REPORT

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Usage of Antivirals and the Occurrence of Antiviral Resistance in Norway 2024

RAVN

Resistensovervåkning av virus i Norge

Resistance to antivirals in Norway

NIPH
Norwegian Institute of Public Health

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Table of Contents

Introduction

It is a pleasure to present the 12th report from the surveillance system for Resistance against Antivirals in Norway (RAVN). In this report, we present data for 2024 on resistance against antivirals for treatment of influenza, SARS-CoV-2, HIV-1 infection, hepatitis B virus infection (HBV), hepatitis C virus infection (HCV), and infections with cytomegalovirus (CMV) and herpes simplex virus, as well as data on the usage of antiviral drugs in Norway in 2024.

In addition to the surveillance data, we have selected two relevant topics that are given special attention in the report.

The first chapter addresses the global spread of Highly Pathogenic Avian Influenza viruses highlighting their impact on birds and mammals, their zoonotic potential, the Norwegian situation, and antiviral susceptibility. Continued surveillance for resistance mutations to mitigate pandemic risks is emphasized.

The second topic is on hepatitis E, focusing on its acute and chronic forms, especially in immunosuppressed patients. The chapter includes a case report, and diagnostic and therapeutic strategies are discussed, including ribavirin resistance and alternative treatments

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 data and perspectives presented in this report will be useful 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 and antimicrobial resistance.

RAVN would like to thank all contributors to 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
RdRP	RNA-dependent RNA polymerase
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDRM	Surveillance drug-resistance mutation
TAF	Tenofovir alafenamide fumarate
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

Sammendrag

Bruk av antivirale midler

Det totale forbruket av antivirale legemidler fortsatte å øke i 2024. Legemidler mot hiv utgjør den største andelen målt i definerte døgndoser, mens det er flest personer som bruker antivirale midler mot herpesvirus.

Oseltamivir er for tiden det eneste antivirale middelet mot influensa på markedet. Av legemidler mot SARS-CoV-2, er det kun nirmatrelvir (peroral behandling) og remdesivir (intravenøs) som er i bruk, monoklonale antistoffer ble i praksis ikke benyttet i 2024. For hiv fortsetter økningen i bruken av kombinasjonspreparater. Økningen i kombinasjoner som inneholder integrasehemmere gjenspeiler norske retningslinjer og anbefalinger for innkjøp. Salg og bruk av antivirale midler mot hepatitt B har også økt, med entecavir og formuleringer av tenofovir som førstelinjebehandlinger. Samtidig har behandlinger for hepatitt C gått ned, noe som kan tolkes som et skritt i retning mot nasjonale helsemål for å bekjempe hepatitt. Antallet pasienter som får valaciklovir mot herpes simplex- og varicella zosterinfeksjoner er fortsatt høyt.

Influensavirus

Influensautbruddet i 2024–25 startet senere enn i fjor (uke 52) og nådde toppen i uke 8/2025. Influensautbruddet var relativt kraftig sammenlignet med tidligere sesonger, med influensa A(H1N1) som den hyppigst påviste typen denne sesongen. Både influensa A(H3N2) og influensa B/Victoria ble imidlertid detektert gjennom hele sesongen, noe som vil si at alle tre virusene sirkulerte samtidig. Blant de 604 influensavirusene som ble analysert for antiviral resistens i løpet av 2024/25-sesongen, ble bare en prøve med H1N1 funnet å være resistent mot behandling med oseltamivir. Ytterligere en prøve med H1N1 viste seg å ha lavere følsomhet for behandling med baloxovir marboxil.

SARS-CoV 2

I 2024 nådde SARS-CoV-2 en smittetopp i uke 35, i denne perioden var SARS-CoV2-varianten KP.3 den mest påviste varianten i Norge. I den første delen av året var BA.2.86 den vanligste varianten blant prøver med påvist SARS-CoV-2, deretter var det KP.3 som var mest vanlig, mens de rekombinante XEC-variantene dominerte på slutten av året. Totalt sett ble 1064 overvåkingsprøver for SARS-CoV-2 analysert i 2024 for resistens mot de antivirale legemidlene nirmatrelvir (Paxlovid) og remdesivir. Ingen sekvenser viste mutasjoner som gir signifikant resistens mot nirmatrelvir eller remdesivir.

Humant immunsviktvirus-1 (Hiv)

I 2024 ble det analysert 110 prøver fra nydiagnostiserte tilfeller av hiv-1 infeksjon i Norge. Dette utgjør 42 % av alle meldte tilfeller. Blant de som smittes i Norge, er fortsatt subtype B hyppigst forekommende, mens en større variasjon sees blant de som smittes i utlandet. Dataene viste i likhet med foregående år lav forekomst (4,5 %) av overvåkingsmutasjoner (SDRMs), hovedsakelig mutasjoner assosiert med nedsatt følsomhet for non-nukleosid revers transkriptasehemmere (NNRTIs) funnet hos pasienter smittet i utlandet. Mutasjonene var særlig assosiert med eldre NNRTIs som historisk er brukt i settinger med begrenset tilgang til ressurser. For 2024 har man for første gang også systematisk overvåking av resistens mot integrasehemmere. Det ble ikke funnet noen relevante resistensmutasjoner mot disse midlene.

Overvåkningen tyder på at midlene som brukes til pre-eksponeringsprofylakse (PrEP) fortsatt er effektive, og det ble ikke funnet mutasjoner som påvirker følsomheten for emtricitabin eller tenofovir. Den generelle forekomsten av primærresistens i Norge er fortsatt lav, og den kliniske betydningen begrenset.

Hepatitt B-virus (HBV)

I 2024 ble til sammen 202 prøver undersøkt for resistans og genotyping. De fleste prøvene var kun sendt inn med tanke på HBV-genotyping. Blant disse prøvene ble det ikke funnet noen resistensmutasjoner. Det var 33 prøver som var innsendt spesielt for resistensundersøkelse, noe som er litt flere enn i fjor. I fire av disse ble det funnet resistensmutasjoner assosiert med nedsatt følsomhet for entekavir.

Hepatitt C-virus (HCV)

I 2024 ble 130 HCV-prøver undersøkt med tanke på forekomst av resistensassosierte substitusjoner (RAS). Resistensdata ble koblet med epidemiologiske data fra MSIS for sammenligning av ulike undergrupper. RAS ble funnet i 45 % av prøvene, men svært få prøver inneholder RAS som kan påvirke alle virkestoffene i kombinasjonsbehandlinger. Resistens utgjør dermed sjelden noe klinisk problem for behandling av HCV-infeksjon. Gjennom overvåkingen følges forekomst av resistensmutasjoner blant nye tilfeller, men tolkningen kan være utfordrende blant annet på grunn av usikkerheter i epidemiologiske og kliniske data.

Cytomegalovirus

I 2024 ble 23 prøver fra 18 pasienter analysert for resistens mot antivirale midler mot cytomegalovirus (CMV). Resistensmutasjoner som gir nedsatt følsomhet mot ganciklovir ble funnet i tre prøver. Til tross for økt bruk av for CMV-behandling og -profylakse, forekommer resistens sjelden. Siden 2019 og 2022 har henholdsvis letermovir og maribavir vært tilgjengelig i Norge, og resistensanalyser inkluderer påvisning av mutasjoner assosiert med resistens mot disse legemidlene.

Herpes simplex virus

Totalt 12 prøver fra 9 pasienter ble sendt inn for undersøkelse av resistens hos herpes simplex-virus (HSV) i 2024. Redusert følsomhet for aciklovir ble funnet i 6 av prøvene. Det var en liten økning i antall prøver som sendes til resistensundersøkelse sammenliknet med i fjor, men det totale antallet forblir lavt- noe som kan utgjøre en risiko for at det er tilfeller av resistens som kanskje ikke fanges opp.

Summary

Usage of antivirals

Sales and usage, both measured in defined daily doses and number of patients treated, have generally increased during the period from 2020 to 2024 according to numbers from The Norwegian Drug Wholesales Statistics Database. Drugs against HIV make up the dominant proportion of sales when measured in defined daily doses, while antivirals against herpesviruses have most users.

Oseltamivir remains the primary antiviral for influenza due to the withdrawal of other options from the market. SARS-CoV-2 treatment includes the oral antiviral nirmatrelvir, and intravenous remdesivir for hospitalized patients, with limited use of monoclonal antibodies. For HIV, the use of fixed-dose combinations continues to increase. The increase in combinations containing integrase inhibitors reflects Norwegian guidelines and procurement recommendations. Sales and usage of HBV antivirals have also increased, with entecavir and formulations of tenofovir as the first-line treatments. Meanwhile, treatments for HCV have decreased, likely indicating progress towards national health objectives to reduce the prevalence and impact of HCV. The number of patients receiving valaciclovir against herpes simplex and varicella zoster infections remains high.

Influenza virus

The 2024-25 influenza outbreak began later than last year (week 52) and peaked in week 8/2025. The intensity of the season was relatively strong compared to the previous seasons. Influenza A(H1N1) was the most commonly detected type this season. However, both influenza A(H3N2) and influenza B/Victoria were detected throughout the season meaning that all three viruses were circulating, to some degree, simultaneously. Among the 604 influenza viruses analysed for antiviral resistance during the 2024/25 season only 1 H1N1 was found to be resistant to treatment with oseltamivir. One additional H1N1 was found to have reduced susceptibility to baloxovir marboxil.

SARS-CoV 2

In 2024, SARS-CoV-2 infections peaked in week 35, during that period the SARS-CoV2 variant KP.3 was the most commonly detected variant in Norway. The most common variant at the beginning of the year was BA.2.86, followed by a period with KP.3, at the end of the year the recombinant XEC variants took over. Overall, in 2024, 1064 surveillance samples for SARS-CoV-2 were analysed for resistance to the antiviral drugs nirmatrelvir (Paxlovid) and remdesivir. No sequences showed mutations conferring significant resistance to nirmatrelvir or remdesivir.

Humant immunsviktvirus-1 (HIV)

In 2024, a total of 110 samples from newly diagnosed cases were analysed for primary HIV-1 drug resistance, representing 42 % of all notified cases. Subtype B remains the most prevalent HIV subtype transmitted in Norway, while a diverse range of subtypes is seen among those infected abroad. The data revealed a low frequency (4.5 %) of surveillance drug resistance mutations (SDRMs), predominantly associated with non-nucleoside reverse transcriptase inhibitors (NNRTIs), mainly found in patients infected abroad. Most of the detected resistance was linked to older NNRTIs used historically in resource-limited settings. In 2024, monitoring of resistance to integrase inhibitors was included for the first time. No relevant resistance was detected.

Surveillance indicates that the drugs used for pre-exposure prophylaxis (PrEP) remain effective, with no detected resistance mutations affecting emtricitabine or tenofovir. The overall prevalence of transmitted drug resistance remains low in Norway, not affecting the efficacy of the recommended first-line treatments for HIV.

Hepatitt B-virus (HBV)

In 2024, 202 samples were analysed in Norway for HBV drug resistance mutations and genotype. Most of these were submitted for HBV genotyping only, and no drug resistance mutations were detected among these samples. 33 samples were submitted specifically for drug resistance testing, a slightly higher number of samples compared to 2023. Out of these, four samples exhibited drug resistance mutations. These mutations conferred resistance or partial resistance to entecavir.

Hepatitt C-virus (HCV)

In 2024, 130 samples were analysed for the presence of resistance-associated substitutions (RASs). Drug resistance data were then cross-referenced with epidemiological data from MSIS to enable comparisons of different subgroups. RASs were found in 45 % of samples, however resistance remains a minor issue in clinical practice, as very few samples show RASs impacting all of the drugs in recommended drug combinations. Surveillance aims to monitor primary resistance among new cases but faces challenges due to uncertainties in epidemiological data and patient treatment history.

Cytomegalovirus

In 2024, 23 samples from 18 patients were analysed for cytomegalovirus (CMV) antiviral drug resistance. Resistance mutations were detected in three samples, all conferring moderate resistance to ganciclovir. Despite increased use of ganciclovir for CMV treatment and prophylaxis, resistance mutations remain rare. Letermovir and maribavir have been available in Norway since 2019 and 2022, respectively, and resistance analysis includes detection of mutations conferring resistance to these drugs.

Herpes simplex virus

A total of 12 samples from 9 patients were submitted for herpes simplex virus (HSV) drug resistance testing in Norway, and reduced susceptibility to aciclovir was found in 6 (66%) of the samples. There was a small increase in the number of samples sent for resistance testing compared to last year, but the overall number remains low and the proportion of samples containing resistant HSV remains high. As such, it is likely that some cases of resistance go undetected.

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.

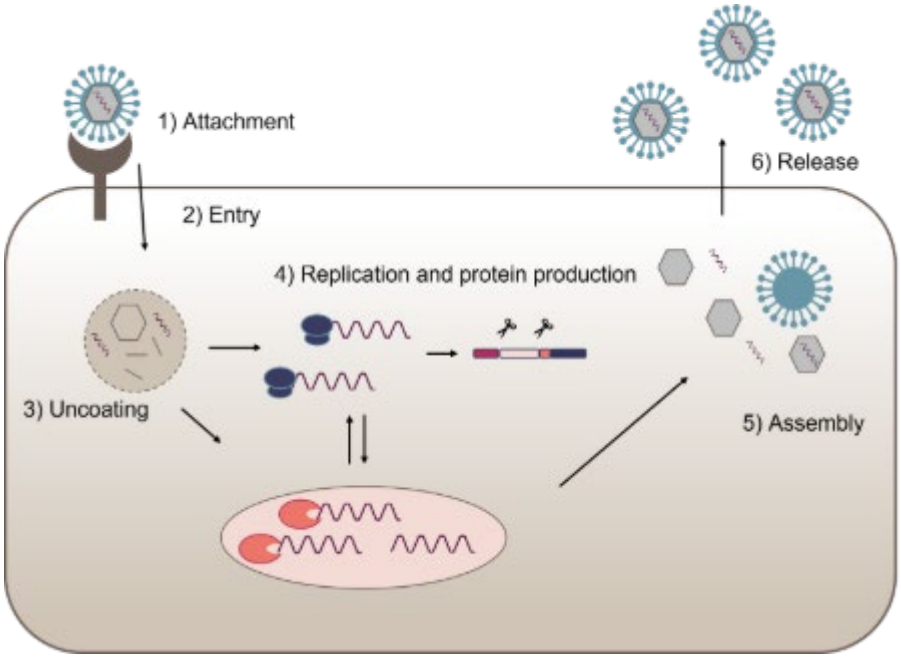

Figure 1.1. Generalized depiction of the viral replication cycle showing the major steps in replication.

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 influenza to influenza virus in human populations (3). Genetic alteration at a key site of the viral genome is usually a disadvantage for the virus, and 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 isapproved in Europe, but market authorization in Norway was withdrawn in 2022. 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. Baloxavir marboxil was licensed for use in 2021, but later withdrawn from the market in 2022. There has been no registered use of this antiviral in Norway. 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 if the mutation that confers resistance does not cause a 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/nucleotide 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).
- Multiple stages: HIV capsid inhibitors inhibit nuclear transport, assembly and release of virus as well as capsid assembly. Examples: Lenacapavir.

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 and hepatitis D virus

Chronic HBV infection can be asymptomatic or cause chronic hepatitis with subsequent liver damage. In line with the UN's global sustainability goals and the WHO's global health strategy, Norway aims to eliminate hepatitis B as a public health problem by 2030. The goal of treating chronic HBV infection is to prevent liver damage and improve survival through suppression of viral replication, and treatment is usually life-long. 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 favourable 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 emerge during 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, at least two mutations are required to confer full drug resistance and occur to some extent. 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 against 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). Drugs: 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. One drug is approved for prophylactic use after stem cell transplantation or kidney transplantation; letermovir.
- Multiple stages: Inhibition of UL-97-kinase leading to reduced phosphorylation of viral and host proteins (multiple effects) and nucleotides for DNA replication. One drug is approved for treatment of refractory CMV infection/disease: maribavir

Ganciclovir and its prodrug valganciclovir are usually 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. Due to their higher toxicity, these drugs are reserved for specific situations such as ganciclovir-resistant CMV infections.

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 and is now also approved for prophylaxis in kidney transplant recipients. 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

Resistance to ganciclovir during anti-CMV treatment typically arises after a cumulative exposure of six weeks or more. The earliest resistance mutations are most commonly detected in the *UL97* kinase gene. These mutations impair ganciclovir phosphorylation but do not affect susceptibility to foscarnet or cidofovir. Subsequent mutations may occur in the *UL54* gene, which encodes the viral DNA polymerase. These mutations often develop later in the course of therapy and can enhance resistance when combined with pre-existing *UL97* mutations. Isolated *UL54* mutations without accompanying *UL97* mutations are rare during ganciclovir treatment. Mutations in *UL54* can confer resistance to one or more antiviral agents, including ganciclovir, foscarnet, and cidofovir, either individually or in combination, depending on the specific mutation profile (11).

Experience with maribavir and letermovir resistance in Norway remains limited, primarily due to the restricted clinical use of these agents. Data from clinical trials suggest that both drugs possess a lower genetic barrier to resistance compared to DNA polymerase inhibitors. Letermovir resistance is primarily associated with mutations in the UL56 gene, although mutations in UL89 and, very rarely, UL51 may also contribute. For maribavir, the principal resistance-conferring mutations are located in UL97, although additional mutations associated with low-level resistance have been identified in UL27 (12).

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: nucleotide analogues aciclovir, valaciclovir, penciclovir, cidofovir and foscarnet

To be effective, aciclovir must be triphosphorylated, first by a viral thymidine kinase (UL23) 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. The closely related drug penciclovir is available in a topical formulation for the 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) (13).

Drug resistant HSV

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

polymerase gene (14). Mutations in the thymidine kinase gene usually result in a nonfunctional gene product, incapable of catalysing the first step in aciclovir activation.

Aciclovir resistance is frequently associated with cross-resistance to other HSV- thymidine kinase dependent nucleoside analogues (15). 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 (15). 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 (14).

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 response rates. 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 weeks after completion of treatment) (16).

There are currently three groups of direct-acting antivirals (DAAs) targeting HCV genome replication/transcription, protein production or multiple stages simultaneously (17):

- Replication: NS5B inhibitors.
  - Nucleotide/nucleoside analogue polymerase inhibitors: Compete with nucleotides 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 nucleotides 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.

Additional antivirals from new drug classes are under development, and some are in clinical trials.

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2 Special topics

Highly Pathogenic Avian Influenza

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Global spread of H5Nx clade 2.3.4.4b viruses

Since 2020, Highly Pathogenic Avian Influenza (HPAI) H5Nx clade 2.3.4.4b viruses have spread globally among birds and other animals, causing a panzootic (1). These viruses trace their H5 gene back to A/Goose/Guangdong/1/1996, first identified in China. From 2021 onward, H5N1 has emerged as the predominant circulating subtype. In Europe, H5N1 has led to an unprecedented number of outbreaks in both poultry and wild birds, resulting in the death of millions of birds.

By late 2021, HPAI became endemic in wild bird populations (2). The virus crossed the Atlantic with migratory birds, reaching Canada in December 2021 (1). Between 2022 and 2024, it continued to spread throughout North and South America, eventually reaching Antarctica. As of August 2025, Oceania remains the only unaffected major geographic region.

Increased spillover to mammals

Between 2021 and 2024, detections and outbreaks among wild and domestic mammals increased significantly, primarily due to spillover events from infected avian populations (1). Carnivorous species such as red foxes and marine mammals, including seals and sea lions, were affected, mainly through ingestion of or close contact with infected wild birds. These animals frequently exhibited respiratory and neurological clinical signs. Outbreaks among farmed fur animals were reported in Spain (2022) and Finland (2023) (3;4). In Poland (2023), multiple domestic cats developed acute illness, most likely linked to the consumption of contaminated poultry meat (5).

In 2024, HPAI was detected in dairy cattle for the first time (6). Between 2024 and 2025, approximately 60% of all dairy cattle farms in the United States reported infections with H5N1. Unlike chickens, infections in cattle were generally mild, with a mortality rate of 1-2% and recovery occurring within a few weeks. Viral replication occurred primarily in the udder, resulting in high viral loads in milk. Transmission between cows and farms occurred via contaminated milk, milking equipment, and the movement of lactating animals. Farm workers also contracted the virus, typically presenting with conjunctivitis and mild respiratory symptoms. Additionally, several farm cats that consumed raw milk developed severe disease and died.

Zoonotic risk

As of 2025, highly pathogenic avian influenza (HPAI) H5Nx viruses have been detected in over 80 mammalian species worldwide (1). Despite widespread circulation in birds and a growing number of infections in mammals, human cases remain sporadic. As of July 2025, the FAO, WHO, and WOAH assessed the risk of zoonotic transmission of influenza A(H5) to the general public as low (7). However, the risk for individuals with occupational or frequent exposure was considered low to moderate.

Situation in Norway

Since the first detection of HPAI in Norway in 2020 (8), HPAI H5Nx clade 2.3.4.4b viruses have been identified in multiple wild bird species along the Norwegian coastline, as well as in

Svalbard and Jan Mayen. The H5N8 subtype circulating in 2020 was subsequently replaced by H5N1, which has co-circulated with H5N5 since 2022. As of 28 August 2025, HPAI H5Nx viruses have caused outbreaks and/or been detected in wild birds, wild mammals, captive birds, commercial poultry, and hobby flocks in Norway. No human infections have been reported.

Virus characterization

HPAI viruses detected in birds and other animals are whole genome sequenced (WGS) at the Norwegian Veterinary Institute, which serves as the national reference laboratory for avian influenza. The resulting sequences are shared with the Norwegian Institute of Public Health via the GISAID platform and with the European Reference Laboratory for Avian Influenza (IZSVe) in Italy. These data are used for virus characterization, monitoring viral spread, and identifying genetic markers associated with increased mammalian adaptation, zoonotic potential, and antiviral resistance.

Virus characterization shows that the HPAI H5Nx 2.3.4.4b viruses circulating in wild birds and animals in Europe, including Norway, are still mainly avian-adapted. However, some markers suggesting mammalian adaptation are present (9). Their occurrence appears to have increased in recent years. An example of this is the PB2-E627K(V) mutation, which is associated with increased replication in mammalian cells and has been detected in viruses from wild birds as well as wild mammals.

Susceptibility to antivirals

Highly pathogenic avian influenza (HPAI) H5Nx clade 2.3.4.4b viruses currently circulating in Europe remain largely susceptible to antiviral medications for human use. These include adamantanes (e.g., amantadine and rimantadine), neuraminidase (NA) inhibitors (e.g., oseltamivir), and polymerase acidic (PA) inhibitors (e.g., baloxavir marboxil) (9).

Despite this overall susceptibility, mutations associated with antiviral resistance have been identified in a small proportion of viruses. Specifically, resistance-associated mutations have been observed in approximately 0.5% of viruses for adamantanes, 1% for NA inhibitors, and 0.5% for PA inhibitors (9). It is important to note that resistance-associated mutations for PA inhibitors have primarily been studied in seasonal influenza viruses and not specifically in A(H5N1) viruses. The M2-A30S mutation, which confers increased resistance to adamantanes and rimantadine, has also been detected in some HPAI H5N1 viruses in Norway (10).

In addition to ongoing surveillance of influenza viruses in animal populations, the FAO-WOAH Network of Expertise on Animal Influenza (OFFLU) contributed antiviral susceptibility data to the WHO Vaccine Composition Meeting held in February 2025 (11). During this meeting, data was presented from avian H5 clade 2.3.4.4b viruses from various geographical regions that had been assessed for susceptibility to NA inhibitors (oseltamivir and zanamivir) using both genetic analysis and functional testing with the MUNANA assay. The majority of viruses tested were found to be susceptible. However, one notable exception was identified during poultry outbreaks in British Columbia, Canada, in 2024. An HPAI H5N1 virus isolated from this outbreak carried the H275Y mutation in the neuraminidase gene, which is known to confer resistance to oseltamivir (11;12).

Conclusion

Given the zoonotic potential and pandemic risk posed by avian influenza viruses, it is essential to maintain and strengthen surveillance efforts, particularly for resistance-associated mutations, in viruses circulating among birds and other animals.

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Chronic Hepatitis E in Immunosuppressed Patients: A Case Report and Overview of Treatment Strategies

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Case History

A man in his 50s was referred from the nephrology department for hepatology evaluation. Five years earlier, he had undergone kidney transplantation for IgA nephritis and was receiving tacrolimus, everolimus, and low-dose prednisolone. He had hypertension treated with candesartan, no other cardio-metabolic risk factors, and a moderate alcohol intake of six units per week.

Four months prior, he was treated for herpes zoster with valaciclovir; during that episode, liver enzymes showed a hepatocellular pattern (peak ALT 700; normal ALP and bilirubin). Mildly elevated transaminases had already been noted one month earlier, when he reported transient loose stools and abdominal discomfort. He had no relevant travel history and no new medications. Transaminases remained persistently elevated (ALT 100–200). Immunological liver tests were negative, and standard viral serology (HAV, HBV, HCV, CMV, EBV) showed no evidence of current infection. He was clinically well without stigmata of chronic liver disease; BMI was 25. Ultrasound showed a morphologically normal liver and normal elastography (4.6 kPa).

Because standard serologies and imaging failed to explain the persistent transaminase elevation, extended virological testing was warranted. Additional testing at the Norwegian Institute of Public Health showed positive anti-HEV IgG and IgM and HEV RNA 400,000 IU/mL. Stored serum taken five months earlier contained HEV RNA at a higher titer (1.4 million IU/mL) and isolated anti-HEV IgM without IgG, establishing chronic HEV infection based on viremia persisting ≥3 months.

Immunosuppression was first reduced to facilitate spontaneous clearance. After three additional months, HEV RNA remained detectable, and ribavirin (RBV) therapy was initiated. As RBV is deregistered in Norway, tablets were imported from the USA under special authorization. After three months of RBV 400 mg twice daily, HEV RNA was undetectable. Sustained virological response (SVR) was confirmed three months post-therapy.

Background and Discussion

In Norway, hepatitis E virus (HEV) is a zoonosis with reservoirs in pigs, wild boar, deer, and reindeer. HEV is now recognized as the most common cause of acute viral hepatitis in Western countries. In immunocompetent hosts, infection typically causes self-limited hepatitis but can be associated with extrahepatic manifestations such as neuropathy, glomerulonephritis, and hematological syndromes (1).

In contrast to this usually self-limited presentation in immunocompetent hosts, chronic HEV, defined as persistent HEV RNA in serum or feces for >3 months, occurs almost exclusively in immunosuppressed patients and is associated with genotypes 3 and 4. Unlike the acute form, chronic HEV can accelerate liver fibrosis and rapidly lead to cirrhosis if untreated (2).

Chronic HEV is frequently asymptomatic; persistent elevation of liver enzymes may be the sole clue. Accordingly, clinicians should adopt a low threshold for HEV testing when faced with

unexplained hepatocellular injury in immunosuppressed patients. In Norway, seven cases of chronic hepatitis E have been identified to date, all in immunosuppressed patients—mainly organ transplant recipients. The average initial blood viral load was 8.9 million IU/mL, and 3/7 patients were seronegative. Because seronegativity is common in this population, HEV RNA PCR should be performed together with serology whenever HEV is suspected in immunosuppressed individuals.

Treatment Principles and Ribavirin Resistance

With the diagnostic framework established, we turn to therapeutic strategies that balance viral clearance with preservation of graft function and immune control. Reduction of immunosuppression is first-line when clinically feasible, and results in spontaneous clearance in about 30% of patients (3); most others require antiviral therapy. Current guidelines recommend three months of RBV monotherapy, extendable to six months for non-response or relapse. Meta-analyses report SVR in ~80% of patients; after initial relapse, retreatment can still succeed in up to 76% (3).

To understand both its strengths and its limitations, it is helpful to consider how RBV exerts antiviral activity against HEV. RBV, a synthetic guanosine analogue, likely acts against HEV primarily via lethal mutagenesis: incorporation into viral RNA increases error rates, rendering genomes nonfunctional. Unlike classical direct-acting antivirals, resistance does not typically arise from single binding-site mutations. Rather, adaptive changes that increase viral fitness or replication fidelity can reduce RBV's mutagenic effect (4).

Mutations in the RNA-dependent RNA polymerase (RdRp; ORF1) and insertions in the hypervariable region (HVR) have been associated with treatment failure. However, current knowledge is limited, and known "resistance" markers have uncertain prognostic value. Outcomes likely depend on a combination of host factors (immunologic reconstitution), pharmacology (RBV exposure), and the quasispecies mutation profile, parameters that are not yet integrated into routine care.

Alternative Strategies and Future Directions

Pegylated interferon-α (peg-IFN-α): The most potent alternative, with reported SVR rates of 85–100% in RBV-refractory patients, but generally contraindicated in transplant recipients due to the risk of acute graft rejection (2;3).

Sofosbuvir (SOF): Although in vitro activity against HEV was promising, clinical responses have been transient with rapid relapse, attributed to selection of A1343V in the polymerase, which reduces SOF sensitivity. Combination with RBV has not demonstrated additional benefit (3).

New antiviral targets: Work is ongoing on viral enzymes such as the methyltransferase (MTase) and papain-like cysteine protease (PCP). Progress is slowed by limited cell and animal models and modest commercial incentives given the small target population; drug repurposing will likely remain central in the near term.

Conclusion

Insights from the index case and the broader evidence base, yields three practical messages for care:

- Chronic hepatitis E should be considered in immunosuppressed patients with unexplained elevated liver enzymes.

- RBV remains the cornerstone of therapy and is effective in most cases, but treatment failure can occur.
- Managing RBV nonresponse is individualized; prolonged RBV is often the safest, most pragmatic approach.

Although resistance testing currently has limited clinical value, integrating virological (mutation profile), immunological, and pharmacological data may enable more personalized treatment for this vulnerable group.

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3 The usage of antivirals in Norway

Many new direct acting antivirals, 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 of direct acting antiviral drugs (DAAs), measured in both defined daily doses (DDDs) and number of patients treated has increased from 2020 to 2024 (Figure 3.1 and Figure 3.2 respectively), although the sales measured in number of DDDs was slightly reduced in 2020 and 2021. 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 can be reduced despite an increase in number of users.

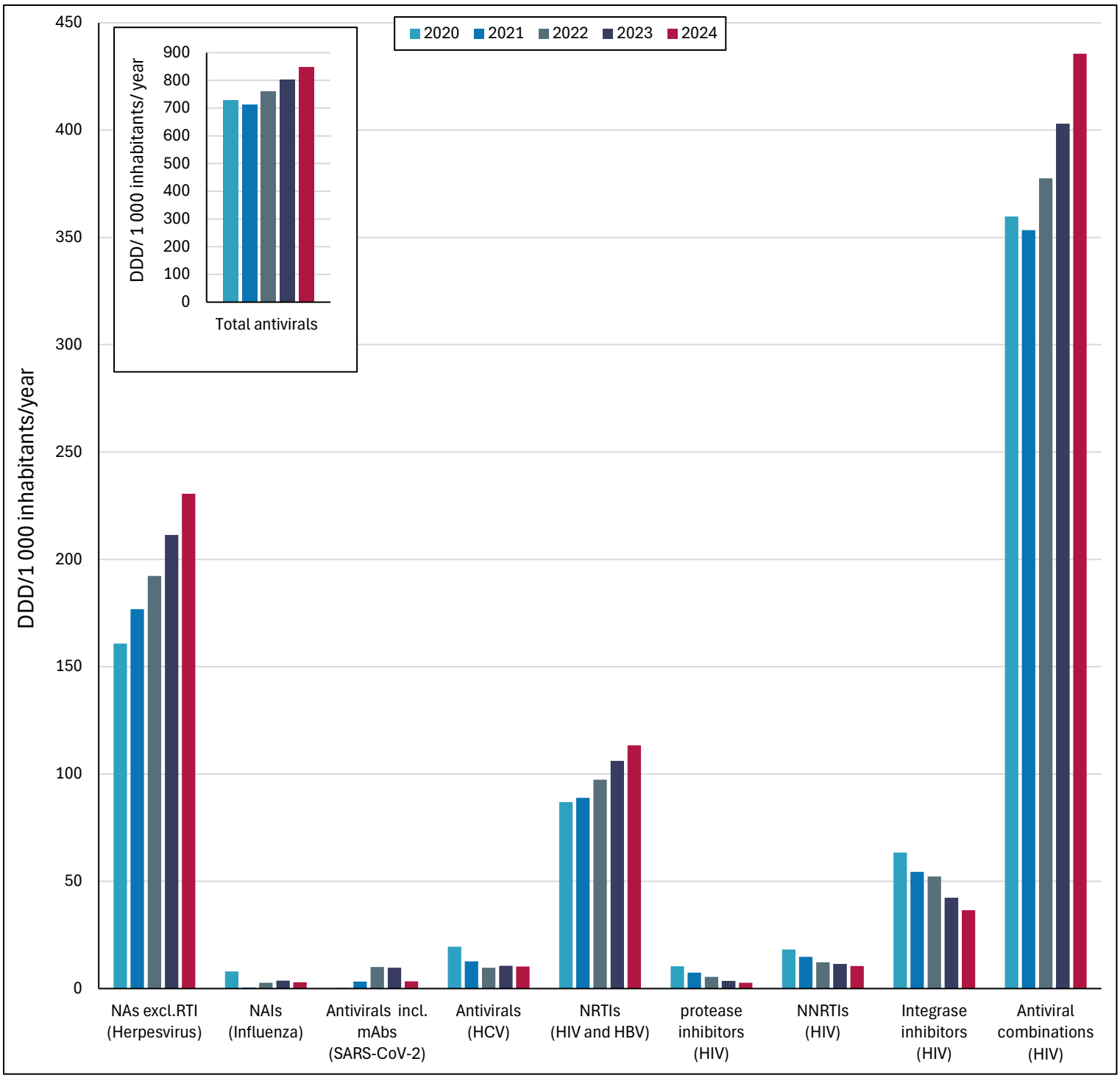

Figure 3.1 Sales of direct acting antiviral drugs for systemic use (ATC group J05A) for 2020-2024.

The figure shows the sales of direct acting antiviral groups over time according to the Norwegian drug wholesales statistics database (1). 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); SARS-CoV-2 : remdesivir, favipiravir, molnupiravir, nirmatrelvir and ritonavir, sotrovimab, tixagevimab and cilgavimab, casirivimab and imdevimab; Antivirals for treatment of HCV infections (J05AP); NRTIs: Nucleo(s/t)ideanalogue 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. The total numbers also include phosphonic acid derivates (J05AD) used against herpesviruses and other antivirals (J05AX), due to low numbers these are not indicated in the main plot. Monoclonal antibodies are not included in the total numbers. Drugs included in wholesale data are not necessarily used in 2024 - they could be stored in pharmacies or in hospitals.

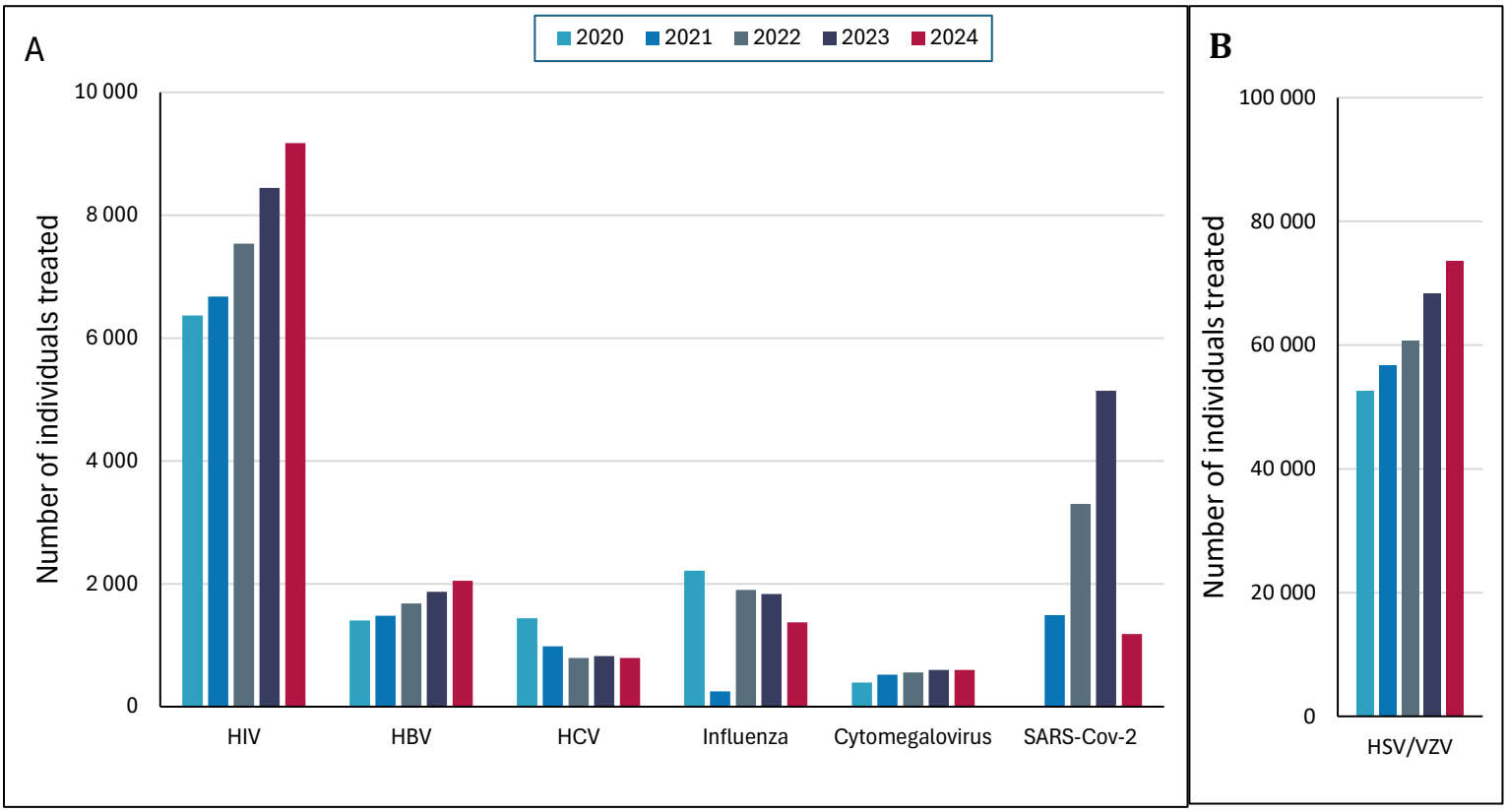

Figure 3.2 Trends in the use of direct acting antiviral drugs for systemic use (ATC group J05A) grouped by virus for 2020-2024 (2).

The figure shows the number of individuals treated with systemic direct acting antivirals for different viruses 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) and Tenofovir (TDF). Single component drugs approved for both HBV and HIV are included in the HBV numbers; Influenza: Neuraminidase inhibitors; cytomegalovirus: valganciclovir, ganciclovir, cidofovir, foscarnet, letermovir and maribavir; SARS-CoV-2: nirmatrelvir and ritonavir and favipiravir. Panel B: Herpes simplex and varicella zoster virus: aciclovir, valaciclovir and famciclovir; Data from the Norwegian Prescribed Drug Registry (NorPD).

The number of individuals treated with DAAs for HIV, HBV and herpes has increased since 2020, while the number of individuals treated for HCV has decreased. The use of DAA against influenza varies from year to year as described below (Figure 3.2). 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 (Figure 3.1), while DAAs against herpesvirus are by far the most commonly used antivirals when measured in number of users (Figure 3.2). The high number of DDDs for HIV drugs reflects the lifelong continuous treatment of HIV, while antivirals against herpes infections are usually given in short courses. For DAAs targeting herpesvirus, the use of topical agents (creams and ointments) is not included in the measurement.

Influenza virus

The usage of neuraminidase inhibitors, antivirals for the treatment of influenza (ATC group J05AH), is shown in Table 3.1. 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 during the COVID-19 pandemic. The high number of cases in the 2024-2025-season is not fully reflected in the numbers shown below, as they only account for the first part of the season.

Due to limited use, zanamivir was withdrawn from the market in 2016 and is only available as an unlicensed medicinal product (200 packages sold in 2024). Likewise, baloxavir marboxil was registered in 2021, but there was no registered sale, and it has now been removed from the market. Consequently, oseltamivir is now the only registered neuraminidase inhibitor available for treatment of influenza in Norway.

Table 3.1 Number of individuals with at least one prescription of neuraminidase inhibitor per year (2).

	2020	2021	2022	2023	2024
Oseltamivir	2214	250	1901	1835	1371

Human immunodeficiency virus

There are currently 36 drugs or combination drugs in Norway that are available for treatment of HIV (2). The use of the different drugs has shifted in the last five-year period. During the whole period, nearly 99% of persons treated received combination drugs. Some of these combination drugs contain complete combination ART (single-pill regimens). Figure 3.3 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 (combinations of two or more substances, typically two NRTIs that are commonly taken together); and single substance drugs that are given in addition to the fixed combinations in order to obtain complete ART.

Tenofovir disoproxil (TDF) is approved for treatment of both HIV and HBV infections. However, since this single substance drug is rarely used for HIV therapy, the users of TDF are neither included in the total number of users of HIV treatment nor in the different groups in Figure 3.3.

The sum of the patients using the different drugs is higher than the total number of patients treated with HIV drugs in Figure 3.2. This is because some patients receive more than one drug or may change treatment regimen during a year. The fixed combination of emtricitabine and tenofovir disoproxil (FTC/TDF) has been the most used combination drug in recent years. It is generally used together with either an integrase inhibitor, boosted protease inhibitor, or an NNRTI in combination ART. 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 2024 was 4470. The use of FTC/TDF increased almost 47% from 2018 to 2019. The yearly increase was reduced to below two percent in the pandemic years 2019 to 2021, followed by an increase of 16%, 13% and 6% in 2022, 2023 and 2024, respectively. It is likely that the extensive infection control measures, e.g. travel restrictions applied in connection with the COVID-19 pandemic 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 although less likely, the changes in the use of FTC/TDF seen the latest years might also have other explanations. Another 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-tablet complete treatment regiments (3). The combination drug FTC/TAF 200mg/25mg is approved as an alternative in continuous PrEP in persons with contraindications for FTC/TDF. This combination had the highest use in 2018 (2526 packs sold) and has decreased since then; in 2024 1041 packs were sold (wholesales data).

When looking at complete ART regimens, combinations containing integrase inhibitors are widely used, which is also in accordance with the Norwegian guidelines (3). This is illustrated in Figure 3.3, which shows that many combination drugs containing integrase inhibitors are among the most sold drugs during the latest years, measured in number of users. The recommendations from The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF), also have an impact on the choice of drugs for treatment of HIV (4). The combination of the two single ingredient drugs; cabotegravir and rilpivirin administered as injections, was approved as complete dual therapy in December 2020. The sales of these injections were limited in 2021 but have since then increased 9-fold in number of DDD (wholesales data).

The use of the integrase inhibitors (INSTI) 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. Dolutegravir is the most widely used integrase inhibitor. Along with bictegravir and cabotegravir the use is increasing when measured in number of prescriptions per active ingredient, while the use of raltegravir and elvitegravir is decreasing. The number of prescriptions per active ingredient over time is shown in Figure 3.4. For NRTIs, there are far more prescriptions for emtricitabine and tenofovir (TDF or TAF) than for lamivudine and abacavir.

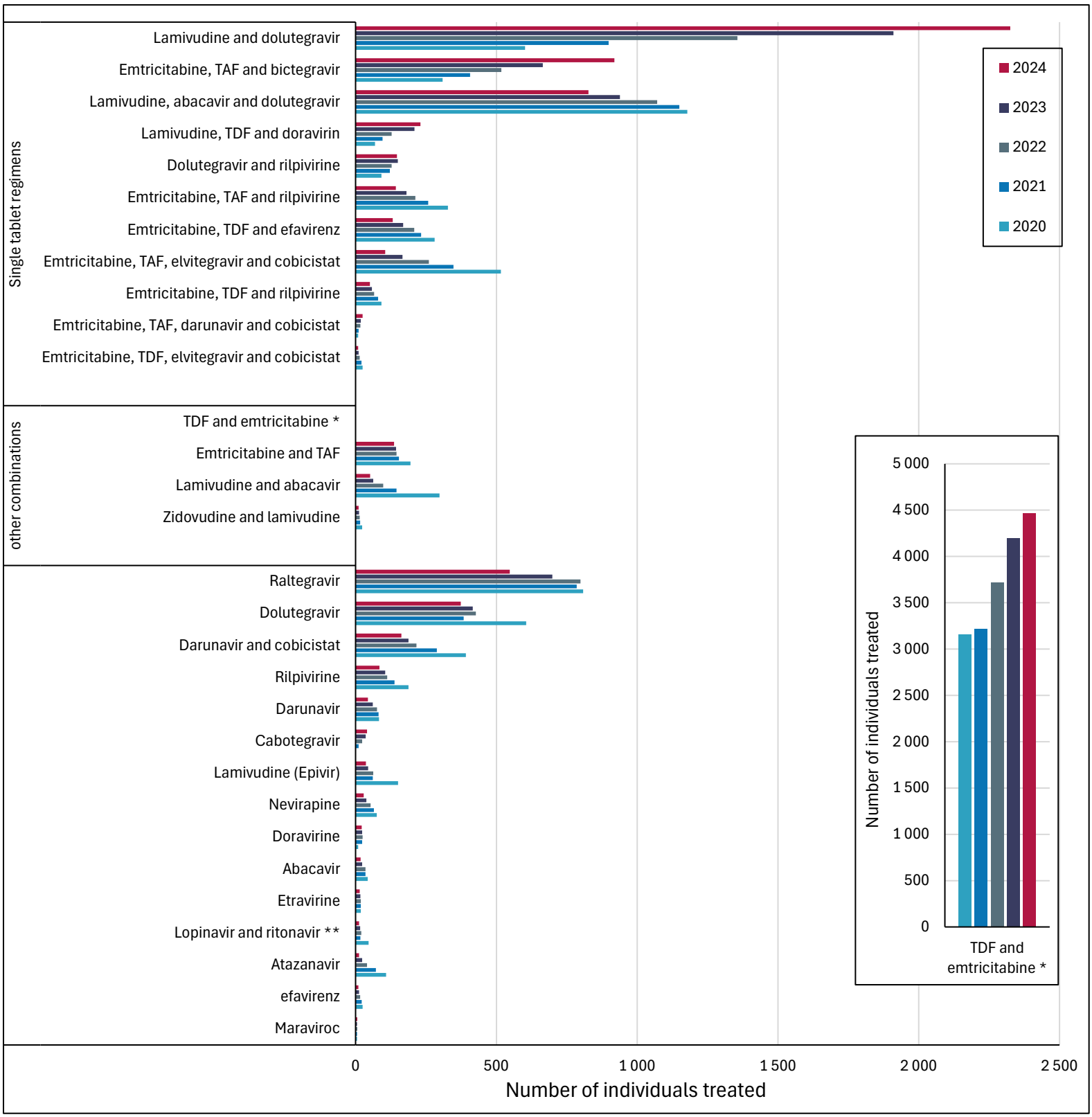

Figure 3.3 Trends in the use of systemic antivirals prescribed for HIV in the periods 2020-2024 (2).

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 none or less than 6 individuals in 2024 are excluded (zidovudine; atazanavir and cobicistat). Ritonavir is also excluded. *This group, which Includes PrEP, is presented in the inserted plot. **Protease inhibitor boosted with ritonavir, considered single ingredient drug

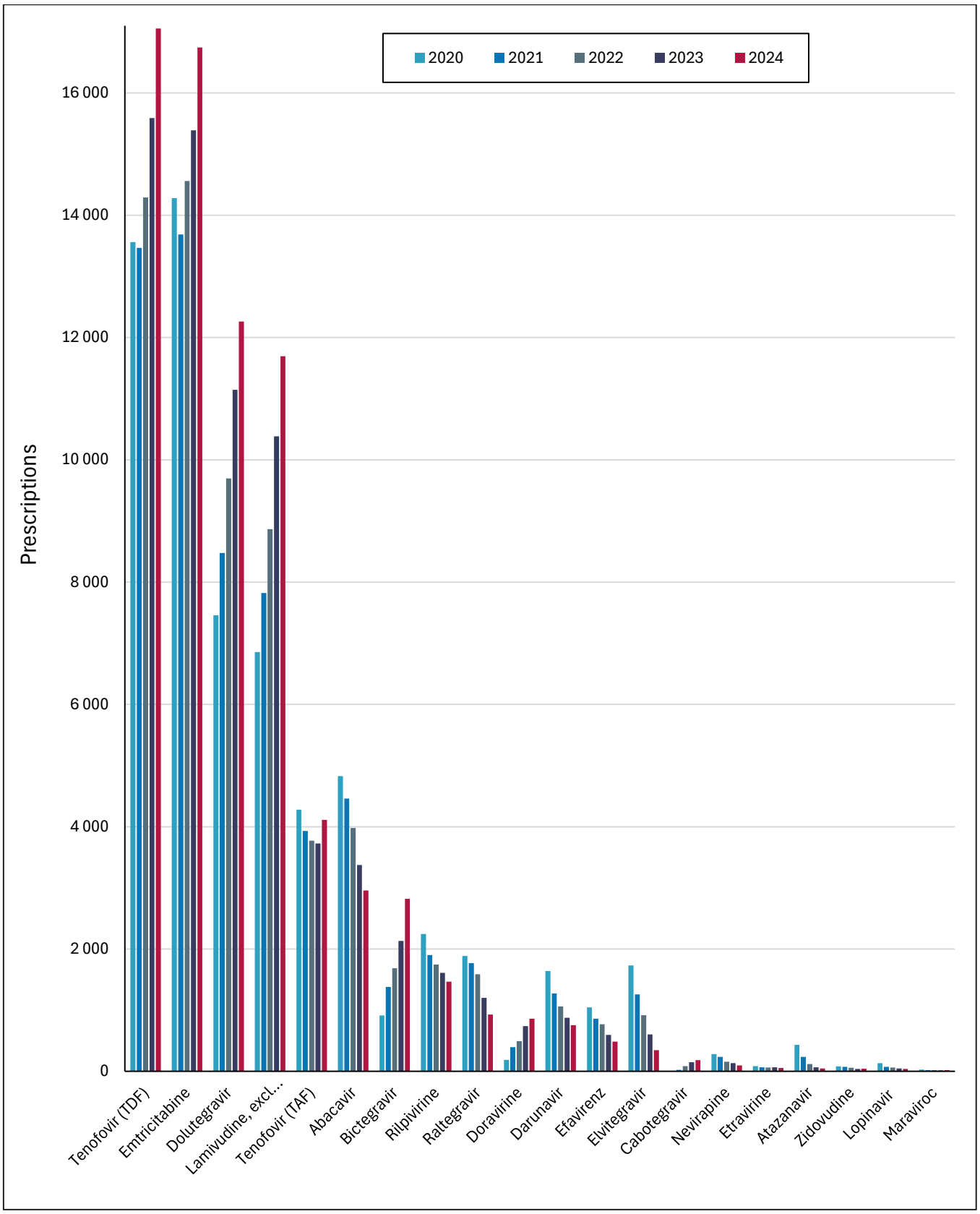

Figure 3.4 Number of prescriptions per active ingredient for HIV drugs (2).

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 has not been prescribed since 2020 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

Antivirals for treatment of HBV are generally given as monotherapy and there are currently six nucleoside/nucleotide analogues (NAs) approved for this indication. The use of antivirals against HBV is shown in Figure 3.5. The data is based on the annual number of patients retrieving at least one prescription per year for the period 2020-2024. Tenofovir disoproxil (TDF) and lamivudine are approved for both HBV and HIV. TDF as a single substance drug is rarely used for HIV therapy and is therefore counted as an HBV antiviral in this report. Lamivudine is considered as an HBV antiviral in the form of Zeffix® but is rarely used due to the considerable risk of resistance development. Entecavir and tenofovir alafenamide (TAF) as single substance drugs, are approved for HBV only. In 2022, bulevirtide was approved for treatment of hepatitis D, which always presents as a co-infection with HBV. There have however been no registered sales of bulevirtide since its approval.

The annual number of persons treated for HBV has increased considerably during the last five years, by 46 % since 2020. 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 NAs, more than 99% received one of these three drugs in 2024. From April 2021, entecavir is recommended as the preferred drug according to procurement recommendations from Sykehusinnkjøp HF (5). This may explain the increase in the use of Entecavir from 2021.

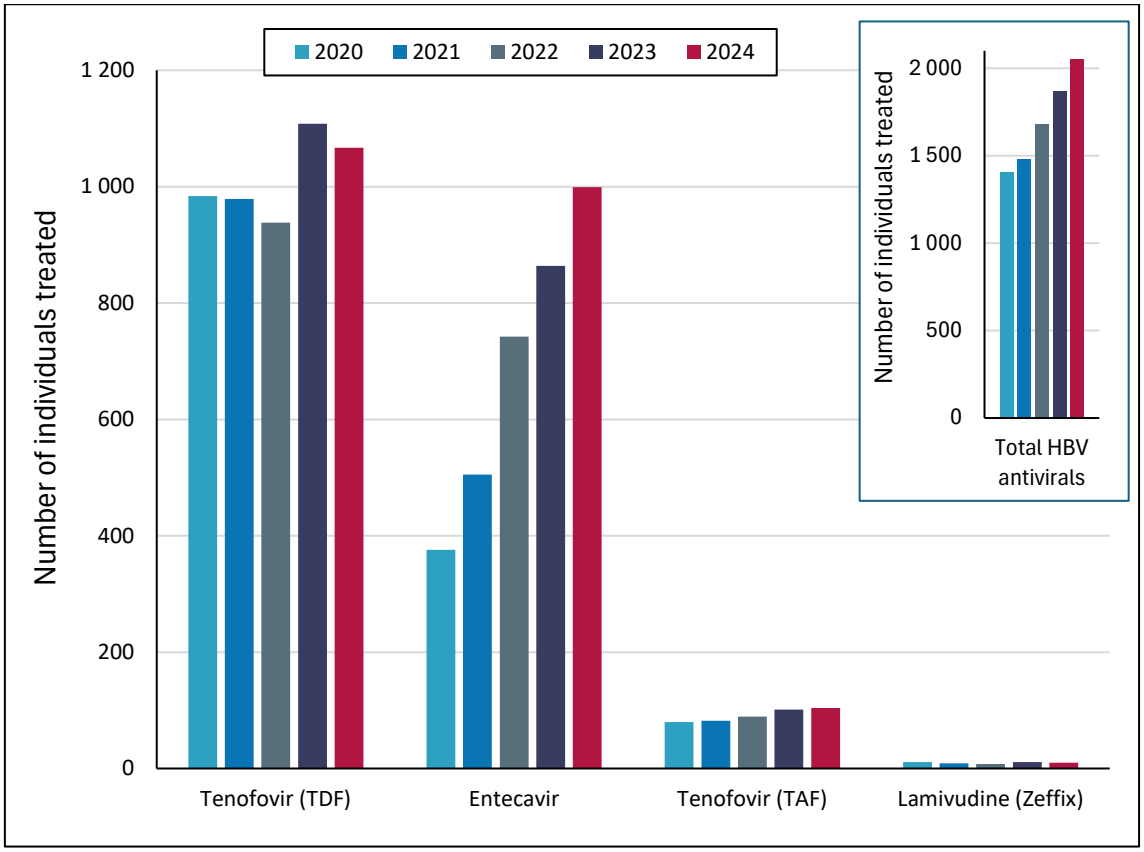

Figure 3.5 Trends in the use of antivirals for treatment of HBV for the period 2020-2024 (2).

This figure shows the trends in antiviral use for the treatment of HBV over time. Single component TDF is counted as an HBV antiviral. Due to small numbers adefovir and telbivudine are excluded from the figure. The number of persons treated is defined as the number of patients given at least one prescription per year.

Human herpesviruses

Figure 3.6 shows the prescribed drugs for systemic use for herpes simplex and zoster virus infections over the last five years. Valaciclovir is the most commonly prescribed substance and there has been an increase of 53 % in the number of individuals treated with this antiviral since 2020. The use of aciclovir has been stable during the five-year period. In 2024, 74764 persons were treated with systemic antivirals for herpes simplex or zoster infections.

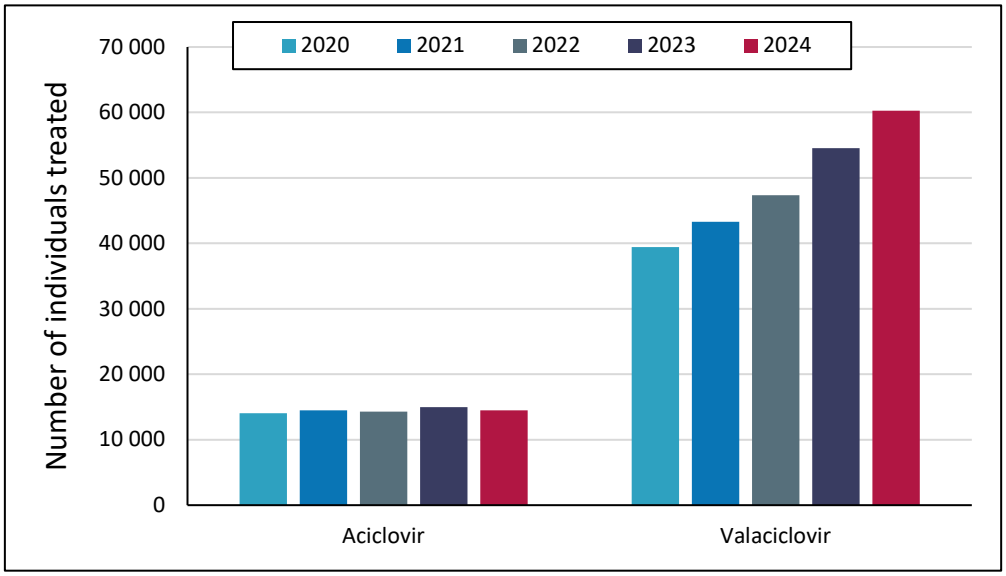

Figure 3.6 Trends in the use of systemic antivirals prescribed for herpes simplex and zoster virus infection for the period 2020-2024 (2).

This figure shows the trends in direct acting antiviral use for treatment of human herpesviruses over time. The number of individuals treated is defined as the number of patients given at least one prescription per year. Famciclovir was rarely prescribed and are 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 in the next couple of years. Since then, 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 3.2).

Table 3.2 Sold packages of topical antivirals containing aciclovir, penciclovir and aciclovir in combination with hydrocortisone.

	2020	2021	2022	2023	2024
Aciclovir	169004	176013	174756	191192	170443
Penciclovir	17229	14054	10272	8906	8196
Aciclovir, combinations*	34727	45996	40585	55562	53047

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 % are nonprescribed medications.
* In combination with hydrocortisone. Data from the Norwegian drug wholesales statistics database.

Prescribed antivirals for CMV over the last five-year period is presented in figure 3.7.

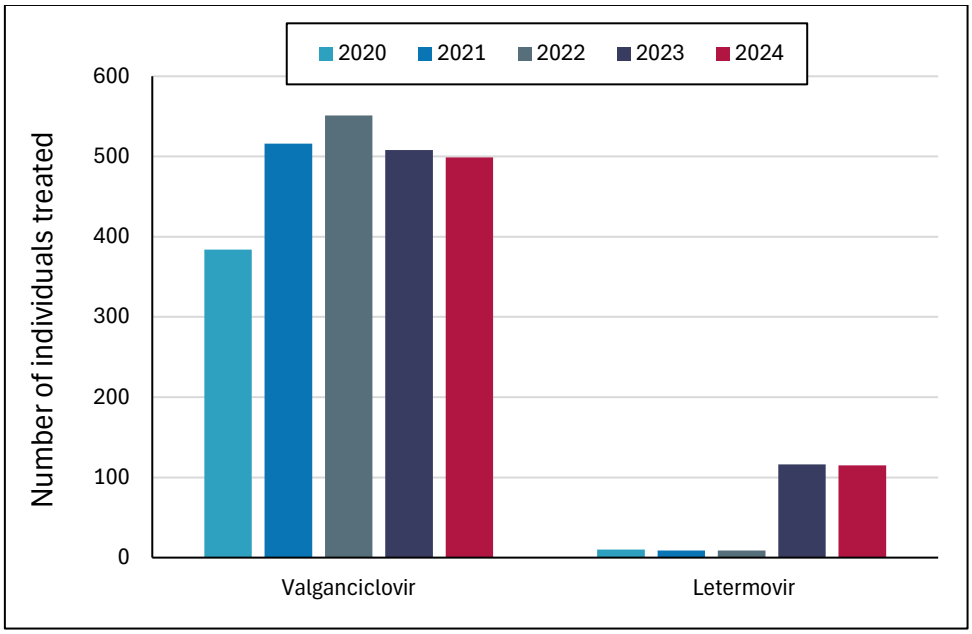

Figure 3.7 Trends in the use of systemic antivirals prescribed for cytomegalovirus infection for the period 2020-2024 (2).

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

Hepatitis C virus

After the new HCV antivirals became available in 2015 there was a steady increase in the overall number of patients treated with DAAs against HCV until 2018, but since then the number of persons treated has decreased (Figure 3.2). The number of persons who received at least one prescription for an HCV drug (except interferons) was 807 in 2024, a reduction by 45 % since 2020. Fixed combinations of two or more active ingredients have almost completely replaced older regimens with single component drugs and ribavirin as shown in Figure 3.8.

Recommended treatment protocols for HCV-infection from the Norwegian Medical Association (NMA) (6), last updated in 2022, depend on both genotype and stage of liver disease. Trends in the use of antivirals against HCV (Figure 3.8) reflect both changes in the NMA-treatment guidelines, and recommendations from The Norwegian Hospital Procurement Trust (7). The procurement recommendations are similar but not identical to the NMA guidelines.

“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.

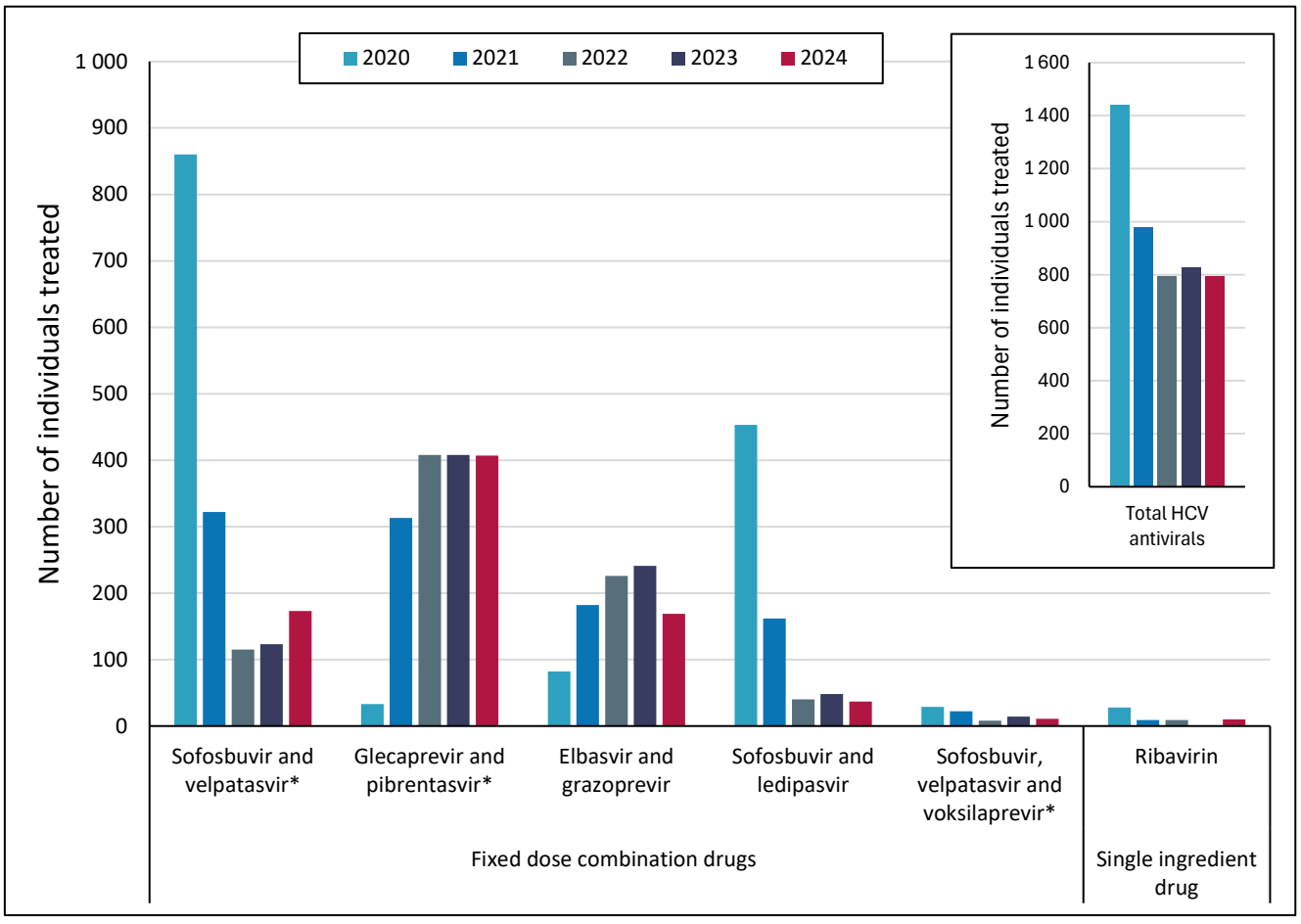

Figure 3.8 Trends in the use of antivirals for treatment of HCV for the period 2020-2024 (2).

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. Drugs not sold in 2024 (ombitasvir/paritaprevir/ritonavir; sofosbuvir; dasabuvir) are excluded from the figure. *Pangenotypic drugs.

SARS-CoV-2

Only one oral antiviral drug against SARS-CoV-2, nirmatrelvir and ritonavir (Paxlovid®), has become available for out-patients in Norway, and 1181 individuals were dispensed a prescription in 2024. Parenteral antiviral treatment of COVID-19 in Norway was only given in hospitals. In Norway, remdesivir has been approved for use against SARS-CoV-2 since November 2020. In 2024, 2008 DDDs were used in Norwegian hospitals. Moreover, 7860 DDDs of Paxlovid® (nirmatrelvir and ritonavir), were used in hospitals in 2024 according to the hospital pharmacies drug statistics database (Sykehusapotekenes Legemiddelstatistikk).

The use of monoclonal antibodies (Mabs) for the treatment of SARS-CoV-2 has been limited in Norway. The neutralizing activity of the individual Mabs against different variants was found to be variable, and thus, recommendations for use depended on the circulating variant. Subsequent studies indicate that the actual clinical efficacy of Mabs may persist despite reduced neutralizing activity (9), In 2021, two new drugs containing monoclonal antibodies (sotrovimab and casirivimab/imdevimab) were 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 (1). In 2023, there was no sale reported for monoclonal antibodies for the treatment of SARS-CoV-2. In 2024, 504 packs of another monoclonal antibody, sipavibart, were purchased for a compassionate use program, but probably not used. Records of actual use in hospitals are not available.

Other remarks

Since 2022, there have been some incidences of mpox in Norway. In 2024 5 packages (70 DDD) of Tecovirimat, an antiviral against orthopoxviruses like mpox, was sold according to data from the Norwegian Drug Wholesales Statistics.

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4 Influenza virus

Fact box: Influenza virus drug resistance	
Treatment	Neuraminidase inhibitor: oseltamivir. zanamivir Polymerase inhibitor: baloxovir marboxil (Licensed in Norway May 2021, removed in 2022). Adamantanes: M2 ion channel blockers (no longer in use)
Resistance testing method	Whole genome sequencing. Phenotypic by neuraminidase susceptibility assay (MUNANA). In Norway, all influenza drug resistance tests are performed at the WHO influenza centre / national reference laboratory for influenza at the Norwegian Institute of Public Health (NIPH).
Target gene	Neuraminidase, polymerase and M2 protein genes.
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 systematic surveillance for treatment-induced resistance.

Surveillance methods

The national reference laboratory for influenza and WHO Influenza Centre in Norway (NIC-Norway), located at NIPH, monitors influenza viruses via samples from sentinel physicians and medical microbiology laboratories to evaluate the vaccine match with circulating viruses, virus evolution, characteristics, and sensitivity to antiviral drugs. Samples from both untreated and treated patients in the community are included.

Surveillance data influenza season 2024-25

The outbreak began late, reaching a 10% positivity rate by week 52/2024 for comprehensive and week 1/2025 for sentinel surveillance. The peak of the season occurred in week 8/2025 with 36% positivity in comprehensive and week 7 with 40% in sentinel surveillance. The intensity of the season was relatively strong compared to previous seasons. Positivity rates fell beneath the 10% threshold in week 17/2025 in both comprehensive and sentinel surveillance.

Influenza A(H1N1) was the main driver of the season, but both A(H3N2) and B/Victoria-lineage were detected all throughout the season in substantial numbers meaning that all three virus types/lineages were circulating at the same time.

Influenza antiviral resistance

Out of 604 influenza viruses tested in the 24/25 season only one A/H1N1 virus sampled in week 40/2024 had the oseltamivir resistance substitution, H275Y, in the NA gene (1). Additionally, we found one influenza A/H1N1 from week 41 2024 that had the E23G substitution in the PA gene, which has been shown to lower the susceptibility towards baloxavir marboxil. The treatment history of both cases is unknown. All other tested viruses were sensitive to oseltamivir, zanamivir, and baloxavir marboxil.

No cases of the newly emerged I223V together with S247N substitution was detected in Norway 2024 (2).

All circulating seasonal influenza A viruses have been resistant to adamantanes since the 2009-H1N1 pandemic and adamantanes are therefore not used for treatment in Norway. Adamantanes do not inhibit influenza B viruses, and are thus not relevant for treatment of influenza B.

Table 3.1. Norwegian influenza viruses with resistance mutations to the neuraminidase inhibitors oseltamivir and zanamivir and adamantanes, during the influenza seasons 2017/18 through 2024/25 (ND=Not Done, NR=Not Relevant)

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
2015/16	10/339	0/32	0/50	0/106	0/31	0/48	ND	ND	ND	ND	ND	ND
2016/17	0/10	0/174	0/54	0/8	0/161	0/54	ND	ND	ND	ND	ND	ND
2017/18	0/120	0/66	1/42	0/28	0/54	0/30	ND	ND	ND	ND	ND	NR
2018/19	0/247	0/108	0/26	0/82	0/107	0/26	ND	ND	ND	ND	ND	NR
2019/20	0/103	0/63	0/42	0/32	0/60	0/42	ND	ND	ND	ND	ND	NR
2020/21	0/2	0/6	0/1	0/2	0/6	0/1	ND	ND	ND	ND	ND	NR
2021/22	0/31	0/634	0/9	0/31	0/634	0/9	0/0	1/442	0/0	19/19	476/476	NR
2022/23	1/494	0/291	0/347	1/494	0/291	0/347	0/74	0/232	0/10	ND	ND	NR
2023/24	1/287	0/206	1/111	0/287	0/206	1/111	0/252	0/190	0/138	287/287	207/207	NR
2024/25	1/260	0/199	0/147	0/260	0/199	0/147	1/222	0/180	0/137	260/260	199/199	NR

Conclusions

Antiviral resistance in influenza remains rare, with only two resistant viruses A(H1N1) found in the 2024/25 season in Norway (0.3 %). However, continued monitoring is crucial as naturally acquired mutations that confer drug resistance can quickly be acquired and spread globally (3).

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5 Severe acute respiratory syndrome 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 sequencing
Target genes	Protease (NSP5) RNA-dependent RNA polymerase (RdRp) Spike
Surveillance	General surveillance for resistance mutations in samples included in the national respiratory surveillance program and submitted to the reference laboratory at NIPH. Only substitutions associated with reduced susceptibility towards drugs targeting the protease or the RNA-dependent RNA polymerase are included in the surveillance.

Surveillance methods

In 2024, the surveillance of SARS-CoV-2 followed a protocol similar to influenza monitoring, carried out by the national reference laboratory for coronaviruses with serious outbreak potential at the National Institute of Public Health (NIPH). This surveillance program employs whole genome sequencing to assess variant prevalence, analyse virus characteristics, and identify drug resistance-associated substitutions.

For the analysis of resistance substitutions, whole genome sequences are specifically examined for mutations in the protease gene NSP5 (related to nirmatrelvir) and the RdRP gene (for remdesivir) of SARS-CoV-2. The substitutions are curated using lists provided by the Stanford Coronavirus Antiviral & Resistance Database (1;2), which is regularly updated to reflect findings from a wide range of publications and clinical trials. In the absence of an internationally recognized standard, this database serves as the most comprehensive source for SARS-CoV-2 drug resistance substitutions. However, uncertainty about levels of resistance and clinical relevance remains.

The program reports Pangolin lineages and relevant mutations to the European Centre for Disease Prevention and Control (ECDC), alongside inclusion in the NIPH's weekly respiratory virus surveillance reports and submissions to the Register for antiviral resistance in viruses in Norway (RAVN).

Surveillance data 2024

In 2024, SARS-CoV-2 infections showed a rise starting in week 20, with positivity rates crossing the 10% threshold by week 28. The highest positivity rate was recorded in week 35 at 14.6%, with rates remaining above 10% until week 38. Initially, the BA.2.86 variant was predominant at the start of the year, but from March and April, it was gradually replaced by its subvariants KP.2 and KP.3. By June, KP.3 had become the most detected variant (Table 5.1).

In August, a new recombinant variant, XEC, was detected, and it steadily increased in prevalence throughout the remainder of the year. By December 2024, XEC had become the most detected variant. This pattern of variant evolution underscores the adaptive nature of SARS-CoV-2, necessitating ongoing surveillance and responsive public health strategies to address the shifting landscape of COVID-19 transmission.

Overall, in 2024, 1078 surveillance samples for SARS-CoV-2 were analyzed for resistance and no sequences showed mutations conferring significant resistance to nirmatrelvir or remdesivir.

After the emergence of Omicron, virtually all variants of SARS-CoV-2 were resistant to neutralisation by the monoclonal antibodies available in Norway and prescription declined (3;4). As SARS-CoV2 continues to accumulate mutations and new therapeutic antibodies are developed we will evaluate the inclusion of antibodies as therapeutics in the future based on clinical feasibility.

Table 5.1 Distribution of major lineages detected in 2024 (n=1078)

Pangolin lineage	Number of samples	Percent of samples
B.1.1.529	1	0.1
BA.2	3	0.3
BA.2.86	530	49.2
BA.5	2	0.2
KP.3	376	34.9
LP.8.1	1	0.1
XBB	1	0.1
XBB.1.5	11	1.0
XEC	125	11.6
Others	27	2.5

Variants are classified according to ECDC's classification in which closely related sub-lineages are assigned to variants of concern or variants of interest to ease in reporting (https://www.ecdc.europa.eu/en/covid-19/variants-concern). Note that this classification is updated frequently. The classification in the table is from May 2025. The group "others" consists of lineages XDD, XDK, XDP, XDQ, XDS, XDV, XDY, XED, XEF, XEK and XEL.

Conclusions

No mutations that infer resistance to antiviral drugs in SARS-CoV-2 viruses were detected in Norway during 2024. Continued genomic surveillance of SARS-CoV-2 is important as the rapid fluctuation in dominant variants illustrates how a possibly resistant variant could emerge in the population.

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6 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 six 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). -HIV capsid inhibitors
Resistance testing method	Amplicon-based next generation sequencing of target genes using the Illumina platform. Identification of mutations associated with drug resistance using Stanford database. Plasma viral load > 1000 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 transmitted drug resistance against protease inhibitors, reverse transcriptase inhibitors (NNRTIs and NRTIs), and integrase inhibitors (since december 2023). Samples from all patients with newly diagnosed HIV-1 infections are tested for resistance mutations.

Surveillance methods

The Norwegian surveillance data is based on resistance testing of samples collected from newly diagnosed patients in Norway. 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. 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). For protease- and reverse transcriptase inhibitors, a standard list of SDRMs was published in 2009, but unfortunately, the list has not been updated since 2009 (2). The SDRM list is not designed for individual patient management, but the listed mutations are 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 that are not included in the list from 2009. Since December 2023, baseline testing of resistance to integrase inhibitors is included in the surveillance of primary resistance in Norway, and 2024 is the first year there is complete data on resistance to integrase inhibitors

Surveillance data 2024

A total of 110 samples from newly diagnosed cases of HIV-1 in Norway were analysed for primary HIV-1 drug resistance in 2024. This corresponds to 42% of the 264 cases notified to MSIS (3). Of the 110 samples submitted for resistance testing, 32% were from female patients, and 65% were from males.

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 6.1. Subtype B is the most 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.

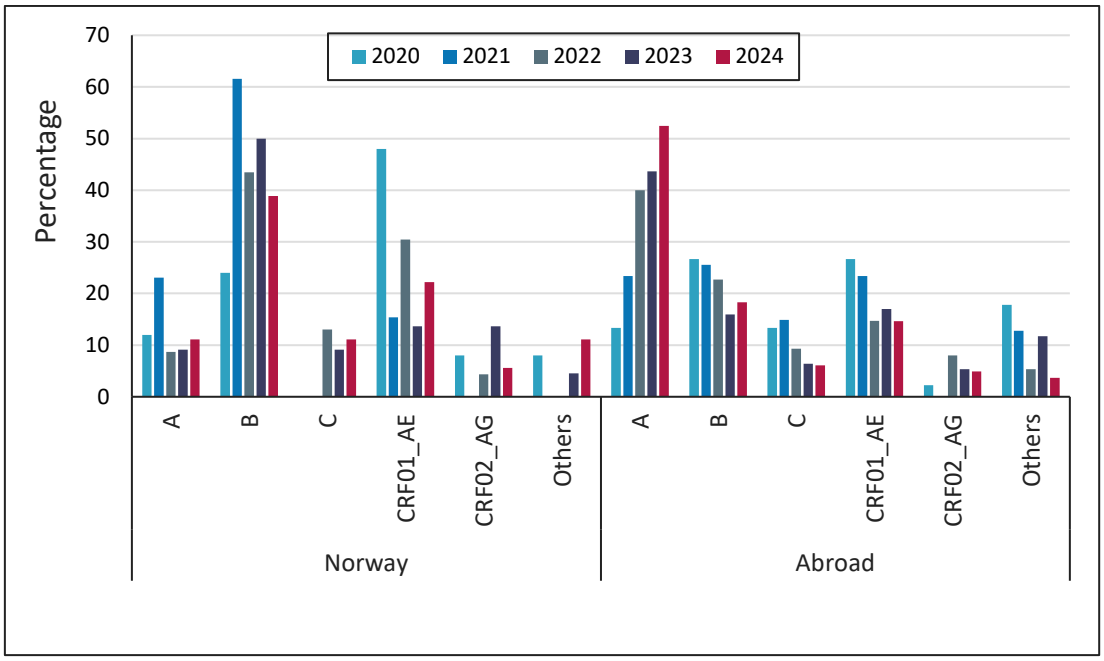

Figure 6.1. Percentage of subtypes among analysed sequences 2020-2024 by country of transmission.

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

Cases tested for drug resistance were cross-referenced to epidemiological cases in MSIS to provide information on both country and route of transmission (Table 6.1 and 6.2).

Table 6.1. Route of transmission in samples from newly diagnosed HIV patients tested for antiretroviral drug resistance in 2024 compared to new cases reported to MSIS in 2024.

Route of transmission	Samples tested for resistance 2024	Cases reported to MSIS 2024	Coverage
Heterosexual	**45**	**90**	**50 %**
- infected in Norway	*6*	*7*	*86 %*
- infected abroad	*37*	*83*	*45 %*
- unknown	*2*	*0*	
Men who have sex with men	**33**	**64**	**52 %**
- infected in Norway	*11*	*12*	*92 %*
- infected abroad	*19*	*51*	*37 %*
- unknown	*3*	*1*	-
Sexual*	**5**	**11**	**46 %**
Injection drug use	**2**	**20**	**10 %**
Other blood exposure	**4**	**14**	**29 %**
Mother to child		**6**	**-**
Nosocomial	**0**	**0**	**-**
Unknown	**21**	**59**	**36 %**
Total	**110**	**264**	**42 %**

*Not specified.

Table 6.2. Coverage of resistance testing by country of transmission, compared to new cases reported to MSIS in 2024

Country of transmission	Samples tested for resistance 2024	Cases reported to MSIS 2024	Coverage
Infected in Norway	18	20	90 %
Infected abroad	*82*	*241*	*34 %*
-Infected abroad, before arrival to Norway	*51*	*203*	*25 %*
- Infected abroad, residing in Norway	*25*	*31*	*81%*
-Infected abroad, unknown residency	*6*	*7*	*86%*
Unknown	10	3	-
Total	*110*	*264*	*42 %*

Only 18 (16%) of the samples submitted to RAVN were from patients infected in Norway, while 82 (75%) were infected abroad. For 10 samples (1%), country of transmission was unknown. Similar to previous years, the coverage of resistance testing for patients infected in Norway was almost complete (90%). The low coverage among patients infected abroad, is explained by the high number of patients who have already started treatment before immigration to Norway and therefore are ineligible for resistance testing due to suppressed viral load. Among patients residing in Norway and infected on vacation or travelling abroad, the coverage was 81%.

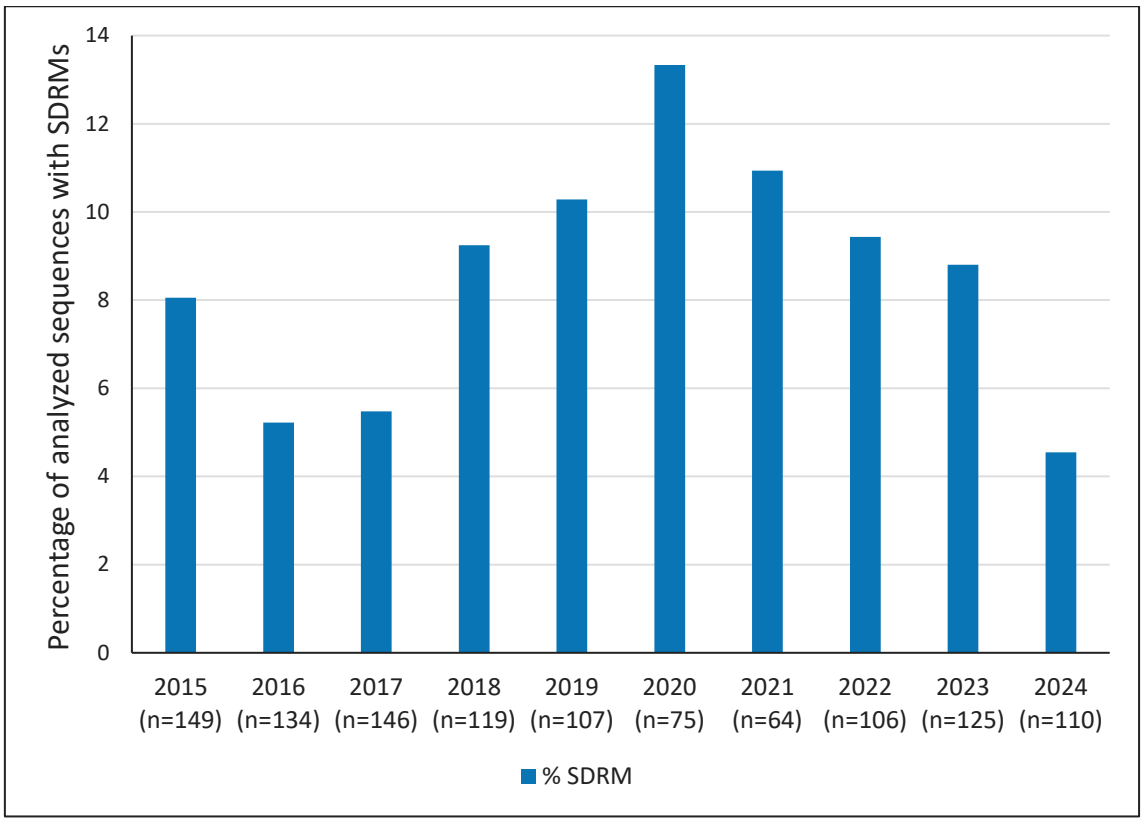

Figure 6.2. Percentage of analysed sequences with detected surveillance drug resistance mutations (SDRMs).

Percentages of the analysed sequences containing one or more SDRMs through the years 2015-2024 are shown as blue columns. There may be several SDRMs per sequence. n = number of sequences analysed for pre-treatment resistance.

In 2024, mutations classified as SDRMs were detected in only five samples, accounting for 4.5% of all cases, as shown in Figure 6.2 The individual mutations detected are depicted in table 6.3. Four of the five mutations detected were associated with resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs). No mutations associated with resistance to nucleoside reverse transcriptase inhibitors (NRTI) were detected, and drug resistance against protease inhibitors was rare. Figure 6.3 shows the frequency of SDRMs for each of the drug classes (NNRTI 3.6%, protease inhibitors 0.9%).

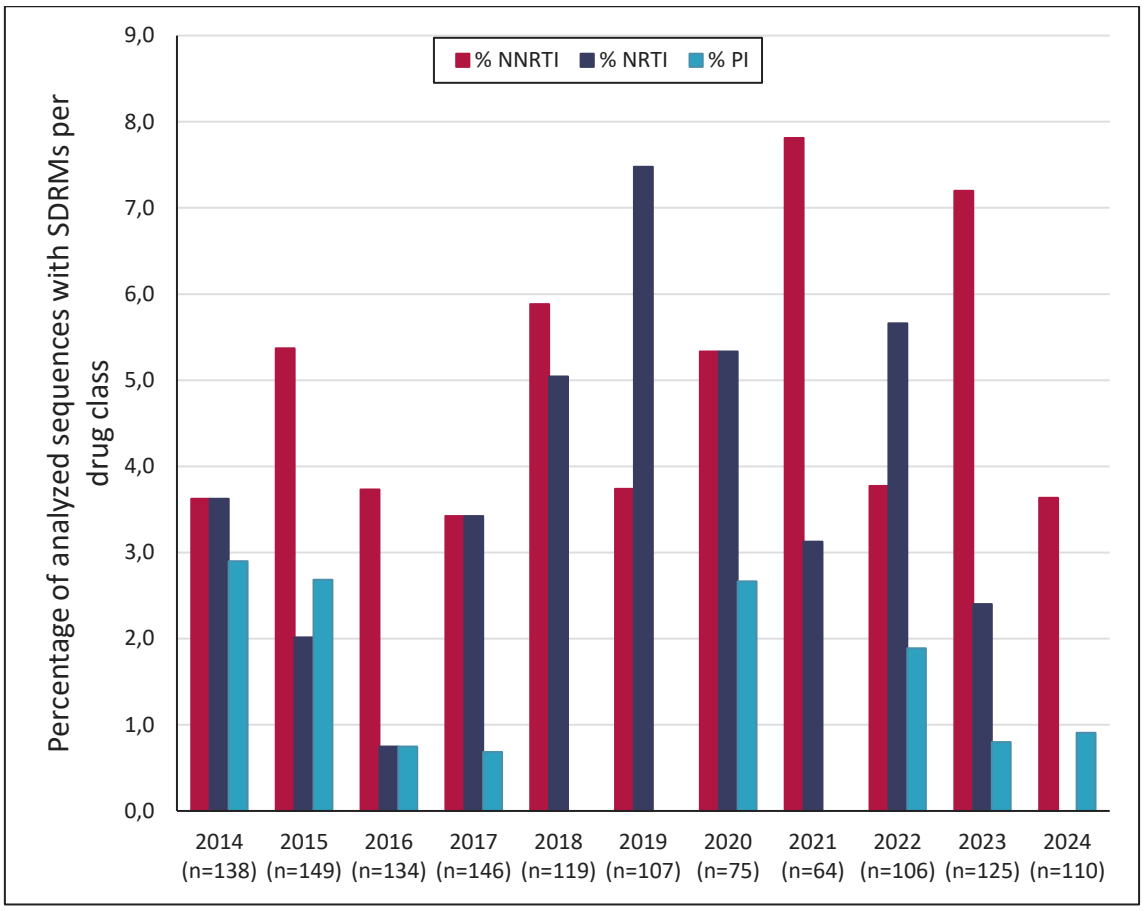

Figure 6.3: Percentage of analysed sequences with detected SDRMs per drug class.

Percentage of mutations affecting the individual drug classes are shown as coloured 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.

Of the five patients with detected SDRMs, four were infected abroad, and one was infected in Norway. The individual mutations detected are specified in Table 6.3 along with place of transmission. The NNRTI- mutations K101E and K103N are both considered to be of clinical significance, whereas the P225H mutation is an accessory mutation which does not confer resistance unless detected in combination with K103N (4). The sole mutation (M46L) in the protease gene does not confer resistance to protease inhibitors, nor does it impact on the susceptibility to darunavir, the most widely used protease inhibitor.

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 the NNRTI resistance-mutation E138A or 138K in a total of three samples. This mutation slightly reduces susceptibility to the NNRTIs etravirine and rilpivirine. All three cases were infected abroad.

Table 6.3. Specification of the surveillance drug resistance mutations (SDRMs) detected in 2024, according to corresponding drug class

Sequence	NRTI	NNRTI	PI	Place of transmission
1	None	K101E	None	Abroad
2	None	K103N	None	Abroad
3	None	P225H	None	Norway
4	None	K103N	None	Abroad
5	None	None	M46L	Abroad

For the first time, resistance to integrase inhibitors (INSTI) is included in the surveillance. No major resistance mutations were detected, but a total of 10 samples had accessory mutations as depicted in Table 6.4. All of the detected substitutions are polymorphisms that are reported to have a prevalence of 1-4% among newly diagnosed patients (5-7). When detected alone, these polymorphisms have minimal effect on susceptibility to integrase inhibitors, and do not affect the virological response to the first line drugs dolutegravir, bictegravir and cabotegravir. All but one of these mutations were detected in samples from patients infected abroad.

Table 6.4. Mutations associated with reduced susceptibility to integrase strand transfer inhibitors (INSTI) detected in 2024

INSTI	Mutation type	Drug	n	Percentage of analysed sequences
E157Q	Accessory	RAL, EVG	5	5%
T97A	Accessory	RAL, EVG	2	2%
L74M	Accessory	RAL, EVG	3	3%

RAL: raltegravir; EVG: elvitegravir

Discussion

The surveillance data is based on resistance testing of samples collected from patients who had their HIV-1 infection confirmed in Norway in 2024, and where a sample was sent to the National reference laboratory for HIV for resistance testing.

The data reported for 2024 has been cross-referenced to epidemiological data from MSIS, enabling detailed analysis of transmitted drug resistance in Norway in different subgroups, such as risk groups or place of transmission. This also provides useful information on the coverage of primary resistance testing in the different subgroups. It should be noted that most of the immigrants infected abroad before arrival to Norway are already successfully treated upon arrival, and therefore not eligible for resistance testing.

Among those infected abroad before immigration to Norway, the coverage has declined steadily from 45% in 2021, to 29% and 24% in 2022 and 2023, respectively. This decrease most

likely reflects the increased number of immigrants from countries with high availability of testing and treatment, such as Ukraine. In 2024, there was a small increase in coverage to 34%.

In 2024, there was a reduction in the prevalence of detected drug resistance mutations. The low prevalence of SDRMs in newly diagnosed patients in Norway has been quite stable over the last years, and in accordance with previous years, most of the mutations detected in 2024 were found in samples from patients infected abroad. The few resistance mutations detected, are mainly mutations associated with reduced susceptibility to older NNRTIs efavirenz and nevirapine. These drugs have previously been widely used in large parts of the world, including several African countries, and are known to have low genetic barriers. The E138A is not a SDRM but is nevertheless monitored in the surveillance as it may reduce susceptibility to NNRTIs that are currently in use such as rilpivirine. The mutation was only detected in samples from patients infected abroad, but further monitoring of this mutation over the next years might be of importance.

In 2024, none of the detected mutations was associated with reduced susceptibility to emtricitabine or tenofovir, the drugs used in pre-exposure prophylaxis (PrEP). This was also the case in both 2022 and 2023, indicating that PrEP can be expected to be effective in preventing new cases in Norway. Continued monitoring of possible PrEP-related resistance will be of importance, although there are no signs so far of any increase in drug resistance associated with PrEP.

Conclusions

The prevalence of transmitted drug resistance remains low in Norway, and most drug resistance mutations were detected in samples from patients infected abroad. None of the mutations detected are known to affect the recommended first line treatment of HIV-infection. For integrase inhibitors, no resistance mutations of clinical importance were found in the surveillance.

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7 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

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 2024

In 2024, a total of 202 samples were analysed for both HBV drug resistance mutations and genotype. The distribution of genotypes among the tested samples is presented in Table 7.1.

Table 7.1: Genotype distribution of analysed HBV samples in 2024

Genotype	Number of samples	Percent of total samples
A	48	24 %
B	27	13 %
C	27	13 %
D	86	43 %
E	12	6 %
Non-typeable	2	1 %

Out of the 202 analysed samples, 169 were submitted for HBV genotyping only (population ii), however, resistance analysis was performed for surveillance purposes and revealed no HBV drug resistance mutations in this group. The remaining 33 samples were submitted with a clinical indication for HBV drug resistance testing, i.e. belonging to population i. Drug resistance mutations were detected in only four of these samples (Table 7.2), all of which appeared to confer resistance to entecavir—a drug administered to two of the affected patients. Two of the 33 samples could not be sequenced successfully due to low viral load.

Table 7.2: Resistance mutations detected in samples from 2024 and the drug resistance they confer

Sample	Genotype	Resistance mutations detected	Treatment*	Resistance				
				LAM	LDT	ETV	ADV	TDF/TAF
1	B	180M;202G;204V	ETV	R	R	R	S	S
2	D	180M;202G;204V	TDF	R	R	R	S	S
3	C	180M;181G;202G; 204V	ETV	R	R	R	S**	S
4	C	180M;184S;204V	TDF	R	R	R	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.
**Unknown mutation in a rated position.

An overview of the resistance mutations detected in Norway between 2020 and 2024 are presented in Table 7.3. During this period, and in particular in 2024, there has been an increase in the number of samples submitted for drug resistance testing, while the number of samples with detected resistance mutations has been stable. Overall, we have detected resistance mutations in 18 of 103 samples.

All the samples with drug resistance contain a substitution at position M204I/V associated with resistance or partial resistance to entecavir. For patients with multiple samples analysed for drug resistance, we have included the earliest sample, as we observe that these mutations are stable over time.

Table 7.3: Resistance mutations in samples submitted for HBV drug resistance testing in 2020 - 2024

HBV-variants resistant to antivirals	Drug resistance	2020	2021	2022	2023	2024
Total analysed		14	17	18	21	33
M204V + (I169T ᵛ S202G ᵛ T184A/S ᵛ M250V) ±L180M	**LAM (R), LDT (R), ETV (R)**	1	3	3	3	4
A181V/T + M204I/V ± L180M	**LAM (R), LDT (R), ETV (I), ADV (R)**		2			
M204I/V + L180M ± 80V	**LAM (R), LDT (R), ETV (I)**			1	1	

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

Conclusions

There was an increase in the number of samples submitted for drug resistance testing in 2024, with only four samples containing drug resistance mutations. All four samples contained a substitution at position M204I/V, conferring resistance or partial resistance to entecavir. No drug resistance mutations were detected in the 169 samples submitted for genotyping, hence no transmitted resistance was detected.

8 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. Both pangenotypic and genotype specific treatment protocols are available.
Resistance testing method	Whole genome next generation sequencing using probe enrichment and the Illumina platform. This method can be used for genotyping as well as detection of RASs. Sequences are analysed using HCV-GLUE (1;2). A viral load of > 100 000 IU/mL was used as a cut-off for resistance testing. 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 (3).	• 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 (1;2) into three categories according to the strength of evidence for resistance against 12 different

direct-acting antiviral (DAA) HCV drugs. When referring to "resistance", we are referring to samples with at least one category I RAS, with the strongest evidence for association with resistance: either (a) *in vitro* resistance level ≥ 5 and found at baseline or treatment-emergent *in vivo*, or (b) both found at baseline and treatment-emergent (2). Epidemiological data related to route of transmission and country of infection from MSIS are combined with the data on RAS to better survey the distribution of these substitutions in the population, in particular among people who inject drugs.

Surveillance data 2024

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 2024, a total of 130 surveillance samples were analysed for HCV drug resistance. For the cases where route of transmission was known, intravenous drug use was the most common route of transmission. RAS (category I) against drugs currently in use were detected in 59 (45%) of the analysed samples in 2024 (Table 8.1).

Table 8.1. Descriptive characteristics of analysed surveillance samples in 2024 (n=130).

	Samples, n (%)	Samples with any RAS, n (%)	Samples that have RAS in resistance category I *, n (%)	Samples that have RAS category I* to drugs currently in use**, n (%)
Route of transmission				
-Sexual	*1 (0.8)*	*1 (0.9)*	*1 (1.5)*	*1 (1.7)*
-Injection drug use	*38 (29.2)*	*32 (29.1)*	*18 (27.7)*	*17 (28.8)*
-Blood/ transpl	*5 (3.8)*	*4 (3.6)*	*3 (4.6)*	*3 (5.1)*
-Nosocomial	*1 (0.8)*	*1 (0.9)*	*1 (1.5)*	*1 (1.7)*
-Other	*2 (1.5)*	*2 (1.8)*	*1 (1.5)*	*1 (1.7)*
-Unknown	*83 (63.8)*	*70 (63.6)*	*41 (63.1)*	*36 (61.0)*
Place of infection				
-Norway	*46 (35.4)*	*37 (33.6)*	*23 (35.4)*	*21 (35.6)*
-Abroad	*44 (33.8)*	*42 (38.2)*	*26 (40.0)*	*23 (39.0)*
-Unknown	*40 (30.8)*	*31 (28.2)*	*16 (24.6)*	*15 (25.4)*
Total	130 (100.0)	110 (100.0)	65 (100.0)	59 (100.0)

*Presence of category I resistance to one or several drugs according to HCV-Glue {Singer, 2018 #54{Singer, 2019 #55}}.

** Active substances that are currently in use include glecaprevir, grazoprevir, voxilaprevir, elbasvir, ledipasvir, pibrentasvir, velpatasvir and sofosbuvir. Substances that are no longer registered for use in Norway and the European Union include paritaprevir, daclatasvir, ombitasvir and dasabuvir.

Prevalence of resistance in samples analysed for surveillance of HCV in 2024 according to antivirals and genotype is shown in Figure 8.1 and Figure 8.2. Figure 8.2 also includes data from surveillance samples in 2022 and 2023, for comparison.

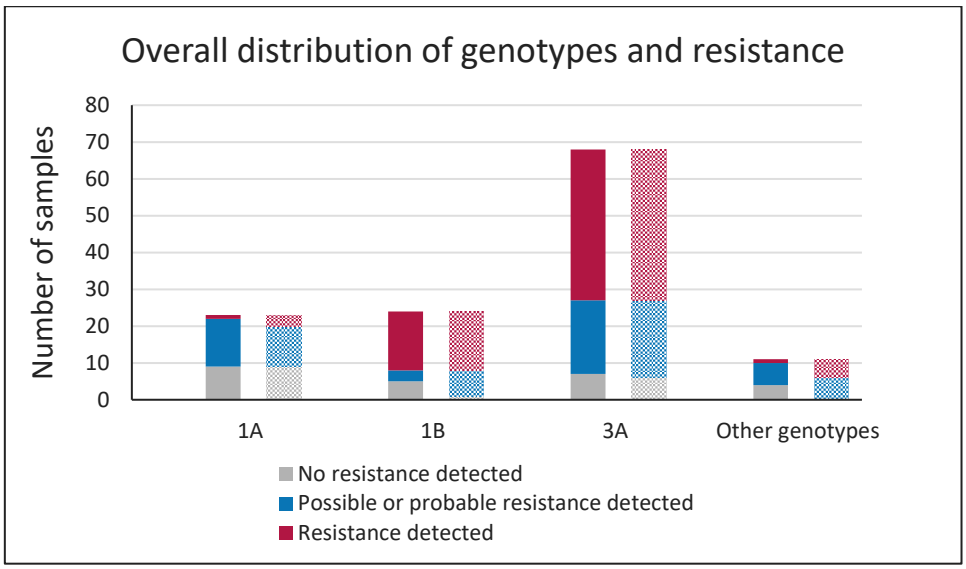

Figure 8.1. Overall distribution of genotypes and resistance in samples analysed for surveillance in 2024 (n=130).

Unknown genotypes are not included. Stacked bars with solid fill represent active substances that are currently in use, whereas shaded bars represent all substances (both currently and not currently in use).

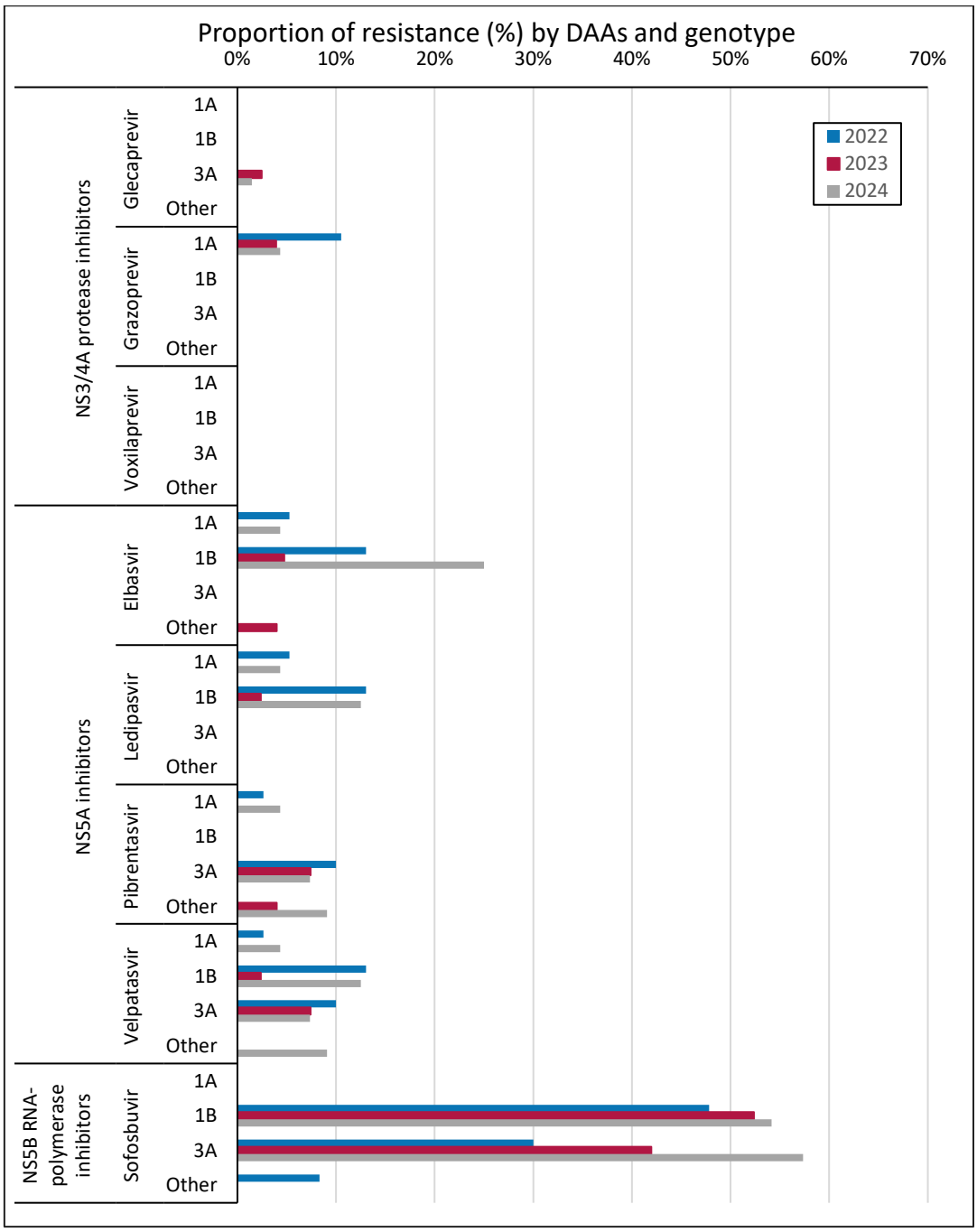

Figure 8.2. Proportion of resistance (%) by DAAs and genotype.

The figure presents prevalence of resistance by DAA (only drugs currently in use) and genotype among analysed surveillance samples in 2022 (n=133), 2023 (n=199) and 2024 (n=130), respectively. The percentage of samples with detected resistance against the individual drugs are shown per main genotype. Please note that samples may be resistant to several drugs. Resistance was defined according to HCV-Glue (presence of at least one category I RAS), excluding possible and probable resistance categories (category II and III RAS). “Other” genotypes include 2, 2K1B, 3B, 3H, 4, 5 and 6. Unknown genotypes are not included.

Among the DAAs that were prescribed in Norway during 2022-24 (4), a prevalence of resistance above 15% was only detected for sofosbuvir and elbasvir in 2024. For sofosbuvir, prevalence increased particularly for genotype 3A (57%), and for elbasvir particularly for genotype 1B (25%). For other active substances, prevalence of resistance remained low, and notably, concurrent resistance against all substances in currently registered combination drugs was very rare (<5% for all genotypes) (Figure 8.3).

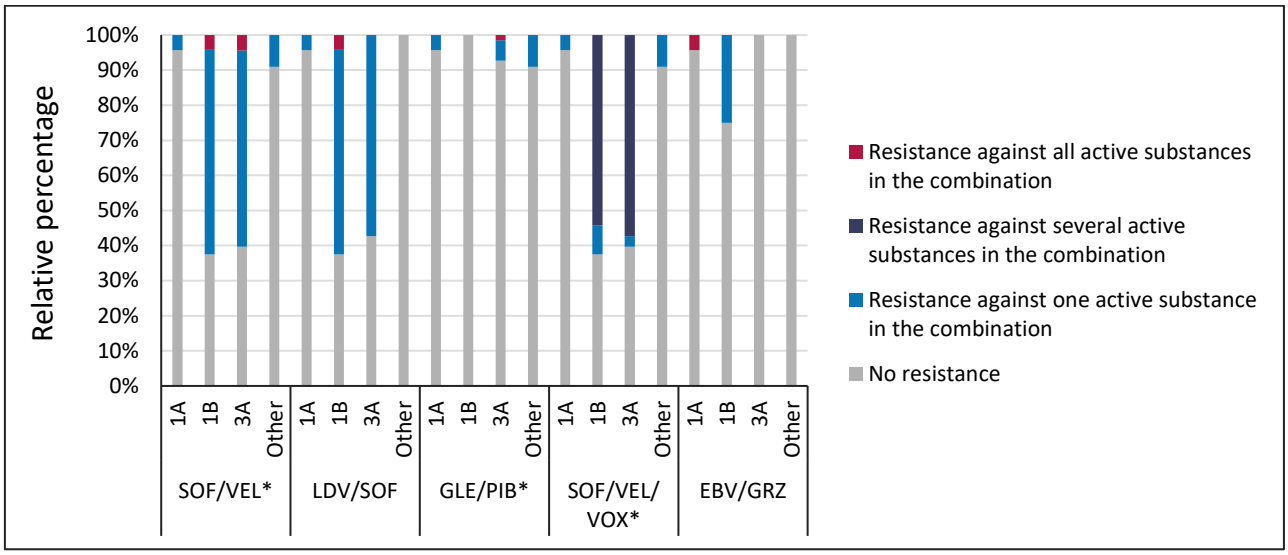

Fig 8.3. Proportion of resistance (%) against the currently registered combination drugs in Norway.

The figure presents prevalence of resistance by combination drug and genotype among analysed surveillance samples in 2024 (n=130). The percentage of samples within each genotype with detected resistance against either one, several or all active substances in the combination are shown per main genotype. The total distribution of genotypes was 1A (n=23), 1B (n=24), 3A (n=68), Other (n=11). "Other" genotypes include 2, 4, and 3H. Unknown genotypes are not included in the figure. SOF: sofosbuvir; VEL: velpatasvir; LDV: ledipasvir; GLE: glecaprevir; PIB: pibrentasvir; VOX: voxilaprevir; EBV: elbasvir; GZR: grazoprevir.*Pangenotypic drugs.

Discussion

Most samples received for surveillance were from people who inject drugs or from patients where the transmission route was unknown. However, hepatitis C is generally associated with injection drug use, and often the individuals do not know how, when and where they were infected.

A lower proportion of the samples received for surveillance in 2023 (36%) and 2024 (35%) were from patients infected in Norway, compared to 2022 (47%). Among patients born outside of Norway, 57% were born in Ukraine (data not shown). Similar trends can be seen among overall notified cases to MSIS: 28% were infected in Norway in 2023 and 2024 vs 38% in 2022, and 60% of patients born outside of Norway were born in Ukraine (5).

Most samples submitted for surveillance contained genotype 3A. Within this genotype, RASs associated with resistance against the NS5B inhibitor sofosbuvir were the most prevalent (57%), and the prevalence has increased since 2022 (30%). Apart from this, the most notable change was an increase in elbasvir resistance for genotype 1B from 5% in 2023 to 25% in 2024. For the other active substances in use in 2024, resistance remained at a low level (<15%).

Five drug combinations were registered for use in Norway in 2024. The updated recommendations from The Norwegian Hospital Procurement Trust (6), valid from 01/04/2025, specifies glecaprevir/pibrentasvir as pangenotypic first line treatment in most cases, while combinations containing sofosbuvir are only recommended as the first choice for patients with decompensated cirrhosis. For the latter patient group, resistance testing is recommended prior to treatment (3). Elbasvir/grazoprevir was not included in the updated recommendation, and was subsequently deregistered in Norway.

Concurrent resistance against all active substances in any of these drug combinations was very rare, with a prevalence of 0 to 4% (Figure 8.3). This could be part of the reason that resistance is rarely seen in clinical practice when treating hepatitis C patients. Moreover, the "resistant" RAS category in HCV-Glue (1;2) only suggests a relatively lower probability of achieving a sustained virological response (SVR), while the absolute probability of achieving SVR may still be high (7). It follows that for RASs to truly affect the expected real-life effect of a particular drug combination, they would probably both need to be highly prevalent in the patient population and appear together conferring resistance to all active substances in a given combination.

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 reinfected.

Conclusions

There is a high prevalence of RASs affecting sofosbuvir, and to a lesser degree elbasvir. For other drugs the prevalence of RASs is low, and very few samples exhibit RASs affecting all active substances in fixed drug combinations. This may contribute to the perception of resistance as a marginal problem when treating patients with hepatitis C in clinical practice. Continued surveillance of RAS should put emphasis on detecting any increase in combined resistance against current drug combinations.

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9 Cytomegalovirus

Fact box: Human cytomegalovirus (CMV) drug resistance	
Treatment	Monotherapy 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 analogue cidofovir, the pyrophosphate analogue foscarnet, or the UL-97 kinase inhibitor maribavir. The CMV terminase complex inhibitor letermovir is approved for prophylaxis in stem cell -or kidney transplanted 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, 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 the first-line 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 in the UL97 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 UL56 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 (1).

Surveillance data 2024

In 2024, 23 samples from 18 patients were analysed for CMV antiviral drug resistance. Out of the 23 samples, relevant resistance mutations were detected in three samples (Table 9.1). The mutations and the resulting resistance are listed in Table 9.2.

Table 9.1: Number of samples analysed for CMV antiviral drug resistance and number of samples with detected CMV drug resistance mutations for the years 2020 - 2024.

CMV-variants resistant to antivirals	2020	2021	2022	2023	2024
Total samples analysed	30	19	24	17*	23**
Number of samples with CMV resistance mutations	5	5	5	1	3
Samples with UL97 mutations	4	5	5	1	3
Samples with UL54 mutations	1	1	1	1	1
Samples with UL56 mutations	-	-	-	0	0

*17 samples from 14 patients were analysed. **23 samples from 18 patients were analysed.

Table 9.2: CMV resistance mutations in samples tested in 2024

Case	UL97 mutations	UL54 mutations	Resistance
1	A594V		Ganciclovir moderate; Maribavir sensitive
2	C603W	T503I	Ganciclovir moderate; Cidofovir low, Foscarnet sensitive; Maribavir sensitive
3	L595S		Ganciclovir moderate, Maribavir sensitive

UL97 encodes the viral kinase. UL54 encodes the viral DNA polymerase.
The degree of antiviral resistance is commonly expressed as the fold change in the drug concentration required to reduce viral replication by 50% (EC50), compared to wild-type virus. Resistance levels are categorized as follows:
Insignificant resistance: <2-fold increase in EC50. This level is generally not clinically relevant.
Low-grade resistance: 2–5-fold increase in EC50. Antiviral efficacy may still be achievable with dose escalation.
Moderate resistance: 5–15-fold increase in EC50. Therapeutic effect is unlikely, even with increased dosage and the antiviral agent must be replaced with an alternative.

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 patients under treatment for CMV-infection 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. In such cases the reference laboratory should be contacted to discuss the indication and practical details.

Maribavir has been registered for use in Norway from 2022, and the resistance analysis performed at the reference laboratory also covers mutations conferring resistance against Maribavir.

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10 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 systematic surveillance of HSV resistance in Norway. The risk of developing drug resistance in immunocompromised patients is increased compared to immunocompetent patients, but information about the patients' immune status is not available for surveillance purposes. For routine testing, only genotypic tests are available, and samples are sent abroad for analysis.

Surveillance data 2024

In 2024, a total of 12 samples from 9 patients were submitted for HSV drug resistance. Among the 9 patient samples, resistance mutations, deletions or insertions that conferred resistance to aciclovir were detected in 6 (66%) of the samples (Table 10.1). One third of the patient samples (n=2) containing resistance mutations associated with aciclovir were also resistant towards other HSV antiviral drugs (such as penciclovir, cidofovir, foscarnet, brivudin).

Table 10.1. HSV resistance associated mutations

Patient sample	HSV-type	Sample material	TK mutations	DNA pol mutations	Resistance
1	HSV-1	Vesicle	Del 674-675		Aciclovir resistance
2	HSV-1	Secretion		R681L	Aciclovir possible resistance
3	HSV-2	Secretion	Ins 548-553		Aciclovir resistance
4	HSV-1	Biopsy		G841C	Aciclovir resistance, Cidofovir resistance, Foscarnet resistance
5	HSV-2	Secretion	D163G		Aciclovir possible resistance
6	HSV-1	Secretion	Ins 430-436, Y53C		Aciclovir resistance; Brivudine resistance, Penciclovir resistance

Conclusions

Systematic surveillance of drug-resistant HSV is currently lacking in Norway, and a limited number of patient samples are submitted for resistance testing. While the number in 2024 has increased compared to previous years (1), the overall sample volume remains low, making it difficult to accurately assess the prevalence of HSV drug resistance in the country. Among the nine samples submitted for resistance analysis, 66% harboured mutations associated with resistance to aciclovir. These findings suggest that additional cases of suspected drug resistance may go unreported due to underutilization of available resistance testing

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