugs are shown separately. Drugs prescribed to less than 5 individuals in 2022 are excluded (atazanavir/ cobicistat; emtricitabine; zidovudine/ lamivudine/ abakavir). Ritonavir is also excluded. *Includes PrEP. **Boosted protease inhibitors are considered single ingredient drugs.

The use of the integrase inhibitors is increasing when measured in number of prescriptions per active ingredient. This is in line with the recommendations in the guidelines and the procurement recommendations. The number of prescriptions per active ingredient over time is shown in Figure 2.4. For NRTIs, there are far more prescriptions for emtricitabine and tenofovir (TDF or TAF) than for lamivudine and abacavir, but the number of prescriptions for complete treatment regimens in comparison to PrEP is not known. The integrase inhibitor dolutegravir is the most used active ingredient that is not an NRTI. The use of the second-generation integrase inhibitors dolutegravir and bictegravir is increasing when measured in number of prescriptions per active ingredient, while the use of the first-generation integrase inhibitor raltegravir is slightly decreased.

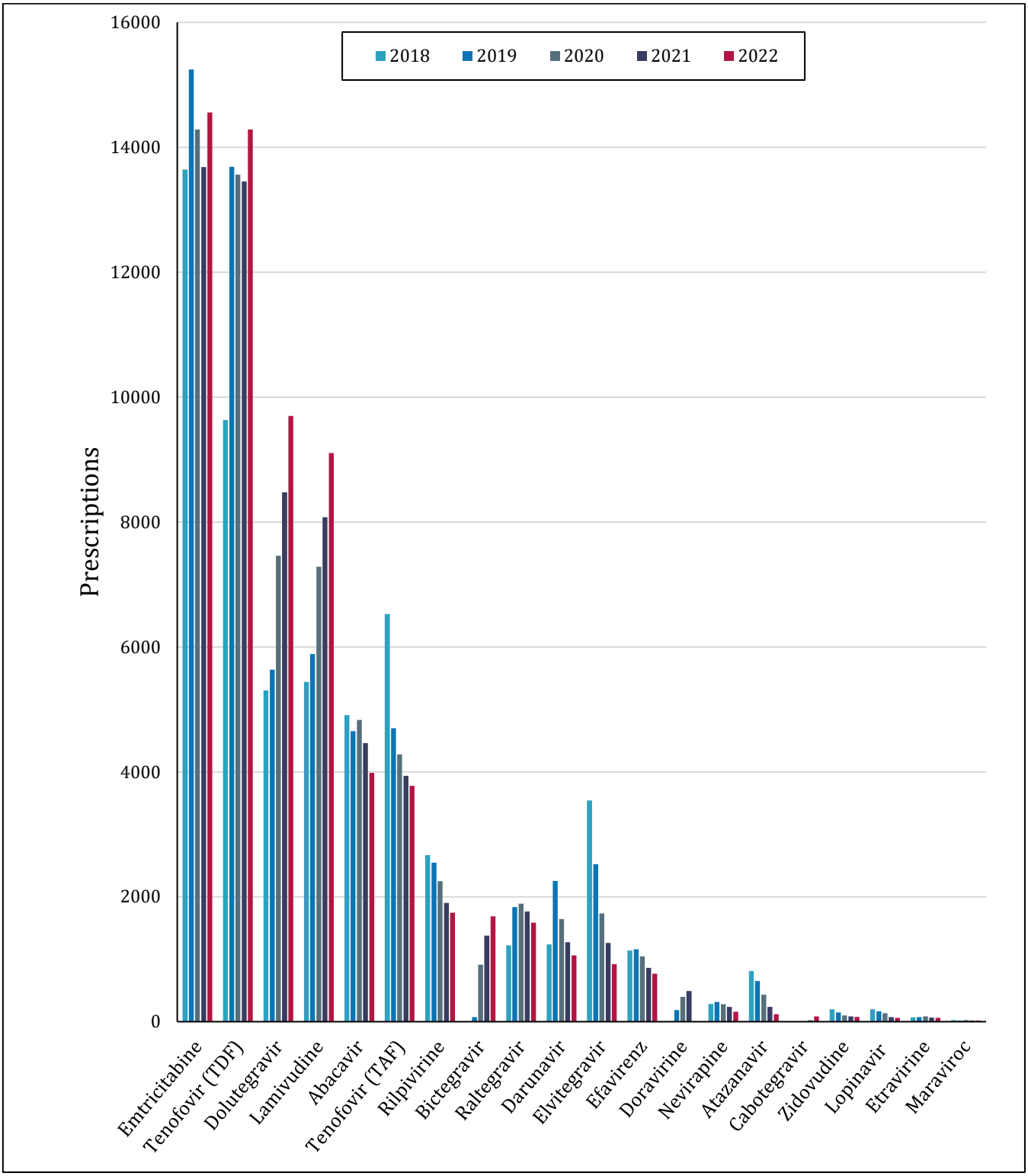

Figure 2.4 Number of prescriptions per active ingredient for HIV drugs (2).

This figure shows the number of prescriptions per active ingredient over time. Many prescriptions contain more than one active ingredient; these prescriptions are counted several times. TDF = tenofovir disoproxil, TAF = tenofovir alafenamide. Saquinavir was not prescribed in 2021 and 2022 and is excluded from the figure. Cobicistat and ritonavir, which are used as boosters to other drugs, have also been omitted from the figure.

Hepatitis B virus

No new antivirals have been introduced for treatment of HBV infection in 2022 and there are currently six nucleoside/nucleotide analogues approved for this indication. Treatment of HBV with antivirals is generally given as monotherapy. The use of the nucleoside/nucleotide analogues is shown in Figure 2.5. The data is based on the annual number of patients retrieving at least one prescription per year for the period 2018-2022. Lamivudine, adefovir dipivoxil, tenofovir disoproxil (TDF), and emtricitabine are approved for both HBV and HIV, while entecavir and tenofovir alafenamide (TAF) as a single substance drug, are approved for HBV only. The number of persons treated for HBV has increased during the last five years. TAF, which was approved for monotherapy of HBV in January 2017, in addition to entecavir and TDF, are considered first line therapies for HBV. Of the individuals receiving HBV treatments with nucleoside/nucleotide analogues, more than 99% received one of these three drugs in 2022. The number of persons treated with TDF decreased and the number of persons treated with TAF was stable from 2021 to 2022, while there was a 47% increase in the number of users of entecavir. From April 2021, entecavir is recommended as the preferred drug according to procurement recommendations, which might explain this observed increase (5).

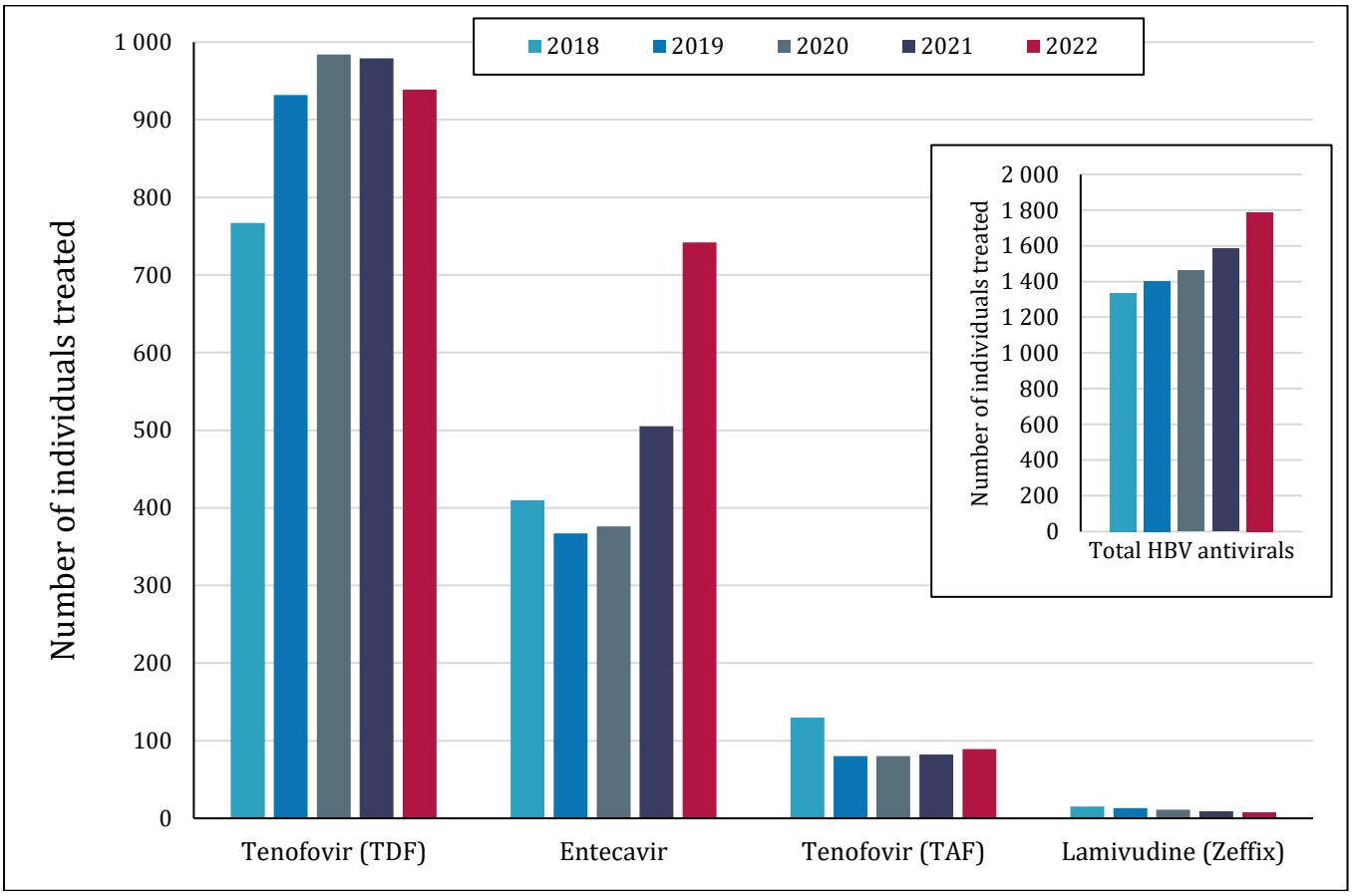

Figure 2.5 Trends in the use of antivirals for treatment of HBV for the period 2018-20221 (2).

This figure shows the trends in antiviral use for the treatment of HBV over time. The number of persons treated is defined as the number of patients given at least one prescription per year. The insert is a plot illustrating the total number of persons given at least one prescription of an antiviral against HBV per year (The total numbers are calculated as the sum of individuals given at least one prescription of each drug. Some individuals might have received prescriptions for more than one drug during one year). Adefovir dipivoxil and emtricitabine are not included in the figure due to very low sales.

Human herpesviruses

Figure 2.6 shows the prescribed drugs for systemic use for human herpes virus infections over the last five years. Valaciclovir is the most commonly prescribed substance and there has been an increase of more than 40% in the number of individuals treated with this antiviral since 2018. The use of aciclovir has been stable during the five-year period. In 2022, 60643 persons have been treated with systemic antivirals for herpes viral infections.

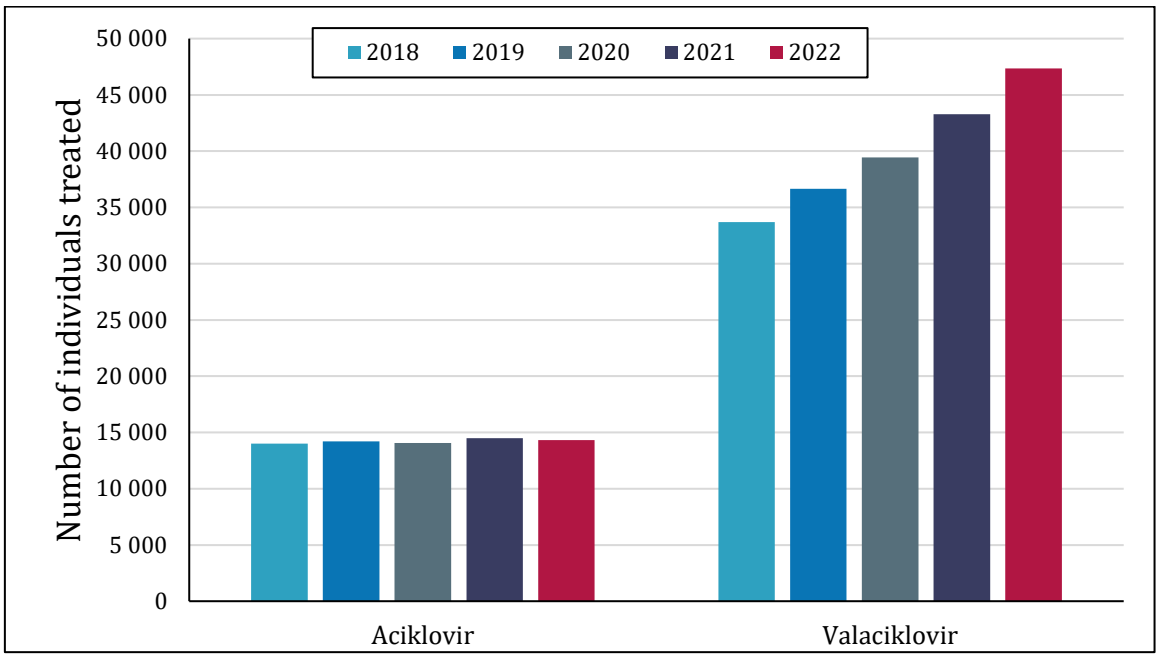

Figure 2.6 Trends in the use of antivirals for treatment of human herpes virus infection for the period 2018-2022 (2).

This figure shows the trends in direct acting antiviral use for treatment of human herpesviruses over time. Number of individuals treated is defined as the number of patients given at least one prescription per year. Ganciclovir, valganciclovir and famciclovir were rarely prescribed and not included in the figure.

Creams for topical treatment of herpes simplex virus infections of the lips and face (herpes labialis) are available in Norway. Aciclovir and penciclovir are the active ingredients in these creams. Small packages of aciclovir cream were made available for over-the-counter sales in 2006, and this resulted in a steep increase in the use of these creams the next couple of years. Since then, the consumption has been quite stable. From 2018 the use of a fixed combination of aciclovir and hydrocortisone has increased at the expense of topical aciclovir and penciclovir alone (Table 2.2).

Table 2.2 Sold packages of topical antivirals containing aciclovir, pencixclovir and aciclovir in combination with hydrocortisone.

	2018	2019	2020	2021	2022
Aciclovir	212 393	180 880	169 004	176 013	174 756
Penciclovir	18 957	18 664	17 229	14 054	10 272
Aciclovir, combinations	21 794	40 618	34 727	45 996	40 585

Most packages contain 2 g of cream; the exception is a 5 g package with aciclovir as the active ingredient where prescription is needed. Approximately 90 % is nonprescribed medications. * In combination with hydrocortisone. Data from the Norwegian drug wholesales statistics database.

Hepatitis C virus

After the HCV antivirals became available in 2015 there was a steady increase in the overall number of patients treated with DAAs against HCV until 2018, since then the number of persons treated has decreased (Figure 2.2). The number of persons who received at least one prescription for an HCV drug (except interferons) was 794 in 2022, a reduction by 75% from 2018 and 19% since 2021. Fixed combinations of two or more active ingredients have almost completely replaced single component drugs including ribavirin as shown in Figure 2.7.

Recommended treatment protocols for HCV-infection depend on both genotype and stage of liver disease. Norwegian treatment guidelines for HCV from the Norwegian Medical Association (NMA) were updated in 2019 (6). However, the recommendations from The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF) probably also have a great impact on the choice of drugs for treatment (7). These recommendations are similar but not identical to the NMA guidelines. From 2018 to 2021 the single-tablet regimen of the NS5B inhibitor sofosbuvir and the NS5A inhibitor velpatasvir, was the most used drug. This combination therapy was listed as the “recommended treatment” in genotype 3 HCV infections, one of the more common genotypes in Norway, in the procurement for 2019. In 2021 the combination of glecaprevir and pibrentasvir, another pangenotypic fixed combination with high treatment response, almost reached the same level of use as sofosbuvir and velpatasvir before it took over as the most used drug in 2022. The combination of glecaprevir and pibrentasvir also replaced the combination of sofosbuvir and velpatasvirand as the first-choice treatment for most cases of genotype 3 HCV infections in the procurement from April 2021. Elbasvir and grazoprevir, which in the 2021 procurement is considered as the first-choice treatment for most patients with HCV genotype 1, also a common genotype in Norway, is now the second most used combination in Norway.

The trends of use shown in Figure 2.7 reflect the change in national recommendations for treatment of HCV and procurement in the five-year period. “The National strategy against hepatitis 2018-2023" has two primary objectives: To reduce the prevalence of HCV by 90% by the end of 2023, and that no one in Norway should die or suffer serious illness caused by HCV (8). Hopefully, the reduction in treated patients after 2018 indicates that the goal is achievable.

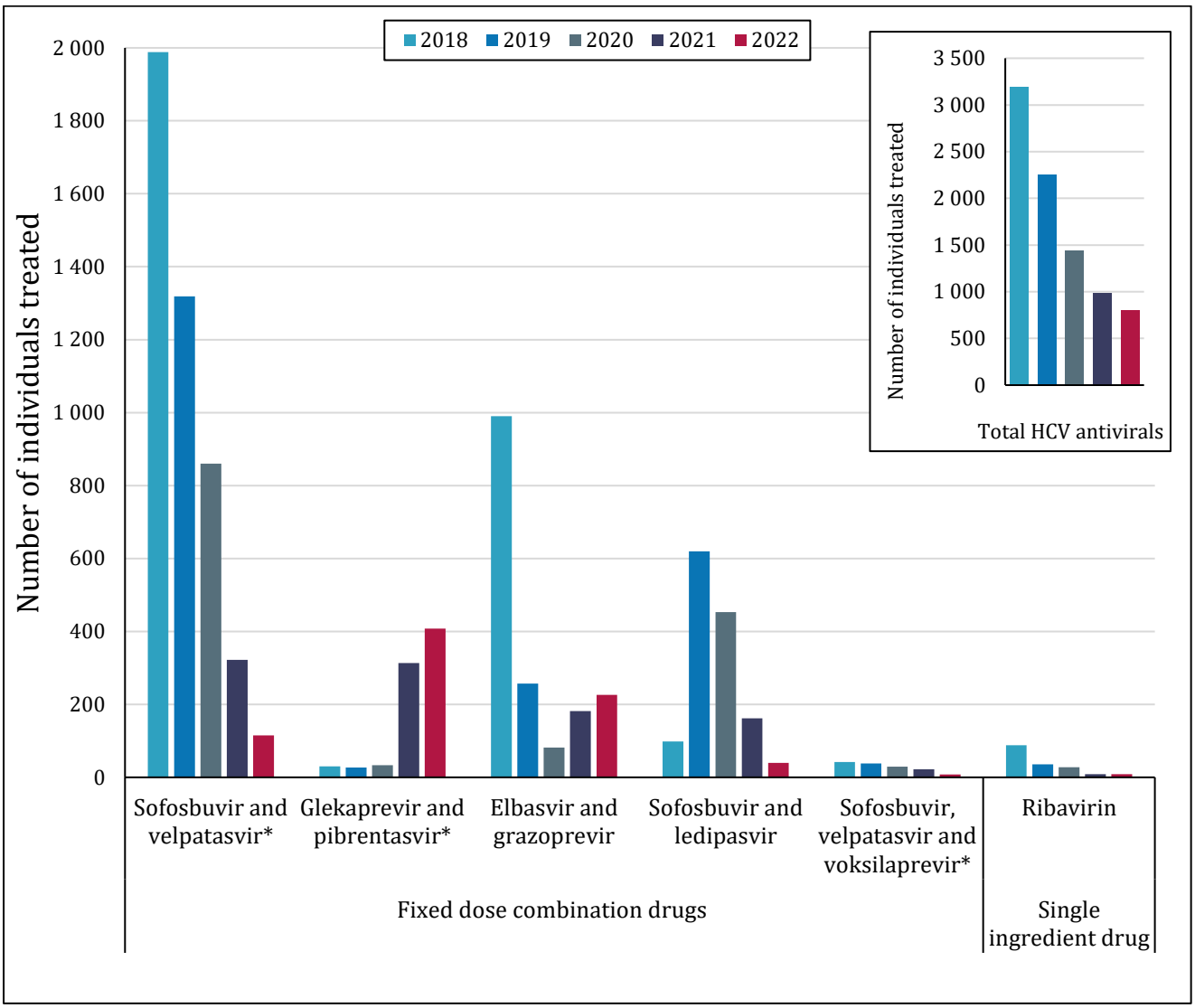

Figure 2.7 trends in the use of antivirals for treatment of HCV for the period 2018-2022 (2).

This figure shows the trends in the use of direct acting antivirals for treatment of HCV over time. The different drugs are sorted in fixed dose combination drugs and single ingredient drugs. The number of individuals treated is defined as the number of patients given at least one prescription per year. The insert is a plot illustrating the total number of persons given at least one prescription of an antiviral against HCV per year. Drugs not sold in 2022 (ombitasvir/paritaprevir/ ritonavir; simeprevir; sofosbuvir; dasabuvir) are excluded from the figure. * Pangenotypic drugs.

SARS-CoV-2

Only one oral antiviral drug against SARS-CoV-2, the combination of nirmatrelvir and ritonavir, has become available for out-patients in Norway, and 614 individuals were dispensed a prescription in 2022. Parenteral antiviral treatment of COVID-19 in Norway were only for hospital use. In Norway, remdesivir has since November 2020 been approved for use against SARS-CoV-2. The sale of remdesivir in 2020 and 2021 was limited, but in 2022, 4240 packs were used in Norwegian hospitals according to Sykehusapotekenes Legemiddelstatistikk (the hospital pharmacies drug statistics database). The increase was seen after treatment recommendations were extended to also include treatment of severely ill patients, and not only early treatment of risk groups.

The use of monoclonal antibodies for the treatment of SARS-CoV-2 has been limited in Norway. The clinical efficacy of the individual drugs against different variants is variable, and thus, recommendations for use depend on the variant currently circulating. In 2021, two new medicaments containing monoclonal antibodies (sotrovimab and casirivimab/imdevimab) have been introduced for treatment of hospitalized patients with SARS-CoV-2 who are at increased risk of progressing to severe COVID-19. and in 2022, tixagevimab and cilgavimab became available. In 2022, a total of 1149 packages of sotrovimab, 203 packages of casirivimab/imdevimab and 1728 packages of tixagevimab and cilgavimab were sold according to data from the Norwegian Drug Wholesales Statistics. Records of actual use in hospitals are not available.

Early efforts in the search for effective antiviral treatment of SARS-CoV-2 included repurposing of existing antiviral drugs used for other infections. Favipiravir is a nucleotide analogue approved in Japan for use against influenza virus, and its effect against SARSCoV-2 is under investigation. In 2022, there were 3178 prescriptions of favipiravir in Norway prescribed to 2690 individuals. The drug is not licensed in Norway as an antiviral against influenza virus, hence it is likely that in 2022, the drug was prescribed primarily against COVID-19 infection.

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3 Influenza virus

Fact box: Influenza virus drug resistance	
Treatment	Neuraminidase inhibitor: oseltamivir. Polymerase inhibitor: Balaxovir marboxil (Licensed in Norway May 2021).
Resistance testing method	Whole genome sequencing. Phenotypic by neuraminidase susceptibility assay (MUNANA). In Norway, all influenza drug resistance tests are performed at the WHO national reference laboratory for influenza, at the Norwegian Institute of Public Health (NIPH).
Target gene	Neuraminidase/ polymerase and matrix gene.
Indication for resistance testing	- Patients treated with antiviral drugs; with a particular focus on immunocompromised patients and young children as they often shed virus long-term, patients with severe or progressive illness who do not clinically improve, and patients with evidence of ongoing influenza virus replication through viral load monitoring. - Patients developing illness after or during antiviral chemoprophylaxis. - Patients infected after exposure to individuals receiving antiviral drugs. - Surveillance.
Surveillance	Screening for resistance as part of the national influenza surveillance program, which involves samples from both untreated and treated patients. There is currently no active systematic surveillance for treatment-induced resistance.

Surveillance methods

The WHO national reference laboratory for influenza in Norway is located at the NIPH and monitors the occurrence of influenza viruses in Norway. A volunteer network of sentinel physicians in all parts of the country provides samples taken from patients with influenza-like illness, and the medical microbiology laboratories submit a subset of confirmed influenza-positive samples for analysis. Samples from both untreated and treated patients in the community are included. In order to facilitate detection of emergence and spread of viruses with resistance, there is a particular focus on samples from patients without known exposure to antiviral drugs.

Surveillance data influenza season 2022-23

The 2022/23 season started early with outbreak threshold of 10 % positive in week 48 (sentinel)/week 49 (comprehensive) and had a sharp first peak in weeks 51-52/2022 with 46 % positive in the sentinel and 25 % positive in the comprehensive surveillance. The positivity rate fell markedly in the following few weeks before it recovered and went through two smaller peaks in weeks 6 and 12, respectively. After this, the numbers declined gradually, falling below 10 % positive in overall testing in week 15 and in sentinel

testing in week 18. The positivity rate has been very low (below 1%) since midsummer but with sporadic detections in every week.

Influenza A(H1N1) viruses predominated in the first and largest peak around New Year. With subsequently declining numbers, the frequencies of H1N1 and H3N2 also became more even. Influenza B/Victoria lineage viruses started to rise after New Year, surpassed influenza A in week 8, and were predominant in the last wave that peaked in week 12. Since midsummer, influenza A viruses have again been in majority among the few detections, most being H1N1. All circulating influenza B viruses that have been tested for lineage have belonged to the B/Victoria/2/1987 lineage.
Resistance to antiviral agents in Norway is reported by the WHO National reference laboratory for influenza, NIPH via the Global Influenza Surveillance and Response System and ECDC/WHO (1). During the 2022-23 season, a total of 1133 influenza viruses have been tested for resistance to neuraminidase inhibitors such as oseltamivir (table 3.1). One virus showed resistance due to a H274Y mutation in the NA gene. This is a treatment-induced case and resistance is known to potentially develop towards the end of a treatment course. All other viruses examined were sensitive to treatment with oseltamivir and all of those tested (316) for resistance to baloxavir marboxil were also sensitive. Phenotypic testing for neuraminidase inhibitor susceptibility was not performed for any of the samples, as antiviral resistance testing of influenza virus has been deprioritized during the COVID-19 pandemic. For many years, all circulating influenza viruses have been resistant to adamantanes, thus these antivirals are not used for treatment in Norway and most other countries.

Table 3.1: Norwegian influenza viruses resistant to the neuraminidase inhibitors oseltamivir and zanamivir, during the influenza seasons 2017/18 through 2022/23 (sequences with resistance/total number of analysed sequences. Percentages > 0 are shown in parentheses).

Season	Oseltamivir resistance			Zanamivir resistance			Baloxavir resistance			Adamantane resistance		
	A(H1N1)	A(H3N2)	B	A(H1N1)	A(H3N2)	B	A(H1N1)	A(H3N2)	B	A(H1N1)	A(H3N2)	B
2017/18	0/120	0/66	1/42	0/28	0/54	0/30	ND	ND	ND	ND	ND	ND
2018/19	0/247	0/108	0/26	0/82	0/107	0/26	ND	ND	ND	ND	ND	ND
2019/20	0/103	0/63	0/42	0/32	0/60	0/42	ND	ND	ND	ND	ND	ND
2020/21	0/2	0/6	0/1	0/2	0/6	0/1	ND	ND	ND	ND	ND	ND
2021/22	0/31	0/634	0/9	0/31	0/634	0/9	0/0	1/442	0/0	19/19	476/476	0/0
2022/23	1/494	0/291	0/347	1/494	0/291	0/347	0/74	0/232	0/10	ND	ND	ND

ND: No data

Conclusions

Antiviral drug resistance in influenza remains low nationally as well as globally, based on the very few cases investigated during the COVID-19 pandemic. Global estimates made before COVID-19, indicated that approximately 0.5% of all viruses tested have reduced susceptibility towards neuraminidase inhibitors and this is expected to be similar for Europe (2). Continued monitoring is important, both in samples from the community and in patients treated with antivirals.

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4 Human immunodeficiency virus

Fact box: Human immunodeficiency virus (HIV) drug resistance	
Treatment	Antiretroviral treatment (ART) of HIV-infection is always given as a combination of drugs from at least two of the five different classes: - Nucleoside reverse transcriptase inhibitors (NRTIs). - Non-nucleoside reverse transcriptase inhibitors (NNRTIs). - Integrase strand transfer inhibitors. - Protease inhibitors. - Entry inhibitors (CCR5 antagonists, fusion inhibitors, attachment inhibitors, post-attachment inhibitors).
Resistance testing method	Genotypic assays based on Sanger sequencing of target genes, and identification of mutations associated with drug resistance. Plasma viral load > 500 copies/mL is usually required. In Norway, all HIV-1 drug resistance tests are performed at the National Reference laboratory for HIV at the Department of Microbiology at Oslo University Hospital, Ullevål.
Target genes	Reverse transcriptase Protease Integrase gp120 envelope (for CCR5/CXCR4 tropism)
Indication for resistance testing	Virological failure during antiviral treatment.
Surveillance	The national surveillance program for HIV-1 monitors primary drug resistance against protease inhibitors and reverse transcriptase inhibitors (NNRTIs and NRTIs). Samples from all patients with newly diagnosed HIV-1 infections are tested for resistance mutations located in the protease and reverse transcriptase genes.

Surveillance methods

The Norwegian surveillance data is based on resistance testing of samples collected from newly diagnosed patients in Norway. Although some of these patients may be previously exposed to antiretroviral drugs, most are treatment naïve, and the data may serve as a proxy for transmitted drug resistance. Since 2019, drug resistance data has been cross-referenced to epidemiological data from MSIS (1), enabling analysis of the prevalence of surveillance drug-resistance mutations (SDRMs) in different subgroups, such as risk groups or country of infection.

New HIV infections are reported to MSIS with full patient identification. Although resistance testing is recommended for all newly diagnosed patients, not all are included in the surveillance system. This could have different explanations: i) sample not submitted for resistance testing, ii) patient not identified as newly diagnosed on the referral form, or iii) viral load was suppressed at the time of diagnosis, usually due to treatment initiated before arrival in Norway.

The World Health Organization (WHO) recommends the use of a consensus genotypic definition of transmitted HIV-1 drug resistance to compare estimates of transmitted drug resistance rates across geographic regions, and over time (2). A standard list of SDRMs was published in 2009, but unfortunately, the list has not been updated since 2009 (3). The list is based on a set of criteria to ensure that the mutations included are nonpolymorphic, are applicable to the most common subtypes, and do in fact contribute to resistance. The SDRM list is not designed for individual patient management as not all clinically relevant drug resistance mutations are included in the list from 2009, and the list may include certain mutations with less clinical relevance for current regimens. The listed mutations are however robust markers of temporal trends in transmitted drug resistance. The monitoring in Norway is based on the WHO SDRM-list from 2009 and analysed using the Calibrated Population Resistance tool at Stanford HIV Drug Resistance Database. All sequences are also analysed using the Stanford genotyping resistance interpretation algorithm in order to identify additional clinically relevant resistance mutations.

There has been an increase in the use of integrase strand transfer inhibitors in first line regimens, but resistance mutations affecting these compounds are still rare in treatment naïve patients. Baseline testing of resistance to integrase inhibitors is therefore not yet recommended (4), and there is no surveillance of primary resistance to inhibitors in Norway.

Surveillance data 2022

A total of 106 samples from newly diagnosed cases of HIV-1 in Norway were analysed for primary HIV-1 drug resistance in 2022. This equals 43% of the 245 cases reported to MSIS in 2022 (5). Of the 106 cases submitted for resistance testing, 37% were female and 63% were male.

The distribution of the most common HIV subtypes detected in samples from newly diagnosed patients in Norway the last five years is shown in Figure 4.1. Subtype B is the most commonly transmitted subtype in Norway, while the transmission of subtype A and C in Norway is low. Distribution of subtypes in samples from patients infected abroad is more diverse, mostly reflecting the prevalence of various subtypes in the country of transmission.

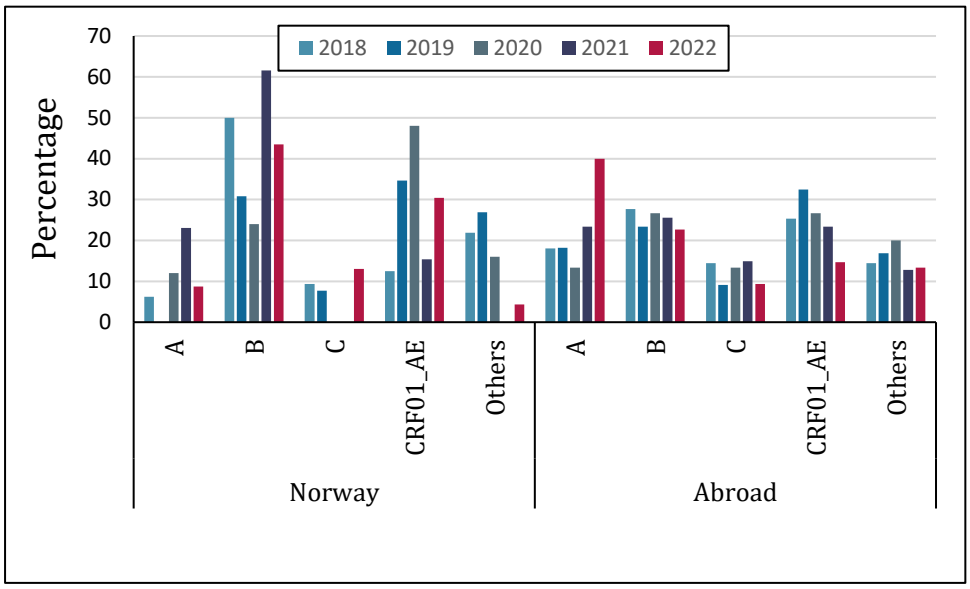

Figure 4.1. Percentage of subtypes among analysed sequences 2018-2022 by country of transmission.

The five most frequent subtypes are shown. The group of others includes the subtypes CRF02_AG, CRF06_cpx, subtypes D, F, and G, as well as single cases of several other circulating recombinant forms (CRFs) and other recombinants.

Information on the route of transmission was obtained by cross-referencing patients tested for drug resistance with epidemiological data from MSIS. The data is shown in Table 4.1. Only 23 (22%) samples submitted to RAVN were from patients infected in Norway, while 75 (71%) were infected abroad. In 2022, a nearly complete coverage of resistance testing was obtained among patients infected in Norway. In fact, the cross reference of data with MSIS even revealed cases that had not been notified to MSIS. Among those infected abroad in 2022, the coverage was significantly lower (37%). However, this group includes both travelers that are infected abroad but residing in Norway at the time of infection, and immigrants that may have been infected before arrival in Norway. Particularly among the latter, many may already be receiving treatment at the time of notification to MSIS and will therefore be ineligible for resistance testing due to a suppressed viral load. Among persons infected abroad while residing in Norway, surveillance resistance testing was performed in approximately 77% of the cases. Data is shown in Table 4.2.

Table 4.1: Route of transmission in samples from newly diagnosed HIV patients tested for antiretroviral drug resistance in 2022 compared to new cases reported to MSIS in 2022.

Route of transmission	Samples tested for resistance, 2022	Cases reported to MSIS, 2022
Heterosexual	63	138
- infected in Norway	9	9
- infected abroad	53	127*
- unknown	1	2
Men who have sex with men	29	59
- infected in Norway	12	11
- infected abroad	17	48*
- unknown	0	0
Injection drug users	3	24
Blood	0	0
Mother to child	2	5
Unknown	9	19
Total	106	245

MSM: men who have sex with men; IDU: injection drug users; MTC: mother to child.
*Includes cases on treatment and with suppressed viral load upon arrival in Norway.

Table 4.2: Coverage of resistance testing by country of transmission, compared to new cases reported to MSIS in 2022 (corresponding numbers for 2021 shown in parenthesis)

Country of transmission	Samples tested for resistance, 2022	Cases reported to MSIS, 2022	Coverage 2022 (2021)
Infected in Norway	23	21	~ 100% (87%)
Infected abroad	75	202	37% (55%)
- before arrival in Norway	49	171	29% (45%)
- while residing in Norway	24	31	77% (89%)
Unknown	8	22	
Total	106	245	43% (63%)

*Approximately 100%. There might be discrepancies between individual cases in MSIS and RAVN

In 2022, SDRMs from the WHO list were detected in ten samples, which equals 9.4% of the analysed sequences. In total, SDRMs were detected in 4 females and 6 males, corresponding to about 10% and 9 % of the analysed samples from females and males, respectively. The frequencies of SDRMs are presented in Figure 4.2, showing the percentage of sequences with detected SDRMs during each year of surveillance.

Of the analysed sequences, 3.8% had SDRMs associated with resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), and 5.7% with nucleoside reverse transcriptase inhibitors (NRTIs), whereas 1.9% had SDRMs associated with resistance to protease inhibitors, as shown in Figure 4.3.

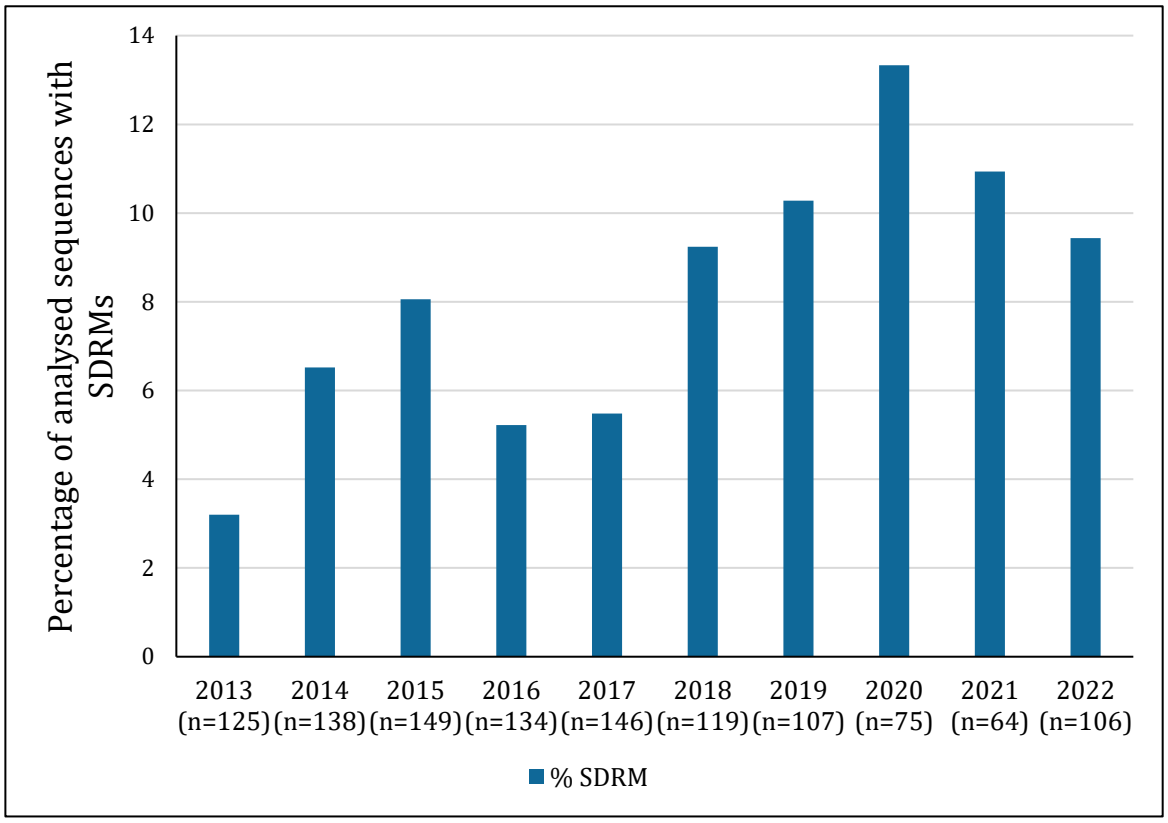

Figure 4.2: Percentage of analysed sequences with detected surveillance drug resistance mutations (SDRMs).

Percentages of the analysed sequences containing one or more SDRMs through the years 2013-2022 are shown as blue columns. There may be several SDRMs per sequence. n = number of sequences analysed for pre-treatment resistance.

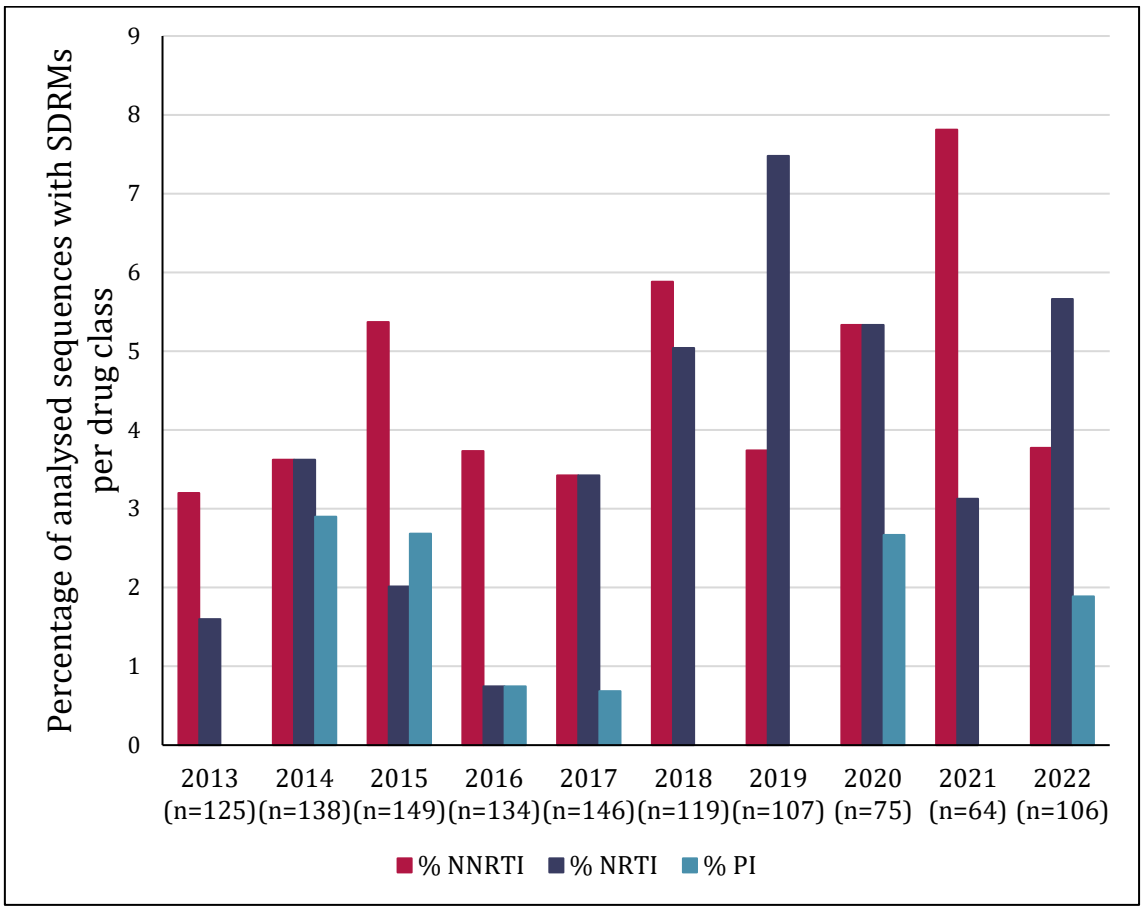

Figure 4.3: Percentage of analysed sequences with detected SDRMs per drug class.

Percentage of mutations affecting the individual drug classes are shown as colored bars; non-nucleoside reverse transcriptase inhibitors (NNRTIs) in red, nucleoside reverse transcriptase inhibitors (NRTIs) in dark blue, and protease inhibitors (PI) in light blue. n = number of sequences analysed for pretreatment resistance.

The individual mutations are specified in Table 4.3 for the ten patients with detected SDRM, along with country of transmission. Two patients (20%) were infected in Norway, and eight (80%) were infected abroad. Furthermore, all patients with detected SDRM were treatment naïve. Each of the four NNRTI-mutations detected is considered to be of clinical significance. As for the NRTI-mutations detected, the mutations in position 215 do not reduce susceptibility to NRTI, but are considered revertants that are often detected in patients primarily infected with strains containing the more significant T215Y/F. The remaining NRTI-mutations do not confer reduced susceptibility to any of the drugs currently in use. The mutation (M46L) in protease is not considered to be of clinical significance as it alone does not confer resistance to protease inhibitors, and it does not affect the sensitivity to the most commonly used protease inhibitor darunavir.

As the list of SDRM has not been updated since 2009, the sequences were also analysed using an interpretation algorithm that identifies additional clinically relevant resistance mutations. In this analysis, we detected a total of five sequences harboring the E138A mutation in reverse transcriptase, a mutation that reduces susceptibility to the NNRTIs etravirine and rilpivirine. Four of these samples were from patients infected abroad, and for one patient the country of transmission was unknown.

Table 4.3: Specification of the surveillance drug resistance mutations (SDRMs) detected in 2022, according to corresponding drug class.

Sekvens	NRTI	NNRTI	Protease Inhibitors	Country of transmission
1	None	Y188L	None	Abroad
2	D67N, T215DV, K219Q	G190A	None	Abroad
3	T215S	K103N	None	Abroad
4	M41L	None	None	Norway
5	None	K103S	None	Abroad
6	M41L, T215D	None	None	Norway
7	None	None	M46L	Abroad
8	K219N	None	None	Abroad
9	T215I	None	None	Abroad
10	None	None	M46L	Abroad

Discussion

The surveillance is based on resistance data from patients who have their HIV-1 infection confirmed in Norway, and where a sample was sent to the National reference laboratory for HIV at Oslo University Hospital for resistance testing. The data reported for 2022 has been cross-referenced to epidemiological data from MSIS, enabling detailed analysis of transmitted drug resistance in Norway by studying the prevalence of SDRMs in different subgroups, such as risk groups or country of infection. This also provides useful information on the coverage of primary resistance testing in the different subgroups.

In 2022, there was an increase in the number of new HIV-infections reported to MSIS compared to 2021. In particular, the number of persons infected abroad increased, which affects both the overall coverage of drug resistance surveillance, as well as the presence of drug resistance mutations among the newly diagnosed patients.

The coverage of resistance testing among patients infected abroad seemed to be slightly reduced in 2022 compared to 2021 both for patients infected before arrival (29% and 45%, respectively) and among patients residing in Norway at the time of infection (77% and 89%, respectively). Although the reduction was not statistically significant (Fisher exact test), focus on maintaining and improving local routines for submission of samples for resistance testing in newly infected patients in Norway is still warranted.

In 2021, there was for the first time since 2016 observed a decrease in detected SDRMs. This was further decreased in 2022 where SDRMs were detected in 9.4% of sequences analysed. Similar to previous years, the detected mutations with the most clinical impact such as K103N, Y188L, or G190A, were found in samples from patients infected abroad. Only 2 of the 10 patients with detected SDRM were infected in Norway, none of which had virus harboring drug resistance mutations of clinical relevance. The clinically relevant mutation E138A was found in the samples from four patients all infected abroad, and in one sample from a patient for which country of transmission was unknown. It is important to mention that there are many treatment options available for patients with detected drug resistance mutations.

In 2022, none of the detected mutations are associated with reduced susceptibility to emtricitabine or tenofovir that are used for pre-exposure prophylaxis (PrEP). This means that PrEP can be expected to be effective in preventing new cases. So far there are no signs of an increase in drug resistance associated with PrEP among patients newly diagnosed

with HIV in Norway, but continued monitoring of possible PrEP-related resistance will be of importance.

Conclusions

The prevalence of transmitted drug resistance remains low in Norway. The majority of the drug resistance mutations detected through the surveillance of newly infected patients, are found in samples from patients infected abroad.

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HIV drug resistance after six years with pre-exposure prophylaxis (PrEP) in Norway

Anne-Marte Bakken Kran

Pre-Exposure Prophylaxis (PrEP) has emerged as an important intervention for effective prevention of HIV in defined risk groups (1). In 2017, Norway was one of the first countries in the world to offer PrEP with full reimbursement of the costs. PrEP is a medication regimen that involves taking antiretroviral drugs to prevent the acquisition of HIV in individuals who are at high risk of HIV-infection, usually as a fixed dose combination of tenofovir disoproxil fumarate and emtricitabine.

When taken consistently and correctly, PrEP is shown to significantly reduce the risk of HIV transmission (2-4). While the significant benefits of PrEP are well documented, concerns have been raised regarding the risk for development and spread of drug-resistant HIV strains by the introduction of PrEP (5). Firstly, the use of PrEP may select for mutations associated with resistance to the drugs commonly used as PrEP, thereby contributing to the spread of HIV drug resistance. Among individuals infected despite using PrEP, the emergence of drug resistance is not uncommon. Secondly, as PrEP protects against the spread of susceptible strains while protection against drug-resistant strains is limited, the prevalence of drug-resistant strains might increase. The high mutation rate and genetic adaptability of HIV is well known, and a pertinent question arises as to whether the use of the same drugs for both treatment and prevention could compromise the efficacy of preferred first-line ART regimens.

In Norway, protocols for initiation and follow-up of PrEP were established in order to minimize the risk for development of drug resistance, including frequent and adequate testing for HIV-infection (6). Furthermore, the ongoing surveillance program for HIV drug resistance was intensified in order to monitor the prevalence of drug resistance and its potential association with PrEP use. So far, the widespread use of PrEP has not been associated with a significant increase in the prevalence of drug resistance at a population level. In the surveillance, only data on patients newly diagnosed with HIV-infection in Norway is included.

However, we have now been able to look at mutations associated with reduced susceptibility to tenofovir and emtricitabine in all samples analysed in Norway during the last 10 years. Here we present the frequency of these mutations both in surveillance samples from newly diagnosed patients and in clinical samples collected due to virological failure. The findings after 6 years with reimbursed PrEP in Norway are summarized below.

Relevant mutations

There are specific mutations in HIV virus that are associated with resistance to the medications used in PrEP. The key mutations to monitor are K65R, K70E, and M184V, all located in the reverse transcriptase gene. The mutation K65R reduces the susceptibility of the virus to tenofovir. K70E may arise as a compensatory mutation along with K65R and further decreases susceptibility to tenofovir. The presence of M184V/I reduces the susceptibility of the virus to emtricitabine.

Results from the drug resistance surveillance of patients newly diagnosed with HIV

In the period from 2016 -2022, mutations with relevance to either tenofovir or emtricitabine were detected in samples from six patients out of the total 645 patients included in the surveillance in the period. Of these six, one patient was infected abroad, one was previously treated with emtricitabine, and for four patients, further information on transmission or previous treatment history was not available. Details are shown in table 4.4.

Table 4.4: Mutations associated with reduced susceptibility for PrEP, detected in the surveillance samples collected from newly diagnosed individuals in the period from 2016-2022.

Year	Number of samples	Mutation	Additional information
2016	0		
2017	3	M184V M184V/K70R M184V/K70R	
2018	1	M184V	
2019	1	M184V	Infected abroad
2020	1	M184I	Previously treated
2021	0		
2022	0		

Clinical samples from patients with virological failure

In Norway, all analyses for drug resistance in HIV are performed at the reference laboratory at Oslo University Hospital. This includes all samples analysed for surveillance purposes. However, the majority of the analysed samples are from patients with detectable HIV viral load during antiretroviral treatment (ART) and submitted for drug resistance testing due to suspected virological failure. Thus, overall data from drug resistance analyses at the reference laboratory includes all mutations detected in samples from patients residing in Norway, that have had a sample submitted for drug resistance testing. Data was collected anonymously, and therefore, the dataset may be biased because the inclusion of more than one sample from the same individual cannot be excluded.

In Figure 4.4, the number of clinical samples containing the key mutations associated with reduced susceptibility for tenofovir or emtricitabine are shown for the years 2012 – 2022. The data shows that although the total number of samples analysed has not decreased during the period, there has been a significant decline in the number of PrEP-related mutations detected.

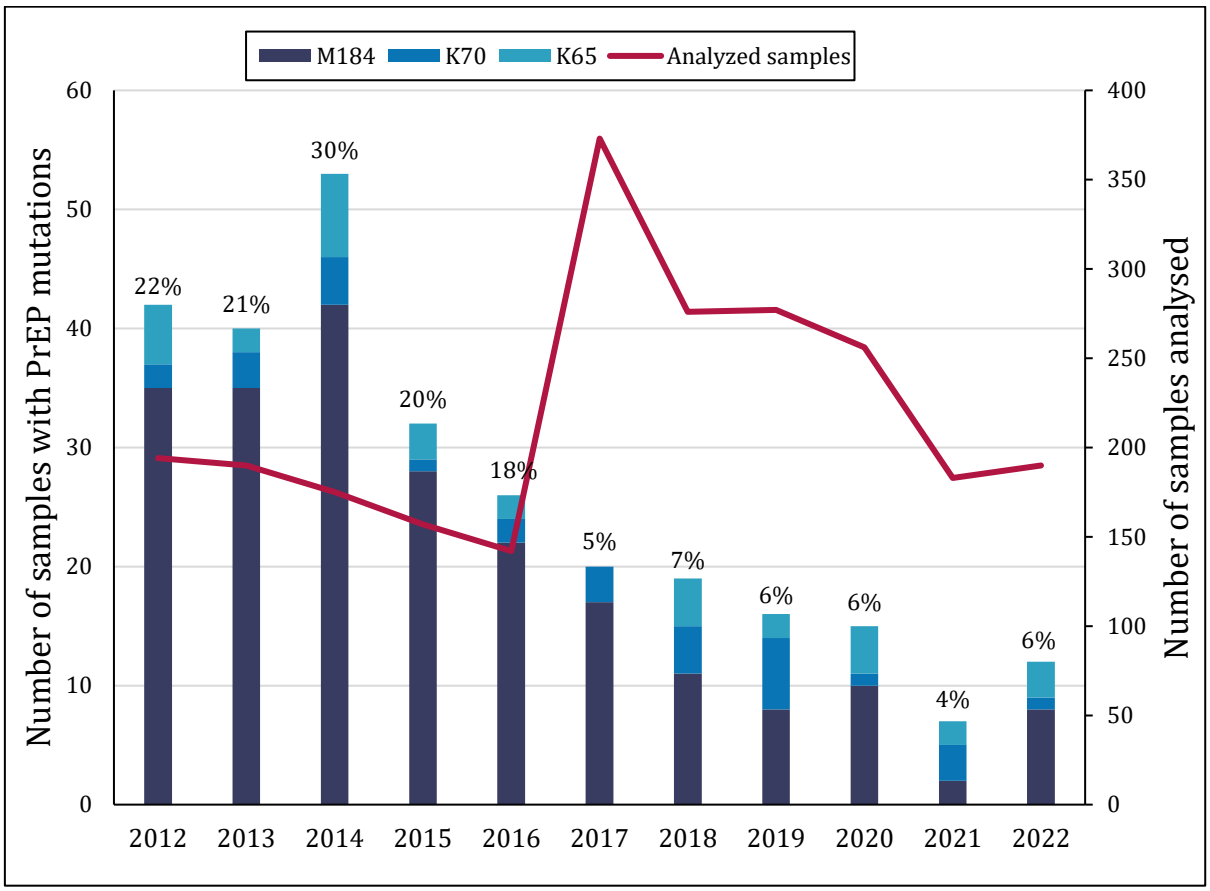

Figure 4.4: Number of clinical samples with virological failure containing one of the three mutations monitored in relation to PrEP for the years from 2012 to 2022.

The mutations in positions M184, K70, and K65 are shown in dark blue, medium blue and light blue columns, respectively. The percentage of samples with PrEP mutations is presented on top of the stacked columns. Total number of samples analysed for drug resistance is shown as a red line.

Conclusion

After 6 years of fully reimbursed PrEP in Norway, data from resistance analyses of samples from newly diagnosed patients does not indicate any increase in the prevalence of the key drug resistance mutations associated with reduced susceptibility to these drugs. Furthermore, clinical samples from patients with virological failure show a significant decline in PrEP-mutations during the last 10 years. This indicates a reduced risk of transmission of PrEP-resistant virus and high levels of protection in Norway for people who take PrEP.

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HIV drug resistance in Eastern Europe

Garth Tylden, Margrethe Larsdatter Storm

The introduction and distribution of antiretroviral therapy (ART) has contributed significantly towards controlling the HIV epidemic, leading to an overall reduction in new HIV infections the past twenty years. However, the global decline in new HIV infections has stalled during the past four years. Eastern Europe and central Asia define one of three regions in the world where new HIV infections are increasing. From 2010-2021, the number of new HIV infections increased by 48% and AIDS-related deaths rose by 32% in Eastern Europe and Central Asia, making this the fastest growing HIV-epidemic in the world (1). The region consists of the former Soviet Union countries Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine and Uzbekistan, as well as the Balkan countries Albania, Bosnia and Herzegovina, Montenegro and North Macedonia. Data on HIV prevalence is not available for all countries in the region, but the majority of reporting countries have an HIV prevalence of around 0.1-0.2% (1). The prevalence, however, varies among the countries in the region and in Ukraine and Russia, HIV prevalence is estimated to be around 1%, indicating a trend towards a more mixed or generalized HIV epidemic (1;2). Although the HIV epidemic in the region was initially driven by injecting drug use, in recent years there has been an increase in heterosexual transmission (2;3). Among 955 HIV positive Ukrainian immigrants arriving in Poland, 70% reported heterosexual transmission followed by 14% intravenous drug use (4). This differs from the situation in Norway where HIV transmission between MSM is dominant and very little is associated with intravenous drug use. Like elsewhere in Europe, most cases are diagnosed late.

In Ukraine, there has been an increase in preventive efforts targeting people who inject drugs over the past 20 years, with the scale up of harm reduction services such as needle syringe programs, as well as legalizing opioid substitution therapy (OST). However, the annexation of Crimea in 2014 led to termination of OST and disruptions in HIV prevention and treatment programs in the conflict-affected areas, as well as overall funding of HIV preventive programs (2). The conflict also led to the forced internal displacement of millions of people and has increased HIV transmission from the conflict areas to other regions of Ukraine (5). The invasion of Ukraine by Russia in February 2022 and the resulting war has led to a humanitarian crisis and further damaged the healthcare system. This has led not only to internal displacement but also a wave of emigration.

During 2022, the number of Ukrainians living in Norway increased by 30 300 (6). Ukrainian immigrants infected with HIV prior to immigration comprised 40% (97/245) of new HIV diagnoses in 2022 (7). This is lower than expected given the estimated prevalence of 1%. At the end of 2022, HIV positive Ukrainian immigrants accounted for about 2% of the total number of individuals living with HIV in Norway (7).

The dominant HIV-1 subtype in Eastern Europe is A6 whereas subtype B dominates in Western European countries (8). The different genetic background with different frequencies of polymorphic mutations may influence resistance patterns. Furthermore, genetic barriers have been shown to differ between different subtypes (4;9). Therefore, it could be interesting to compare resistance profiles between patients from Eastern and Western Europe.

Data on HIV drug resistance in Eastern Europe is scarce. However, a recent study that has investigated clinical and laboratory characteristics of Ukrainian refugees diagnosed with

HIV at entry to Poland found that among ART naïve patients where sequence data was available, drug resistance mutations of clinical significance were found in 15.7% (4). Only two of 51 sequences (3.9%) contained surveillance drug resistance mutation (SDRMs). Both conferred reduced susceptibility to NRTIs. All drug resistance mutations detected were in reverse transcriptase.

Out of the 106 samples submitted to RAVN in 2022 from patients with newly diagnosed HIV-infection, 75 were infected abroad. Among the 75 infected abroad, 49 were infected before immigration to Norway, of which 21 (43%) were infected in the Ukraine (Table 1). Sequence analysis of the reverse transcriptase and protease genes of the 21 samples from newly diagnosed patients infected in Ukraine revealed only one SDRM, which amounts to 4.8% of the samples and is lower than the total SDRM detection rate in 2022 (see figure 4.2). This mutation was M46L, which is associated with reduced susceptibility to protease inhibitors, but does not confer clinically relevant drug resistance. However, two drug resistance mutations of clinical significance (E138A and E138K), which are not on the SDRM list, were detected in newly diagnosed patients infected in Ukraine. These mutations confer reduced susceptibility to NNRTIs (Table 2).

Table 1. Samples submitted to RAVN infected abroad (n=75)

Country of transmission	Frequency (%)
Infected abroad, residing in Norway	24 (32)
Infected abroad, before arrival to Norway	49 (65)
Ukraine	*21 (43)*
Other countries abroad/unknown	*28 (57)*
Unknown	2 (3)
Total	75 (100)

Table 2. Resistance mutations in samples from patients infected in Ukraine

Resistance mechanism analysed	Frequency (%)	Substitutions
PI	1 (4.8)	M46L
NRTI		
NNTRI	2 (9.5)	E138A and E138K
Total	21 (100)	

In summary, with the continuing influx of refugees from Ukraine, changes in HIV prevalence and transmission patterns should be expected. Considering the different HIV genetic background, patterns of resistance mutations may also change. However, based on the drug resistance mutations detected in patients infected in Ukraine so far, the relative prevalence of antiviral resistance is not expected to change significantly.

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5 Hepatitis B virus

Fact box: Hepatitis B virus (HBV) drug resistance	
Treatment	Treatment of HBV infection with antivirals is generally given as monotherapy: - Nucleoside/nucleotide analogues, usually entecavir, tenofovir disoproxil, or tenofovir alafenamide.
Resistance testing method	Genotypic assays based on Sanger sequencing of the RT domain of the HBV polymerase (P) gene. The sequences are analysed for amino acid substitutions associated with drug resistance using geno2pheno (version 2.0) resistance database from Max Planck Institute of Informatics. A plasma viral load > 1000 IU/mL is preferable for the analysis. In Norway, all HBV drug resistance tests are performed at the Norwegian Institute of Public Health.
Target gene	Polymerase gene
Indication for resistance testing	Virological failure/breakthrough on antiviral treatment.
Surveillance	Surveillance of both treatment experienced and treatment naïve patients: 1) Monitoring of patients with virological failure (samples submitted for resistance testing) 2) Population-level surveillance in treatment naive patients (samples submitted for genotyping).

Surveillance methods

The surveillance of HBV resistance in Norway aims to monitor two populations; i) samples submitted for drug resistance testing primarily in relation to treatment failure (acquired resistance) and ii) samples submitted for HBV genotyping in the course of diagnostic investigations, generally prior to treatment. Monitoring of the latter population can therefore be regarded as surveillance of primary resistance. Mutations altering amino acids in specific positions within the polymerase gene can give rise to resistance to the various antivirals for the treatment of HBV.

Surveillance data 2022

In 2022, a total of 156 samples were analysed for HBV drug resistance mutations. Of these, 18 patient samples were submitted for HBV drug resistance testing, and 138 samples were submitted for HBV genotyping only. The distribution of genotypes among the tested samples is presented in Table 5.1.

Table 5.1: genotype distribution of analysed HBV samples in 2022

Genotype	Number of samples	Percent of total samples
A	34	22 %
B	24	15 %
C	27	17 %
D	57	37 %
E	14	9 %

An overview of the resistance mutations detected in Norway between 2018 and 2022 are presented in Table 5.2.

Table 5.2: Resistance mutations in samples submitted for HBV drug resistance testing in 2018 - 2022

HBV-variants resistant to antivirals	Drug resistance	2018	2019	2020	2021	2022
Total analysed		20	14	14	17	18
M204V + (I169T ᵛ S202G ᵛ T184A/S ᵛ M250V) ±L180M	**LAM (R), LDT (R), ETV (R)**	4	1	1	3	3
A181V/T + M204I/V ± L180M	**LAM (R), LDT (R), ETV (I), ADV (R)**				2	
M204V + L180M	**LAM (R), LDT (R), ETV (I)**					1
Mutation in rated position, unknown effect)		1[a]	1[a]			

LAM: lamivudine; LDT: telbivudine; ETV: entecavir; ADV: adefovir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; R: resistant; I: intermediate; S: sensitive.
[a] A181S

In 2022, drug resistance mutations were detected in four samples (Table 5.3), all from patients on entecavir treatment. No drug resistance mutations were detected in patient samples submitted for HBV genotyping only.

Table 5.3: Resistance mutations detected in samples from 2022 and the drug resistance they confer

Sample	Genotype	Resistance mutations detected	Treatment*	Resistance				
				LAM	LDT	ETV	ADV	TDF/TAF
1	D	L180M, M204V, T184S	ETV	R	R	R	S	S
2	A	I169T, L180M, M204V, M250V	ETV	R	R	R	S	S
3	D	L180M, M204V, S202G	ETV	R	R	R	S	S
4	C	L180M, M204V	ETV	R	R	I	S	S

LAM: lamivudine; LDT: telbivudine; ETV: entecavir; ADV: adefovir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; R: resistant; I: intermediate; S: sensitive.
*Treatment specified at the time of resistance testing.

Conclusion

The number of samples with HBV drug resistance remains low, as in previous years. Drug resistance mutations were found in 4 samples, all from patients on entecavir treatment.

New treatments for hepatitis D

Dag Henrik Reikvam

Background
Hepatitis D virus (HDV) is an incomplete virus i.e. it can only infect individuals who are infected with hepatitis B virus (HDV always presents as a co-infection together with hepatitis B virus (HBV). It is the most severe form of chronic viral hepatitis in immunocompetent individuals. More than 50 % of those infected with HDV will develop cirrhosis within 5-10 years after diagnosis, and the risk is more than tripled compared to HBV mono-infection(1;2). Furthermore, the risk of developing hepatocellular carcinoma is increased more than two-fold in HDV-HBV co-infection compared to HBV mono-infection(3).

There is a lack of data on the incidence and prevalence of HDV infection. It is estimated that worldwide around 5 % of all chronic HBV infections are superinfected with HDV, but there are regional and demographic variations (2). In attempts to estimate the total number of HDV infections worldwide, between 12 and 60 mill cases have been reported (4;5). There are no published data on incidence or prevalence in Norway. However, based on positive tests performed on clinical indication at Norwegian Institute of Public Health, one can estimate the occurrence of HDV infection to be about 1 % of all HBV infections (personal communication Rikard Rykkvin; NIPH). With estimates of 25 000 persons with chronic HBV infection living in Norway, this implies that there are approximately 250 chronic HDV infections.

To understand the approach to treatment of HDV infection, it is essential to know some of its basic virology (Figure 1) (Reviewed in references (1;2)). HDV is a single-stranded RNA virus consisting of 1672 to1697 ribonucleotides. The RNA strand is circular and covalently closed. The RNA encodes a single protein, the hepatitis D antigen (HDAg) in two isoforms, neither of which have enzymatic activity (1). The entire replication cycle is therefore dependent on the infected cells' transcriptional and translational machinery. Based on sequencing, HDV has been classified into eight different genotypes. The significance of the genotypes for disease progression and response to therapy are yet to be decided, and genotype is currently not relevant for clinical decision making (6).

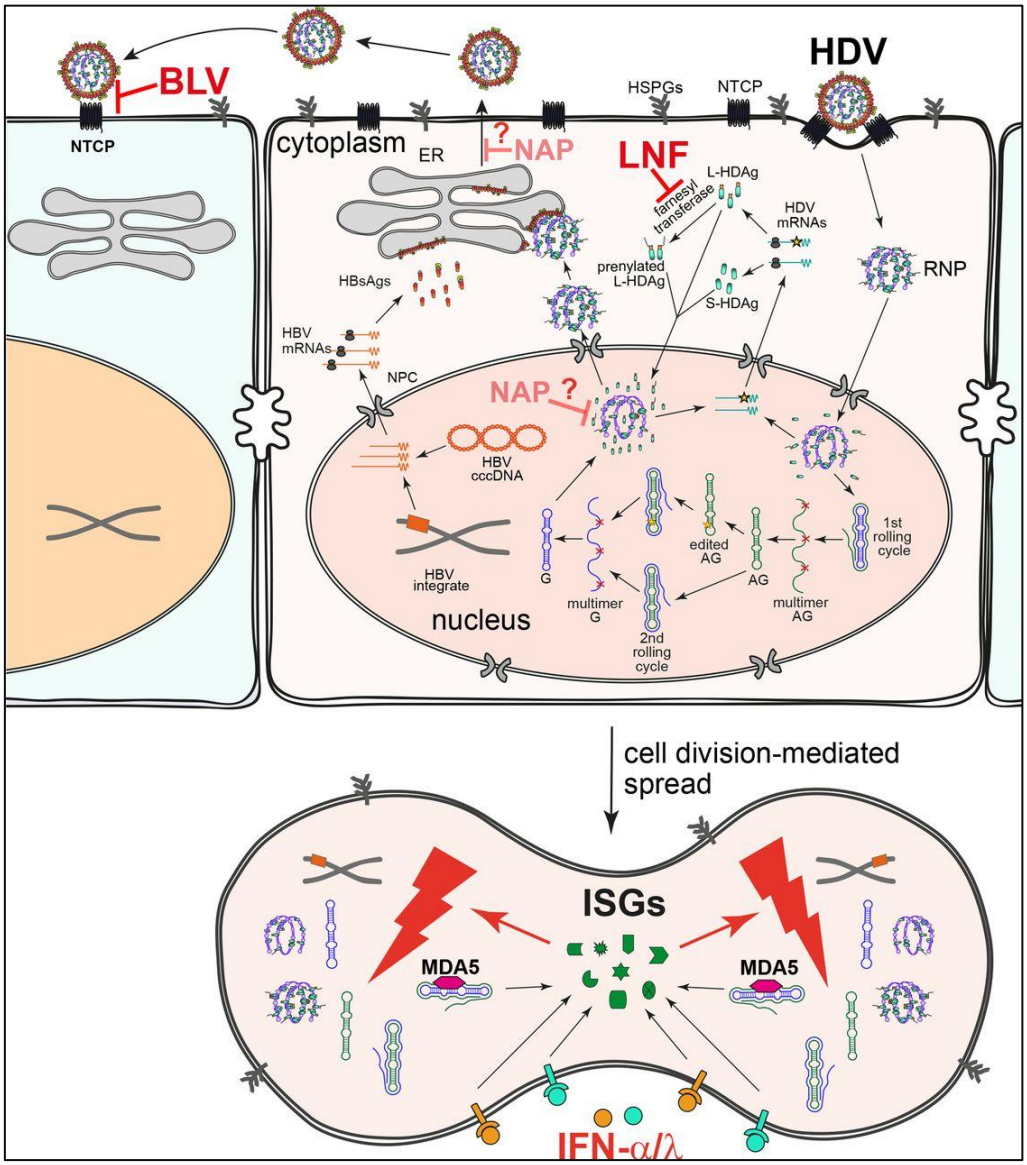

Figure 1: This figure is published in Stephan Urban et al. Gut 2021;70:1782-1794 (1).

HDV life cycle, spreading pathways and drug targets. HDV virions first attach to heparan sulfate proteoglycans (HSPGs) and then to the viral receptor NTCP to enter host cells. After membrane fusion, the ribonucleoprotein (RNP) is released and further transported to the nucleus to initiate RNA replication. The incoming genome (G) serves as the template for the first rolling circle amplification. The resulting antigenome (AG) multimers are cleaved in cis by the intrinsic ribozyme and ligated into circular monomers. After a second rolling cycle using the AG as the template, HDV G multimers are synthesised and further cleaved to produce monomers. The HDV AG might be edited by ADAR1, yielding an extended HDAg ORF that produces L-HDAg, some of that is further prenylated. S-HDAg and L-HDAg (intact and prenylated) are transported into the nucleus to regulate virus replication or bind to the HDV RNA to form RNP. The G-containing RNP can be exported to the cytoplasm and encapsulated into HBV envelope through the interaction between L-HDAg and S-HBsAg. HDV virions are released through the ER-Golgi secretory pathway. besides the HBV envelope-dependent de novo infection, HDV can also spread through division of infected cells in an HBV-independent manner (below). Bulevirtide (BLV) blocks de novo infection by efficient binding of the viral receptor NTCP. Lonafarnib (LNF) prevents the prenylation of L-HDAg by inhibiting the farnesyl transferase and consequently impairs HDV assembly and secretion. The target(s) of nucleic acid polymer (NAP) is unclear. It may inhibit assembly/release of HDV virions and/or HDV ribonucleoprotein assembly via direct interaction with the HDAg. IFNs, including MDA5-mediated HDV-induced IFNs and therapeutic IFNα and IFNλ, induce IFN stimulated genes (ISGs) which profoundly suppress HDV amplification during cell division. HBV, hepatitis B virus; HDV, hepatitis D virus; IFN, interferon; L-HDAg, large hepatitis D antigen; NTCP, sodium taurocholate cotransporting polypeptide; S-HBsAg, small hepatitis B surface antigen (Figure re- used from (1)) with permission obtained via RightsLink® service).

Infectious HDV is enveloped in HBV surface antigen (HBsAg), hence the close and necessary association with HBV infection. For infectious HDV to be produced, the infected cell must also transcribe and translate HBsAg from HBV's covalently closed circular DNA (cccDNA) or HBV DNA integrated in the cells' genome. However, HDV replication is not dependent on production of complete and infectious HBV virions.

Infection of a hepatocyte with HDV (or HBV) is based on HBsAg affinity for the bile acid transporter Na+-taurocholate co-transporting polypeptide (NTCP), which both HBV and HDV exploit for cell entry. The progression of HDV infection within the liver requirepropagation of virus particles from cell to cell via the NTCP receptoror via dissemination to new hepatocytes through mitosis of liver cells.

Taking these basic aspects of the HDV replication cycle into account, it is clear that i) there are no traditional targets for direct-acting antiviral compounds, and that ii) the current first-line therapy of HBV infection, nucleos(t)ide analogues that block the final stage of HBV replication without directly affecting HBV protein production, will likewise have no effect on the HDV life cycle.

The sole treatment for HDV infection has so far been off-label use of pegylated interferon alpha (pegIFN) for 48 weeks (6;7). The exact mechanisms for how pegIFN exerts its antiviral effects are not known, but it is believed to act through induction of antiviral interferon stimulated genes, inhibition of mitosis-mediated HDV spread, and activation of adaptive immunity (1). Only one half of all patients respond to pegIFN with HDV viral suppression and less than half of these primary responders have persistent off-therapy viral suppression (6). There is no known viral resistance to pegIFN. Documentation of the effect of pegIFN on clinical endpoints (i.e. cirrhosis, hepatic decompensation, hepatocellular carcinoma, or death) in HDV infectionis limited (8).

Bulevirtide

In 2020, the European Medical Agency (EMA) issued conditional approval for bulevirtide (Hepcludex®) a new compound against HDV infection. In the recently published international guidelines for HDV infection, which is the first ever to be published, the drug is recommended to be used in cirrhotic patients when pegIFN is contraindicated (6).

Bulevirtide is a synthetic peptide that binds to the NTCP receptor, blocking the interaction between the receptor and HBsAg, thereby halting cell-to-cell propagation of HDV within the liver (1). Results from a phase 3 study was recently published reporting 45 % of patients achieving the primary endpoint of 2xlog10 reduction of HDV RNA (9). Earlier phase studies have indicated that patients receiving combination treatment of bulevirtide and pegINF have higher response rates than bulevirtide monotherapy (10). Bulevirtide is generally well tolerated. As the compound targets a central cellular protein, the risk of resistance is believed to be lower than for antivirals that target viral proteins (1). There are no reports on viral breakthrough that has not been related to reduced adherence to therapy (11).

The medicine is administered as a daily 2 mg subcutaneous dose. Treatment duration is undefined, but reports indicate that a majority of patients experience viral relapse after treatment cessation (10;12). Hepcludex® was registered in Norway in 2022 with an off-the-shelf price of 90 136 kr./month. It is currently being reviewed by the "Nye metoder beslutningsforum" (New Methods Decision Forum) regarding government reimbursement. It is not known if it has yet been prescribed to any patients in Norway.

In the pipeline?

Lonafarnib is a compound that inhibits farnesyl transferase in hepatocytes (1). It prevents interaction between HBsAg and HDAg and consequently assembly of HDV virions. The compound has not been submitted to EMA and has so far only been tested in early phase studies. Its clinical usefulness remains to be determined.

Another approach to curb HDV replication is to reduce HBsAg production in hepatocytes by inhibiting HBsAg mRNA with small interfering RNA. Proof-of-concept studies have shown that such compounds are able to reduce both circulating HBsAg and HDV virions (13). The clinical utility of these agents also remains to be determined. Intuitively, this treatment principle would be more prone to viral resistance than drugs targeting cellular motifs.

Conclusion

HDV infection is a relatively rare disease in Norway but the prognosis in infected individuals is grave. Bulevirtide is a new medicine against HDV infection whose main advantage over traditional pegIFN treatment is greater tolerability. It should not be prone to antiviral resistance, but to what extent it will be prescribed in Norway remains to be seen. Other novel treatment principles are being explored.

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6 Human herpes viruses: Cytomegalovirus

Fact box: Human cytomegalovirus (CMV) drug resistance	
Treatment	Mono therapy is standard. Unless there are contraindications, the first choice is the nucleoside analogue ganciclovir/valganciclovir. In cases with contraindications or resistance, alternative drugs are nucleotide analogues cidofovir and foscarnet, and the UL-97 kinase inhibitor maribavir. The CMV terminase complex inhititor letermovir (is approved for prophylaxis in stem cell transplanted patients.
Resistance testing method	Genotypic assays based on Sanger sequencing. The sequences are analysed for amino acid substitutions associated with drug resistance. In Norway, all CMV drug resistance tests are performed at the National Reference laboratory for CMV at the Department of Microbiology at the Oslo University Hospital, Rikshospitalet.
Target genes	CMV kinase (UL97), DNA polymerase (UL54), and CMV terminase complex (UL56).
Indication for resistance testing	Persistent high viral load in blood or other compartments during antiviral treatment.
Surveillance	Population-level surveillance is currently not necessary.

Surveillance methods

The antiviral drug resistance has been characterized by comparing phenotypic and genotypic test results. For routine testing only genotypic tests, looking for known resistance mutations, are applicable. Resistance to ganciclovir develops by mutations in the viral kinase CMV UL97 and/or the DNA polymerase CMV UL54 gene. Normally resistance mutations in the CMV UL97 gene precede mutations in the CMV UL54 gene, as ganciclovir is first choice of treatment, and the fitness cost of mutations in CMV UL54 is higher. Therefore, as a standard, the UL97 gene is investigated first. Maribavir resistance mutations are also located to the UL-97 gene and will be detected by the primary analysis. For patients treated with ganciclovir alone, the UL54 gene is analysed only if resistance mutations are first detected in the UL97 gene. Foscarnet and cidofovir resistance is conferred by mutations in the UL54 gene, and both genes are investigated in samples from patients treated with these drugs. In cases with suspected drug resistance after use of Letermovir, the UL-56 gene can be analysed for resistance-mutations.

There is no population-level surveillance of CMV drug resistance, and the surveillance is based on samples from patients with suspected resistance, usually due to persistent high viral load despite ongoing therapy. Immunocompromised patients are more prone to developing drug resistance. Resistance mutations usually occur after several weeks of treatment, and thus resistance testing is usually relevant in treatment failure only after at least 2-3 weeks of treatment or in patients that have previously received prophylaxis or treatment.

Surveillance data 2022

In 2022, 34 samples from 24 patients were submitted for analysis of CMV drug resistance mutations, and resistance mutations were detected in samples from five patients (Table 6.1). The mutations detected are listed in Table 6.2.

Most of the resistance mutations detected that affect ganciclovir susceptibility, are located within the interaction region for ganciclovir in the kinase domain (1), and many of them clustering within a small region ranging from positions 590 to 607 in the UL97 (2). The mutations detected all confer low or moderate resistance, but in immunosuppressed patients, even low-grade resistance to an antiviral drug may be of clinical importance.

Table 6.1: Number of samples analysed for CMV antiviral drug resistance and number of samples with detected CMV drug resistance mutations for the years 2018 - 2022.

CMV-variants resistant to antivirals	2018	2019	2020	2021	2022
Total samples analysed	21	21	30	19	24*
Number of samples with CMV resistance mutations	4	6	5	5	5
Samples with UL97 mutations	2	6	4	5	5
Samples with UL54 mutations	2	2	1	1	1

*34 samples from 24 patients were submitted.

Table 6.2: CMV resistance mutations in samples tested in 2022

Patient	UL97 mutations	UL54 mutations	Resistance
1	L595S		Ganciclovir moderate
2	L595S		Ganciclovir moderate
3	L595S	E745D	Ganciclovir moderate; Foscarnet low
4	Del 599-603		Ganciclovir low to moderate
5	A594V		Ganciclovir moderate

UL97 encodes the viral kinase. UL54 encodes the viral DNA polymerase.

Conclusions

Despite an increase in the use of ganciclovir for therapeutic and prophylactic treatment of CMV-infections, drug resistance mutations are only rarely detected. However, in immunosuppressed patients with CMV-infection, early discovery of antiviral drug resistance can be of vital importance. Therefore, the reference laboratory encourages clinicians and laboratories to consider drug resistance testing in cases with treatment failure.

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Human herpes viruses: Herpes simplex virus

Fact box: Herpes simplex virus (HSV) drug resistance	
Treatment	Nucleoside/nucleotide analogues: aciclovir/valaciclovir (first choice), cidofovir and foscarnet (second choice).
Resistance testing method	Genotypic assays based on Sanger sequencing. The sequences are analysed for mutations associated with drug resistance. All HSV drug resistance tests for Norway are performed at Sahlgrenska University Hospital, Gothenburg.
Target gene	HSV thymidine kinase (UL23) and HSV DNA polymerase (UL30).
Indication for resistance testing	Persistent HSV-infection despite ongoing therapy.
Surveillance	Population-level surveillance is currently not necessary.

Surveillance methods

The surveillance is based on samples from patients with persistent HSV-infection despite ongoing therapy. There is no population level surveillance of HSV resistance. Immunocompromised patients are more prone to development of drug resistance, but information about the patients' immune status is not available for surveillance purposes. For routine testing, only genotypic tests are applicable.

Surveillance data 2022

In 2022, three samples from Norway were submitted for HSV drug resistance analysis. Out of the three samples, only one sample was analysed successfully, while two could not be analysed due to low viral load. No resistance mutations were found.

Figure 6.1 shows the number of samples submitted and analysed for HSV drug resistance testing the past five years, as well as the number of samples with resistance mutations.

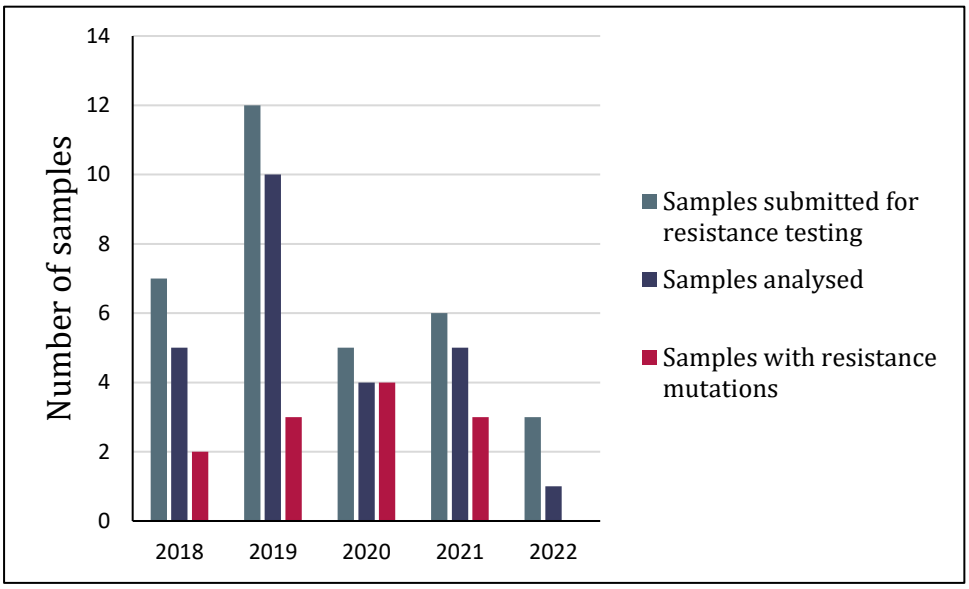

Figure 6.1. Number of samples submitted for HSV drug resistance testing, number of samples analysed and number of samples with drug resistance mutations in 2018-2022.

Conclusions

The low number of samples submitted and analysed for HSV drug resistance mutations both in 2022 as well as previous years, makes it difficult to infer anything about HSV drug resistance in Norway. The average number of samples submitted and analysed for HSV drug resistance during the past five years has been very low considering the high consumption of HSV antivirals in the same time period. There is no systematic surveillance of drug resistant HSV. However, a large proportion of the isolates analysed over the past five years has exhibited resistance or possible resistance. Although the risk for development of drug resistance in HSV is known to be very low, at least in immunocompetent patients, these numbers might indicate that there could be more cases with suspected drug resistance that are not submitted for resistance testing.

7 Hepatitis C virus

Fact box: Hepatitis C virus (HCV) drug resistance	
Treatment	Antiviral treatment of HCV infection consists of a combination of drugs from at least two of the three different classes: - Nucleotide analogue polymerase inhibitors (NS5B) - Protease inhibitors (NS3/4A) - NS5A inhibitors Direct-acting antivirals may be supplemented with ribavirin. Treatment protocols are pangenotypic and may depend on stage of liver disease.
Resistance testing method	Next generation sequencing of the complete HCV genome based on probe enrichment. This method can be used for genotyping, as well as detection of RASs. The sequences are analysed using HCV-GLUE (1;2). A viral load of > 10 00 IU/mL was used as a cut-off for NGS-analysis. In Norway, HCV drug resistance testing is only available at the Norwegian Institute of Public Health.
Target genes	NS3–NS4A (protease) NS5A (replication and assembly factor) NS5B (polymerase)
Indication for resistance testing	• Virological failure during treatment. • New cases of HCV infection. • Baseline testing of patients with HCV genotype 1a and high viral load (>800 000 IU/ml) considered for treatment with elbasvir + grazoprevir. • Baseline testing of cirrhotic genotype 3 patients considered for treatment with sofosbuvir + velpatasvir. • Patients with decompensated cirrhosis when liver transplantation is not an option.
Surveillance	Systematic surveillance of newly diagnosed HCV infections was launched in May 2022.

Surveillance methods

A surveillance system for HCV drug resistance in Norway was implemented in 2022. The system is based on resistance testing of samples collected from patients assumed to be newly diagnosed in Norway, hence focusing on the surveillance of primary resistance. In this surveillance program, resistance-associated substitutions (RAS) are classified by HCV-Glue into three categories according to the strength of evidence for resistance against 12 different direct-acting antiviral (DAA) HCV drugs.

As part of a drug resistance surveillance project approved by the regional ethics committee, data from MSIS are combined with the RAS data to better understand the distribution of these substitutions. This cross-referencing to epidemiological data provides an overview of RASs in relation to route of transmission and country of infection.

Surveillance data 2022

The occurrence of RAS in the HCV genome may limit the efficiency of treatment, but the clinical consequences of the presence of RAS prior to treatment are uncertain. RAS may occur naturally and are therefore commonly observed before treatment. RAS may also be developed or enhanced during treatment.
In 2022, a total of 133 samples were analysed for HCV drug resistance. Of the analysed samples, 79 (59.4%) were from male patients and 40 (30.1%) were from female patients. For the cases where route of transmission was known, intravenous drug use was the most common route of transmission. RASs (of any evidence category) were detected in 106 (79%) of the analysed samples in 2022. Almost half of these had at least one category I RAS, which is associated with resistance against one or several drugs (Table 1).

Table 1. Descriptive characteristics of samples submitted to RAVN in 2022 (n=133).

	Samples submitted to RAVN, n (col %)	Samples submitted that have RAS, n (row %)	Samples submitted that have RAS associated with resistance*, n (row %)
Route of transmission			
Sexual	6 (4.5)	5 (83.3)	0 (0.0)
IDU	58 (43.6)	44 (75.9)	18 (31.0)
Other	69 (51.9)	57 (82.6)	28 (40.6)
Country of transmission			
Norway	62 (46.6)	44 (71.0)	18 (29.0)
Abroad	39 (29.3)	32 (82.1)	14 (35.9)
Unknown	32 (24.1)	30 (93.8)	14 (43.8)
Total	133	106	46

***** Resistance against one or several drugs defined as resistance based on resistance category I according to HCV-Glue.

Resistance patterns in submitted samples according to antivirals and genotype is shown in Figure 1 and Figure 2. Samples presented in Figure 2 are defined as resistant based on detection of at least one category I RAS according to HCV-Glue.

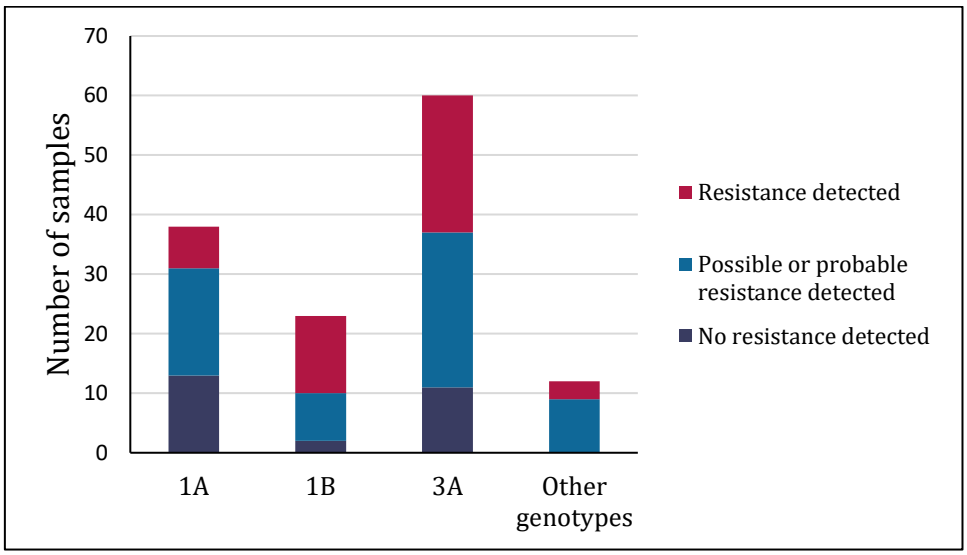

Figure 1. Resistance patterns distributed by genotypes in samples submitted to RAVN in 2022 (n=133).

Number of samples with either no resistance, possible or probable resistance, or resistance towards any of the HCV DAAs according to GLUE are shown (resistance in red, possible or probable resistance in light blue and no resistance in dark blue). Other genotypes include genotype 2 and 4.

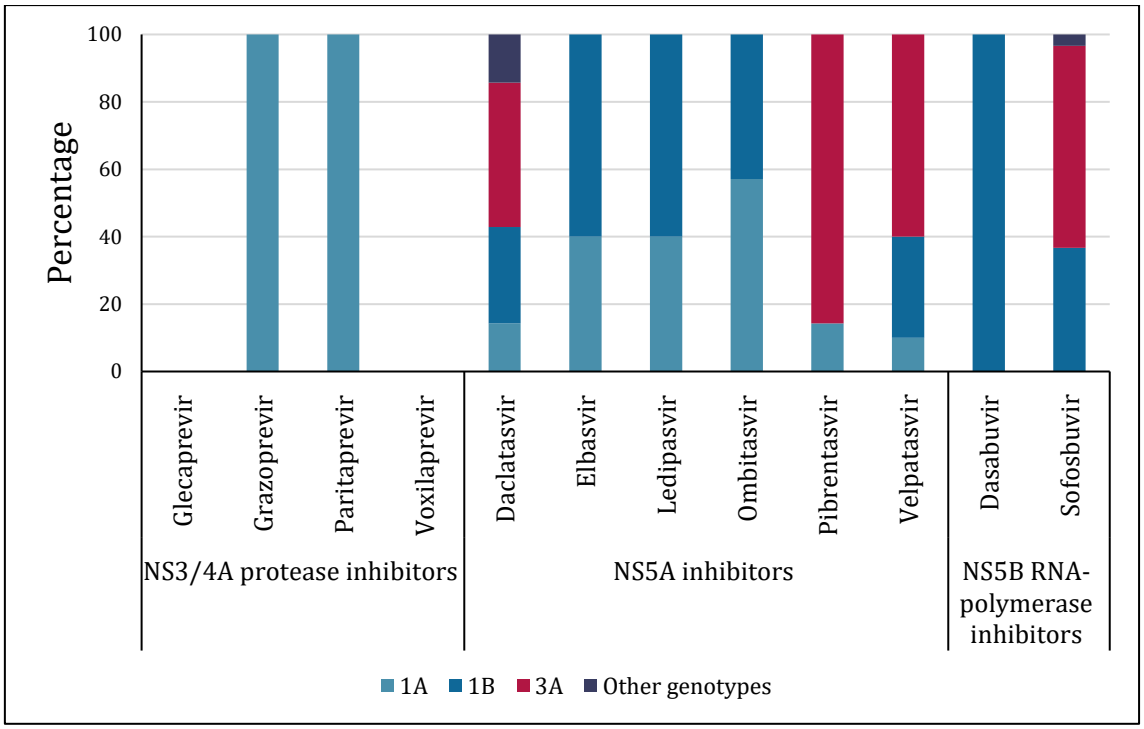

Figure 2. Genotype distribution among samples submitted to RAVN in 2022 where resistance was detected.

Genotype distribution with resistance patterns against the individual HCV DAAs in samples submitted to RAVN where resistance was detected according to HCV-Glue category I (samples with possible or probable resistance (category II and III) are excluded). Proportions of genotypes among sequences with resistance to the individual drugs and drug classes are shown. Other genotypes include 2, 4 and HCV co-infection.

Note: Figure 2 shows relative genotype proportion per drug resistance, and hence is not adjusted for unequal genotype frequency among analysed samples (see Figure 1), e.g. resistance against sofosbuvir was actually more frequently detected in genotype 1B than 3A, but gt 3A is more common overall.

Discussion

The majority of samples received for surveillance are from intravenous drug users or from patients where the transmission route is unknown. Approximately half are infected in Norway. However, HCV is generally associated with intravenous drug use and often the individuals do not know how, when and where they are infected.

The majority of samples submitted are infected with genotype 3A, and this genotype dominates among the samples that have RAS associated with reduced susceptibility for commonly used DAAs Sofosbuvir and Pibrentasvir. Only samples with genotype 1A have RAS against Grazoprevir, which is another commonly used drug. Furthermore, there are several RAS found in genotype 1A and 1B strains against several of the NS5A inhibitors. Despite a high frequency of detected RAS in samples collected from newly diagnosed patients before treatment, the success rate of HCV treatment with DAA is excellent (3). This indicates that the impact of preexisting RAS on the treatment outcome is low.

The surveillance aims to monitor primary resistance among newly diagnosed patients that are expected to be treatment naïve. However, there is uncertainty both in the epidemiological data and whether patients have been previously treated or even re-infected.

Conclusions

In conclusion, RAS are commonly detected in samples from individuals newly diagnosed with HCV. RAS affecting the susceptibility for commonly used antivirals are detected in all the genotypes most frequently found in Norway, but the clinical impact on treatment outcomes is uncertain.

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8 Severe acute respiratory syndome-coronavirus-2

Fact box: SARS-CoV-2 drug resistance	
Treatment	Nucleotide analogues (example: remdesivir). Protease inhibitors (example: nirmatrelvir/ritonavir). Monoclonal antibodies (example: sotrovimab).
Resistance testing method	Whole genome next generation sequencing.
Target genes	Protease RNA-dependent RNA polymerase Spike
Surveillance	Samples used for surveillance of variants will also be used for surveillance of resistance. Only mutations associated with reduced susceptibility towards drugs targeting the protease or the RNA-dependent RNA polymerase are included in the surveillance.

Surveillance methods

To monitor the epidemiological situation in Norway and the emergence of new variants, the microbiology laboratories are encouraged to submit a proportion of positive SARS-CoV-2 samples to the reference laboratory for SARS-CoV-2 at the Norwegian Institute of Public Health. To get a representative selection of samples, the drug resistance surveillance is based on the same samples used for national surveillance of SARS-CoV-2 variants.

The whole genome sequences from the samples selected for surveillance are subjected to Stanford SARS-CoV-2 Sequence analysis (1;2). The Pango lineage and relevant mutations are included in RAVN. Due to the high degree of lineage-specific variations in the spike protein, mutations associated with reduced susceptibility for monoclonal antibodies targeting this protein are not currently included in RAVN.

Surveillance data 2022/2023

This is the first RAVN report including surveillance data for SARS-CoV-2. Data from January to March 2023 is presented as a pilot. In this period the lineages XBB and BQ were most common in Norway (Table 8.1). Mutations associated with reduced susceptibility towards nirmatrelvir, relative to Wuhan-Hu-1 (NC 045512.2), were detected in 12 of the 2095 samples included in the surveillance data. (Table 8.2). However, the mutations detected are associated with only a small reduction in susceptibility (below 10-fold reduction) that is not expected to confer a significant degree of resistance affecting clinical response to treatment with nirmatrelvir/ritonavir (3). Most of the mutations detected, are mutations that represent possible steps in common mutational pathways to nirmatrelvir resistance (4). No mutations associated with reduced susceptibility towards remdesivir was detected.

Table 8.1: Distribution of the most common lineages detected

Pango lineage	Number of samples	Percent of samples
XBB	673	32.12
BQ	566	27.02
CH	267	12.74
BA.5	118	5.63
BN	107	5.11
EG	74	3.53
BF	66	3.15
EL	29	1.38
CL	24	1.15
EF	21	1.00
Others	150	7.16
Total	2095	100.00

Only the Pango lineage prefix is considered, except for BA where the first suffix is included. The group "others" consists of lineages that comprise less than one percent of the total number of samples (In descending order: BA.4, XBK, DF, BA.2, XBF, EU, XAY, BE, BM, BR, XBZ, DV, BY, CK, CM, BA.1, CJ, CQ, DS, EC, BL, BW, DB, DN, DT, DU, EA,EJ, EM, EQ, XBC, XBL, XBU).

Table 8.2: Detected mutations with 5-9 fold reduced susceptibility towards nirmatrelvir according to lineage

Mutation	BA.5	BQ	CH	XBB
T21I	0	2	1	1
A191V	0	3	0	0
A194S	0	0	3	0
P252L	2	0	0	0
Total	2	5	4	1

Conclusions

A total of 2095 samples were analysed. Mutations associated with slightly reduced susceptibility to nirmatrelvir were found in a total of 12 samples, but all the detected mutations confer below 10-fold reduced susceptibility. None of the sequences harboured any of the mutations known to confer partial or complete resistance to nirmatrelvir.

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