

REPORT

2026

Usage of Antivirals and the Occurrence of Antiviral Resistance in Norway 2025

RAVN

Resistensovervåkning av virus i Norge

Resistance to antivirals in Norway

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INTRODUCTION

It is a pleasure to present this year's report from the surveillance system for Resistance against Antivirals in Norway (RAVN), which provides data on antiviral use and antiviral drug resistance in Norway in 2025. This report marks ten years of annual reporting from RAVN. To acknowledge this occasion, we have included a chapter presenting a ten-year overview of surveillance data.

In addition, we have chosen to highlight two selected topics within the field. In the first chapter, we comment on the national One-Health strategy against antimicrobial resistance (AMR) from a virological perspective, including the role of antiviral resistance surveillance as an integral part of these efforts.

The second topic examines mutagenic antiviral drugs and their potential to suppress viral populations by driving viral evolution beyond its limits. The chapter discusses both the promise of this novel therapeutic principle and the remaining uncertainties regarding antiviral resistance.

Antiviral drugs play an increasingly important role in treating and preventing viral infections, while emerging resistance remains a major public health challenge. Continued surveillance is essential to improve knowledge and awareness, inform treatment recommendations and prevention strategies, and strengthen preparedness. We hope the data and perspectives in this report will support colleagues working in the fields of infection control, infectious diseases, and antimicrobial resistance.

RAVN would like to thank everyone who has contributed to this report for their 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 2025. Legemidler mot hiv utgjør fortsatt den største andelen målt i definerte døgndoser, mens antivirale midler mot herpesvirus er mest brukt målt i antall personer behandlet. Antall personer behandlet for hepatitt C er ytterligere redusert i 2025, og trenden fra de senere år ser dermed ut til å fortsette.

Når det gjelder behandling av hiv-infeksjon, er det kombinasjonsbehandling med en-tablett regimer som dominerer, og bruken av integrasehemmere øker i tråd med gjeldende retningslinjer og innkjøpsanbefalinger. I tråd med anbefalingene var glecaprevir/pibrentasvir det mest brukte legemidlet mot hepatitt C i 2025.

Influensavirus

Influensasessongen 2025/2026 startet tidlig med en positivitet på over 10 % allerede i november, og nådde toppen mot slutten av desember. Influenza A(H3N2) var den hyppigst påviste typen denne sesongen, men A(H1N1) ble imidlertid detektert gjennom hele sesongen, noe som vil si at begge virusene sirkulerte samtidig. Influenza B/Victoria ble påvist på slutten av sesongen og hadde begrenset forekomst.

Totalt ble 836 influensavirusprøver analysert for antiviral resistens. Fire prøver hadde mutasjoner som ga redusert følsomhet mot oseltamivir. Én prøve hadde i tillegg redusert følsomhet mot zanamivir. Resistens mot adamantaner har vært utbredt blant sirkulerende influensa A-virus siden A(H1N1)pdm09-pandemien i 2009. Denne sesongen ble det imidlertid identifisert fire prøver som manglet de kjente substitusjonene assosiert med adamantanresistens.

SARS-CoV-2

I 2025 nådde andelen SARS-CoV-2-positive prøver en topp på 10,9 % rundt uke 34. Den vanligste varianten blant de analyserte prøvene var den rekombinante varianten XFG, etterfulgt av BA.2.86 og NB.1.8.1. Blant de 678 overvåkingsprøvene av SARS-CoV-2 som ble analysert for resistens, var det ingen sekvenser som viste mutasjoner som medførte betydelig redusert følsomhet for nirmatrelvir eller remdesivir.

Humant immunsviktvirus-1

I 2025 ble det analysert 79 prøver fra personer nydiagnostisert med hiv-1-infeksjon i Norge. Dette utgjør 38 % av de 208 tilfellene meldt til MSIS. Blant de som smittes i Norge, er fortsatt subtype B den hyppigst forekommende subtypen, mens en større variasjon sees blant personer smittet i utlandet. Dataene viste en forekomst på 7,6 % av overvåkingsmutasjoner (SDRM), hovedsakelig mutasjoner assosiert med nedsatt følsomhet for non-nukleosid revers transkriptasehemmere (NNRTI). Alle påviste SDRM ble funnet hos personer smittet i utlandet, og resistensen var i hovedsak knyttet til eldre NNRTI med lav genetisk barriere som tidligere har vært mye brukt særlig i lavressursland. Overvåkingen av resistens mot integrasehemmere fortsatte i 2025, og det ble ikke påvist klinisk relevante resistensmutasjoner.

Hepatitt B-virus (HBV)

I 2025 ble det analysert 149 prøver for genotype og resistensmutasjoner. De fleste prøvene var sendt inn for genotyping, og det ble ikke påvist resistensmutasjoner i disse. Av 21 prøver sendt inn for resistensundersøkelse ble det påvist mutasjoner assosiert med nedsatt følsomhet eller resistens mot entekavir i to prøver. Begge var fra pasienter som fikk behandling med entekavir.

Hepatitt C-virus (HCV)

I 2025 ble 120 prøver analysert for å kartlegge forekomsten av resistensassosierte substitusjoner (RAS). Resistensdata ble sammenstilt med epidemiologiske opplysninger fra MSIS for å undersøke forskjeller mellom ulike undergrupper. Klinisk relevante RAS ble påvist i 28 % av prøvene, men svært få prøver inneholder RAS som kan påvirke alle virkestoffene i kombinasjonsbehandlinger. Resistens representerer derfor sjelden en klinisk utfordring ved behandling av HCV-infeksjon. Overvåkingen bidrar til å følge utviklingen av resistensmutasjoner blant nye tilfeller, men tolkningen kan være utfordrende blant annet på grunn av usikkerheter i epidemiologiske og kliniske data.

Cytomegalovirus

I 2025 ble 18 prøver fra 16 pasienter analysert for resistens mot antivirale midler mot cytomegalovirus (CMV). Resistensmutasjoner som gir nedsatt følsomhet mot ganciklovir ble funnet i to prøver. Til tross for økt bruk av CMV-behandling og –profylakse, forekommer resistens sjeldent. Resistensanalyser inkluderer også påvisning av mutasjoner assosiert med resistens mot letermovir og maribavir, som har vært tilgjengelig i Norge siden henholdsvis 2019 og 2022.

Herpes simplex virus

Totalt 10 prøver fra 8 pasienter ble sendt inn for undersøkelse av resistens hos herpes simplex-virus (HSV). Redusert følsomhet for aciklovir ble funnet i tre av prøvene. Det lave antallet prøver som sendes inn til resistensundersøkelse gjør at overvåkingen av HSV forblir begrenset, og resistens kan derfor være underrapportert.

SUMMARY

Usage of antivirals

The total sales of direct-acting antiviral drugs continued to increase in 2025. Medications for HIV still accounted for the largest share when measured in defined daily doses, while antivirals against herpesviruses had the highest number of users. The number of individuals treated for hepatitis C has continued to decline.

Single-tablet-regimens with multiple antiretroviral drugs remain dominant in HIV treatment, and the use of integrase inhibitors continues to increase in line with current treatment guidelines and procurement recommendations. In accordance with treatment recommendations, glecaprevir/pibrentasvir was the most used medication for hepatitis C in 2025.

Influenza virus

The 2025/2026 influenza season started early with a positivity rate above 10% in November and peaked in late December. Influenza A(H3N2) was the main driver of the season, A(H1N1)pdm09 was also detected throughout the season, indicating co-circulation of both subtypes. Influenza B/Victoria was detected at the end of the season and had a limited prevalence. A total of 836 influenza virus samples were tested for antiviral resistance and four samples had mutations conferring reduced susceptibility to oseltamivir. One sample also showed markers conferring reduced susceptibility to zanamivir. Adamantane resistance has been widespread among circulating influenza A viruses since the 2009 A(H1N1)pdm09 pandemic. However, four samples identified during the 2025/2026 season lacked the known substitutions associated with adamantane resistance.

SARS-CoV-2

In 2025, SARS-CoV-2 test positivity peaked at 10.9 % around week 34. The most frequent variant of the analysed samples was the recombinant variant XFG, followed by BA.2.86 and NB.1.8.1. Of the 678 SARS-CoV-2 surveillance samples that were analysed for resistance, no sequences showed mutations conferring significantly reduced susceptibility to nirmatrelvir or remdesivir.

Human immunodeficiency virus (HIV)

In 2025, a total of 79 samples from newly diagnosed HIV-1 cases were analysed for primary drug resistance, representing 38% of the 208 cases notified to MSIS. Subtype B remained the most prevalent HIV subtype transmitted in Norway, while the distribution of subtypes among patients infected abroad was more diverse. Surveillance drug resistance mutations (SDRMs) were detected in 7.6% of analysed samples, predominantly associated with reverse transcriptase inhibitors. All detected SDRMs were found in patients infected abroad, and most resistance was linked to older NNRTIs with low genetic barriers that have previously been widely used globally. Baseline surveillance of integrase inhibitor resistance continued in 2025, and no clinically relevant resistance mutations were detected.

Hepatitis B virus (HBV)

In 2025, 149 samples were analysed for genotype and drug resistance mutations. Most samples were submitted for genotyping, and no resistance mutations were detected in these samples. Of the 21 samples submitted for drug resistance testing, mutations associated with reduced susceptibility or resistance to entecavir were identified in two samples. Both samples were from patients receiving entecavir treatment.

Hepatitis C virus (HCV)

In 2025, 120 samples were analysed to assess the presence of resistance-associated substitutions (RAS). Drug resistance data were linked with epidemiological information from MSIS to investigate differences between various subgroups. Clinically relevant RAS were detected in 28% of the samples, but very few samples show RASs impacting all of the drugs in recommended drug combinations. Resistance therefore rarely represents a clinical challenge in the treatment of HCV infection. Surveillance monitors the occurrence of resistance mutations among newly diagnosed cases; however, interpretation of the findings can be challenging, partly due to uncertainties in epidemiological and clinical data.

Cytomegalovirus

In 2025, 18 samples from 16 patients were analysed for cytomegalovirus (CMV) antiviral drug resistance. Resistance mutations causing reduced sensitivity to ganciclovir were detected in two samples. Despite increased use of ganciclovir for CMV treatment and prophylaxis, resistance mutations remain rare. Resistance analysis includes detection of mutations conferring resistance to letermovir and maribavir, which have been available in Norway since 2019 and 2022, respectively.

Herpes simplex virus

A total of 10 samples from 8 patients were submitted for herpes simplex virus (HSV) drug resistance testing in Norway, and reduced susceptibility to aciclovir was found in three of the samples. The low number of samples submitted for resistance testing means that surveillance of HSV remains limited, and resistance may be underreported.

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 immunisation, 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.

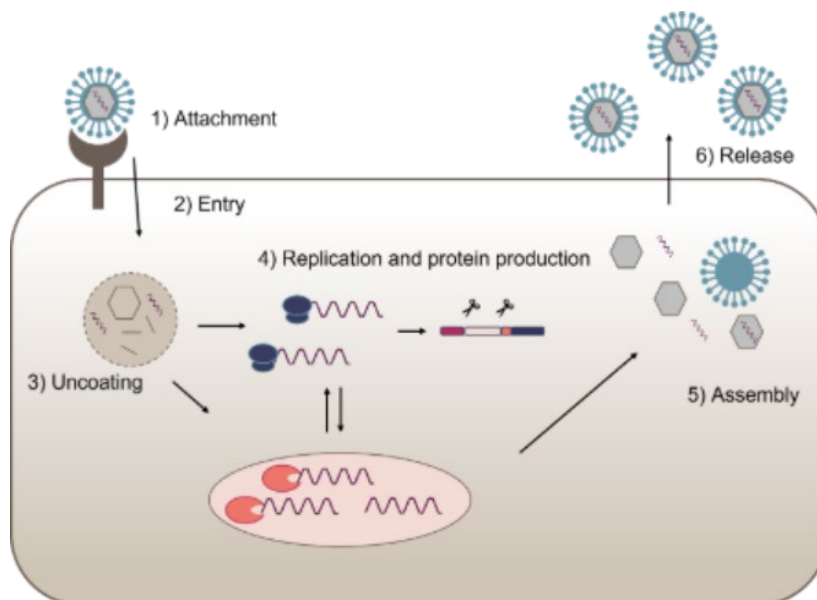


Figure 1.1. Generalised depiction of the viral replication cycle showing the major steps in replication.

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, transcription during 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).
- Transcription: The polymerase inhibitor baloxavir marboxil is approved in Europe, but market authorisation 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 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.

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 (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 (INSTIs) 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 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) (11).

There are currently three groups of direct-acting antivirals (DAAs) targeting HCV genome replication/transcription, protein production or multiple stages simultaneously (12):

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

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

Drug resistant CMV

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 (13).

Experience with maribavir and letermovir resistance in Norway remains modest, primarily due to the limited 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 (14).

Antivirals against herpes simplex virus and varicella zoster 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 (VZV). 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) (15).

Drug resistant HSV and VZV

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 localised in the DNA-polymerase gene (16). 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 (17). 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 (17). 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 (16).

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2 SPECIAL TOPICS

Ten years of annual reporting on antiviral resistance surveillance in Norway

Sustained surveillance of antiviral drug resistance is essential for detecting changes over time and supporting clinical guidance, prevention and preparedness. The surveillance system RAVN (Resistance against Antivirals in Norway) has been formally responsible for collecting and reporting national surveillance since the regulations governing RAVN came into effect in 2014. As new viruses and antiviral drugs have emerged, the surveillance system has expanded to include additional viruses, genomic targets, and new sequencing technologies. While antiviral resistance has remained a relatively minor problem in Norway, the surveillance system has evolved in response to scientific and technological developments.

The first RAVN reports summarized surveillance data from previous years and were not published annually. Since 2016, the RAVN report has been published annually, providing systematic, yearly updates on the occurrence and development of antiviral resistance and the usage of antiviral drugs in Norway. This means that 2026 marks ten years of continuous annual reporting. To recognise this milestone, we here present a ten-year overview of the surveillance, with figures in this section illustrating resistance patterns and changes over time. Furthermore, several of the surveillance chapters in the report also includes data showing trends of the last decade.

Direct acting antivirals

Data on antiviral drug consumption provides important context for interpreting resistance patterns and understanding how resistance may be influenced by changes in treatment practices. Since the first RAVN report, surveillance of antiviral drug consumption has been an integral part of the report. Data from the Norwegian Drug Wholesales Statistics show a steady increase in the use of direct-acting antivirals over the past decade, as shown in Figure 2.1. Trends in antiviral use for individual viruses and drug groups are further detailed in Chapter 3.

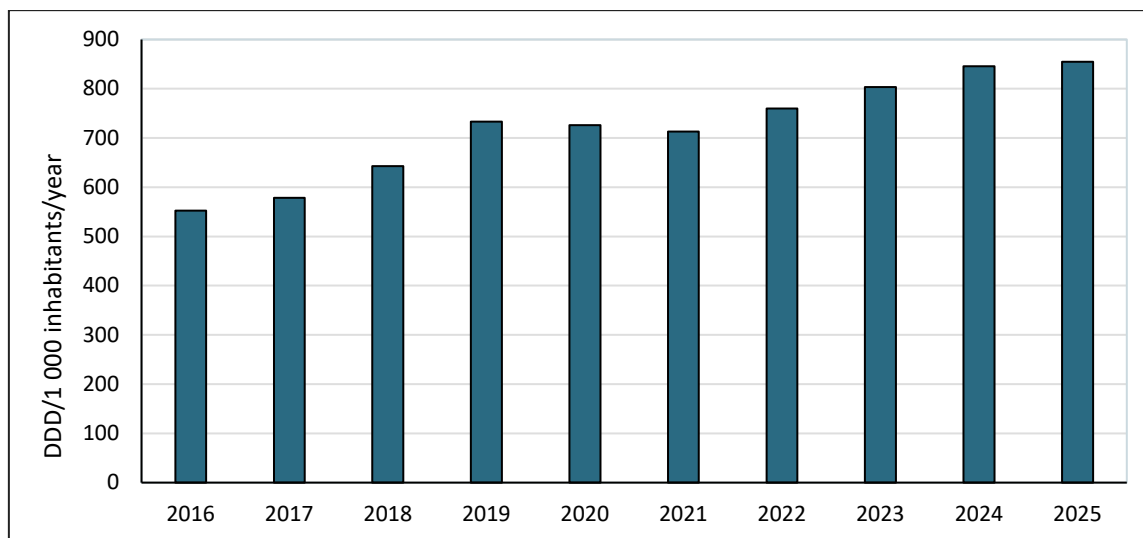


Figure 2.1. Sales of direct acting antiviral drugs for systemic use (ATC group J05A) for 2016-2025.

The figure presents the total sales of direct acting antivirals 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. Monoclonal antibodies are not included in the plot. Drugs included in wholesale data are not necessarily used in the year of inclusion they could be stored in pharmacies or in hospitals.

Influenza virus

Surveillance of drug resistant influenza virus has been ongoing since 2005. The number of influenza virus samples analysed for resistance against oseltamivir has increased the past five years, in line with implementation of improved sequencing methods. The frequency of samples with resistance against oseltamivir has remained low, with only sporadic cases detected over the past ten years (Figure 2.2). Since the 2009 A(H1N1)pdm09 pandemic all influenza virus samples have been resistant towards adamantane, however this season one A(H1N1) virus and three A(H3N2) viruses lacked known adamantane resistance substitutions (for more information see the chapter on surveillance of influenza virus).

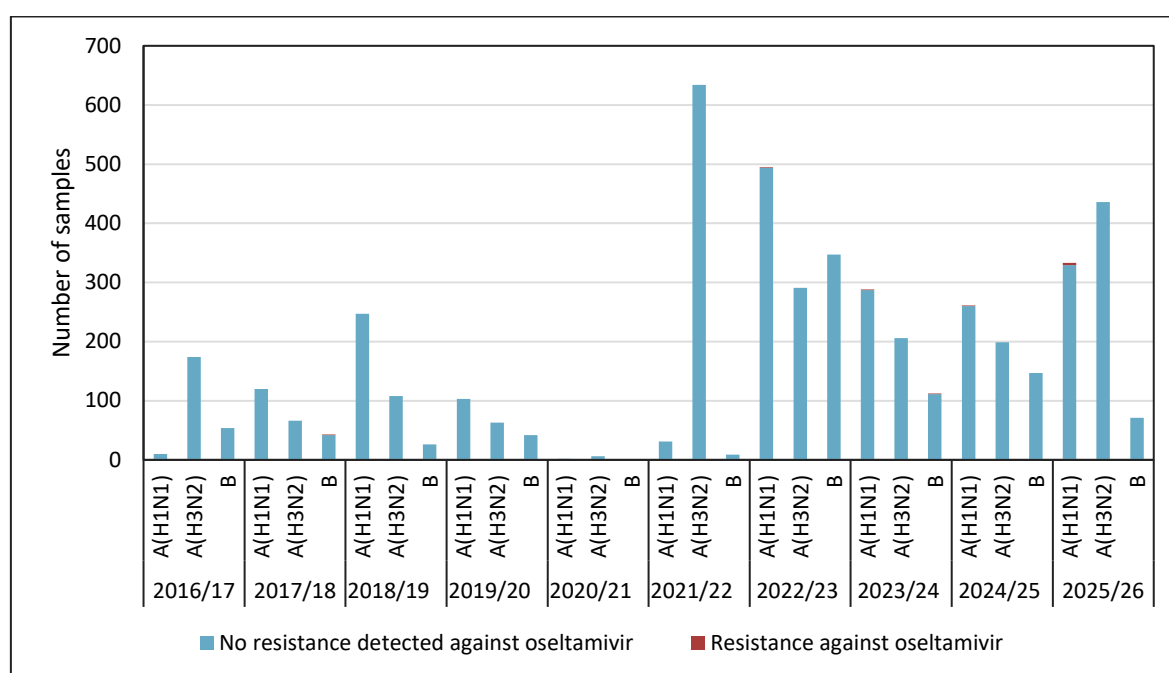


Figure 2.2. Number of samples analysed for resistance towards oseltamivir by influenza subtype for the past ten influenza seasons. Samples with detected resistance are marked red.

SARS-CoV-2

Sequencing of SARS-CoV-2 was established early in the pandemic, even before the first direct acting antiviral drug was available. Sequencing of SARS-CoV-2 was initially introduced for the identification and surveillance of viral variants. The same sequence data can also be used to assess antiviral resistance and data has been reported to RAVN since 2023. The extensive sequencing performed for variant surveillance resulted in a very large number of samples being available for resistance analyses during the first year. However, as shown in Figure 2.3, the number has decreased since drug resistance surveillance began in 2023. No clinically significant resistance mutations affecting the activity to nirmatrelvir or remdesivir have been detected during the period.

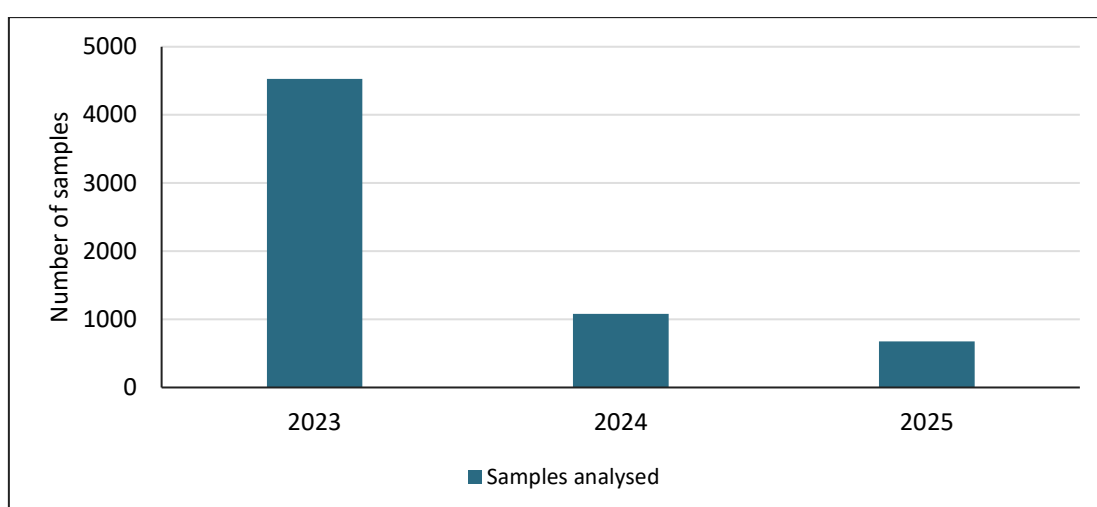


Figure 2.3. Number of SARS-CoV-2 samples analysed from the start of the surveillance in 2023.

Human immunodeficiency virus

Systematic national surveillance of transmitted HIV drug resistance has been conducted in Norway since 2006 and is based on resistance testing of samples from individuals newly diagnosed with HIV. Throughout the surveillance period, the prevalence of transmitted HIV drug resistance has remained consistently low in Norway (Figure 2.4). Resistance prevalence is partly affected by the countries of origin of newly diagnosed individuals, reflecting differences in migration patterns and HIV epidemiology in the countries of origin. Since 2019, linkage with epidemiological data from MSIS has provided important context for interpreting surveillance findings, including information on individuals who acquired HIV abroad and had initiated treatment before arrival in Norway. Surveillance has also included targeted monitoring of resistance patterns with potential relevance for HIV pre-exposure prophylaxis (PrEP), documenting that widespread PrEP did not lead to the rise in transmitted drug resistance that was initially feared.

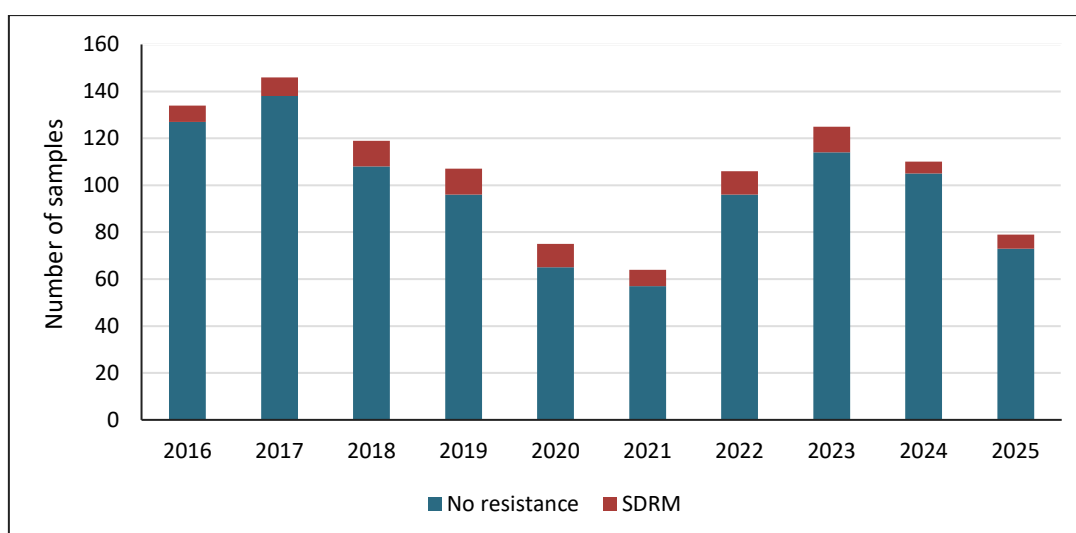


Figure 2.4. Number of HIV samples analysed over the past 10 years, showing the number of samples with detected

Surveillance Drug Resistance Mutations (SDRMs) in red, and the number with no resistance in blue.

Hepatitis B virus

Resistance testing of hepatitis B virus (HBV) has been performed as part of clinical management of patients for many years. The HBV drug resistance surveillance data includes information on both acquired resistance associated with treatment failure and primary resistance pre-treatment. Surveillance of primary resistance is not a systematic national surveillance programme but is based on samples submitted for genotyping in routine diagnostic investigations. No resistance has been detected among treatment-naïve patients, and the small number of resistant cases identified have occurred in patients experiencing treatment failure. Even if the number of samples tested are low, the data indicate that the prevalence of antiviral resistance in HBV has remained very low throughout the 10 year surveillance period (Figure 2.5).

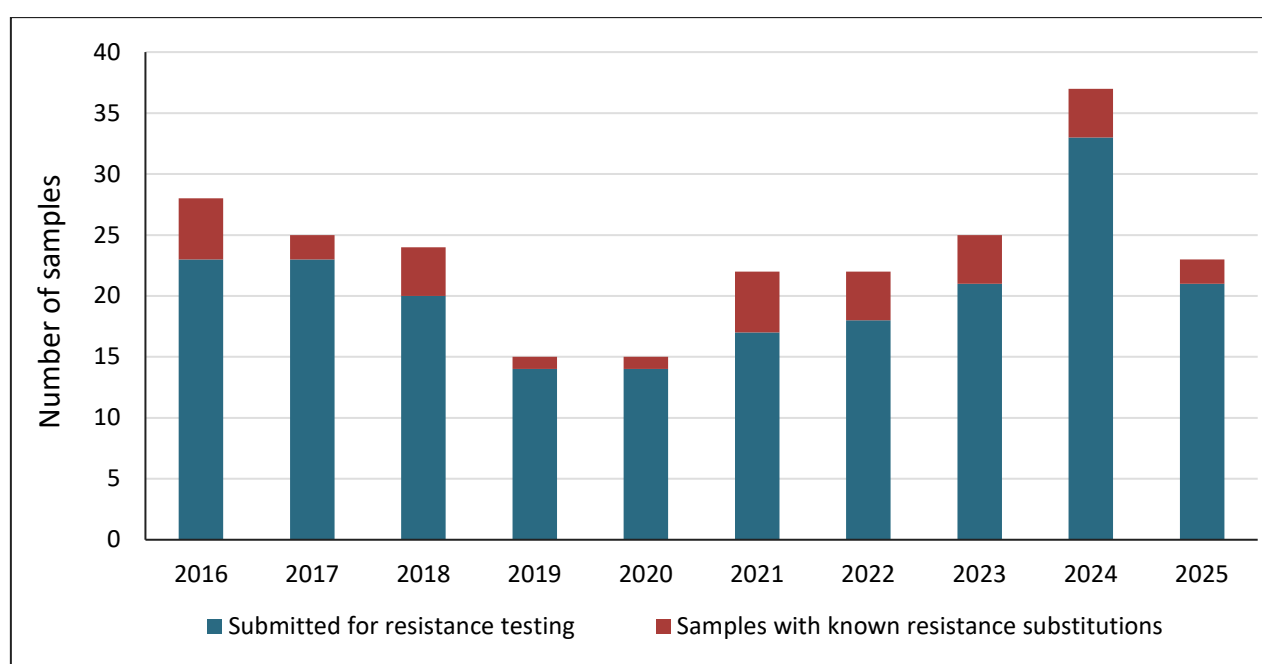


Figure 2.5. Number of HBV samples submitted for resistance testing, and the number of samples with detected resistance mutations.

Hepatitis C virus

As Norway works towards the elimination of hepatitis C infection (HCV) as a public health threat, surveillance of resistance-associated substitutions (RAS) provides valuable information on resistance patterns and treatment effectiveness at the population level. However, the clinical value of routine HCV resistance testing has been debated given the high effectiveness of current DAA therapies.

Following the establishment of methods for resistance testing, systematic national surveillance of HCV was implemented in 2022. RAS in HCV are classified by HCV-Glue (2;3) into three categories according to the strength of evidence for resistance against 12 different direct-acting antiviral (DAA) HCV drugs. The number of samples analysed for resistance substitutions, and the occurrence of category I RAS to drugs currently in use is shown in Figure 2.6. The number of samples analysed is partly limited by laboratory capacity, and only a representative selection of submitted samples is analysed.

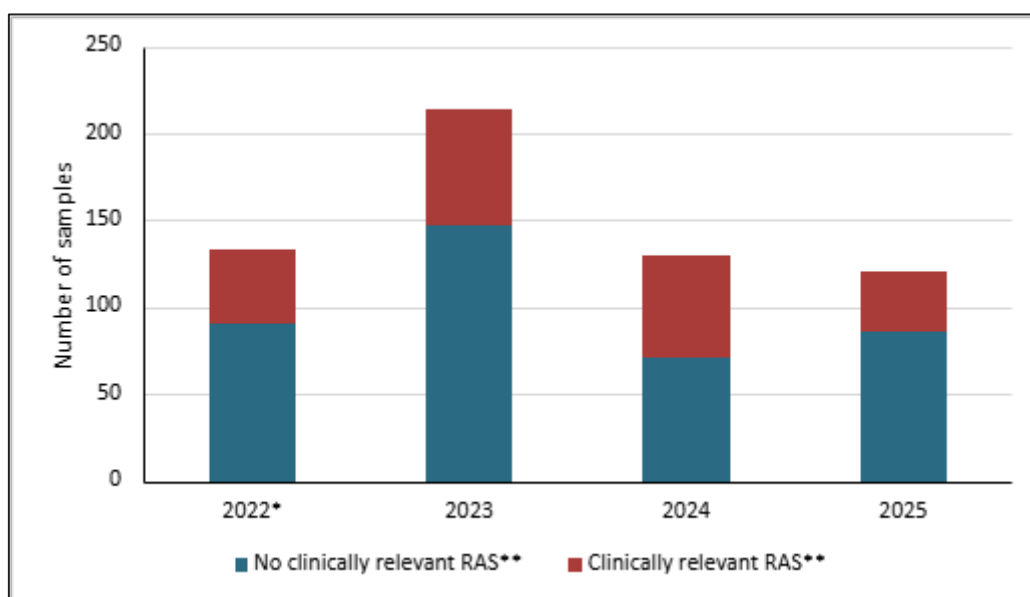


Figure 2.6. Number of samples analysed for HCV antiviral drug resistance, showing samples with category I RAS to drugs currently in use (red) and samples with no detected category I RAS to drugs currently in use (blue) for the years 2022-2025.

**Data from 2022 are available for only half of the year. **Clinically relevant RAS are defined as category I RAS to drugs currently in use.*

Herpes simplex virus

None of the laboratories in Norway perform drug resistance testing of herpes simplex virus, and samples are sent abroad. Generally, few HSV samples are submitted for analysis, as shown in Figure 2.7. In general, a high proportion of the submitted samples harbour drug resistance mutations. These findings probably reflect that submitted samples are typically obtained from patients with persistent HSV infection despite ongoing antiviral therapy, many of whom are immunocompromised (4). However, the high proportion of samples with detected resistance mutations raises the question whether resistance testing is currently underutilized in patients with treatment-refractory infection.

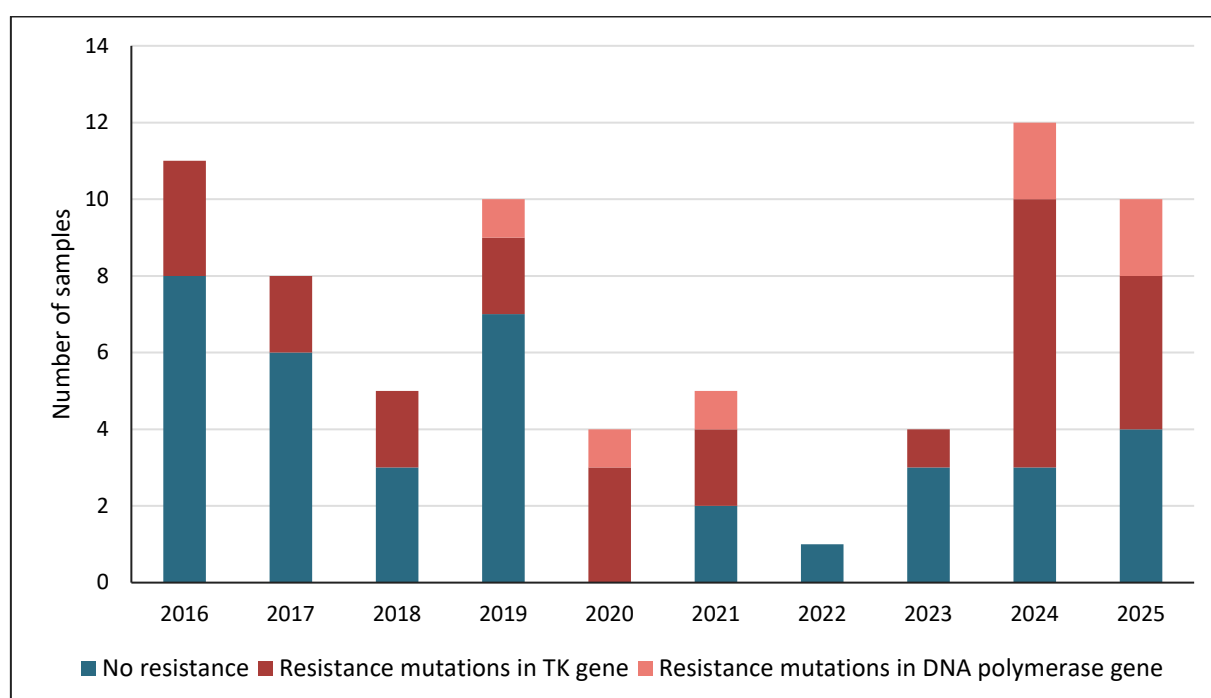


Figure 2.7. Number of HSV samples analysed for antiviral drug resistance over the 10 past years, showing the number of detected resistance mutations in the DNA polymerase gene (orange), the number of resistance mutations in the TK gene (red), and the number of samples with no detected resistance (blue).

Cytomegalovirus

Surveillance of CMV drug resistance is based on samples from patients with persistent high viral load despite ongoing therapy, and suspected drug resistance. However, the number of samples with detected CMV resistance mutations has remained relatively stable at a low level (Figure 2.8). All detected resistance mutations in the UL97 and UL54 genes are listed in table 9.3 in the CMV surveillance chapter. Since 2023, the UL56 gene has been analysed for resistance-mutations when there are indications of letermovir resistance. So far, no mutations have been detected.

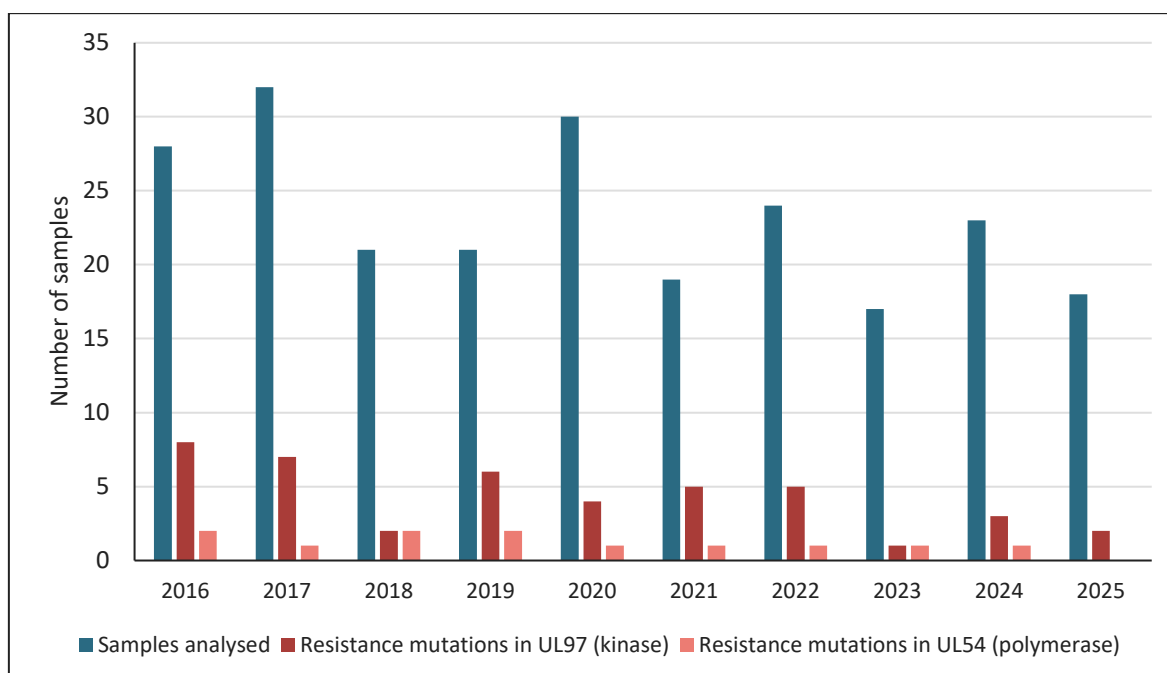


Figure 2.8. Number of samples analysed for CMV antiviral drug resistance (blue) and number of samples with detected CMV drug resistance mutations in the UL97 gene (red) encoding the protein kinase and the UL54 gene (orange) encoding the DNA polymerase for the years 2016 - 2025.

Antiviral resistance surveillance in Norway, looking ahead

Over the past decade, RAVN has documented consistently low levels of antiviral resistance in Norway. New systems and analytical infrastructures for surveillance of infectious diseases are currently being developed, enabling more integrated and automated use of data. As microbial genomic data become increasingly incorporated into infectious disease surveillance, new opportunities emerge for antiviral resistance monitoring. In this context, we welcome a discussion on the future of antiviral resistance surveillance.

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A Virological Perspective on the AMR Strategy

Tuva Marie Hall Borge, Anne-Marte Bakken Kran, and RAVN advisory council

Introduction

Antimicrobial resistance (AMR) is one of the top 10 global public health and development threats, requiring action to prevent further escalation in the coming years (1). In 2021, antibacterial resistance was associated with approximately 1.14 million deaths globally, and reducing this burden by 2030 is a central goal for the World Health Organization (WHO) (1). The Norwegian government has developed a national one-health strategy to guide a cross-sectoral response to AMR in the coming years, and an associated action plan is under development (2). The term AMR includes resistance in bacteria, viruses, fungi and parasites, and the strategy explicitly adopts this broad definition. However, the proposed measures are mainly directed at antibacterial resistance, reflecting its substantial implications for public health. Antiviral resistance differs from antibacterial resistance in important ways and therefore requires a distinct approach.

This chapter highlights two complementary virological perspectives on AMR: Firstly, the prevention and control of antiviral resistance, and secondly, the contribution of viral infection prevention, diagnosis and treatment to reducing antibacterial resistance. Using the six goals of the national AMR strategy as a framework, we discuss how both perspectives can contribute to AMR prevention and control.

Antiviral resistance matters

Compared to antibacterial resistance, antiviral resistance poses a more limited public health concern in interpandemic periods. Nevertheless, it remains an integral part of the overall AMR challenge that requires attention. Effective treatment of chronic viral infections such as HIV, hepatitis B (HBV) and hepatitis C (HCV) is essential at the individual level. For example, effective antiretroviral therapy has transformed HIV infection into a manageable chronic condition, while direct-acting antivirals have turned hepatitis C into a curable disease. Effective antiviral treatment of epidemic viral infections, like influenza and SARS-CoV-2, can reduce disease burden, limit transmission(3;4), and strengthen pandemic preparedness. Resistant variants may emerge rapidly under antiviral selective pressure and can spread within populations if not detected and monitored. Preserving the effectiveness of these drugs requires an understanding of how antiviral resistance emerges and spreads, and how it differs from antibacterial resistance, as part of a comprehensive AMR response.

Drivers and mechanisms for antiviral resistance development and propagation

As for antibacterial resistance, exposure to antiviral agents is a key driver of the initial development of antiviral resistance, due to the selective pressure on viral variants in the treated individual. However, the mechanisms for development and the propagation dynamics of antiviral resistance differ somewhat from those of antibacterial resistance.

A central difference is how genetic variation is generated and disseminated. Antiviral resistance is almost exclusively a result of spontaneous point mutations that occur randomly during viral replication and are subsequently selected and expanded within the host under antiviral pressure (5). Bacteria can acquire resistance genes through horizontal gene transfer, for example via plasmids or transposons, allowing resistance determinants to spread across bacterial populations. Unlike bacteria, viruses cannot take up and assimilate foreign genetic information. For viruses, horizontal transfer of resistance determinants is limited to genetic exchange such as recombination between viruses of the same species, simultaneously infecting a single cell.

The intrinsic mutation rate of viruses is on average much higher than that of bacteria but varies both by genome type (RNA > DNA, single stranded > double stranded) and other factors. High mutation rate is favoured by low-fidelity replication in many RNA viruses, large viral population size, high replication rates and long duration of infection, and causes genetic variation within the infected individual that may give rise to resistant variants. These factors, together with host- and antiviral drug-related factors, shape the probability that mutations will arise, and whether variants with reduced susceptibility to antiviral agents are produced.

For both viruses and bacteria, selective pressure is crucial in determining whether a resistant variant becomes dominant. Drug exposure does not necessarily induce resistance mutations, but it can enrich resistant variants already present or newly generated during replication. The selective pressure is affected by the inhibitory effect and concentration of the drug, the duration of exposure, and the use of mono- or combination therapy.

However, selection of antiviral resistance occurs only within hosts, and resistant variants must be fit enough to navigate the bottleneck of transmission, more or less directly, to new hosts to propagate in the population. Resistance mutations often impose a fitness cost on the virus, which may limit their ability to persist or spread in the absence of antiviral treatment. Since viruses do not replicate outside host cells, environmental exposure exerts no direct selection pressure. However, selection may occur when the animal host of a zoonotic virus is exposed to antiviral-pollution in the environment. This is particularly relevant in the context of enzootic influenza viruses with pandemic potential (6;7).

Factors that determine survival and spread in the population are similar for antibacterial- and antiviral resistance. These include the replication capacity and virulence of the variant, the host's immune response, the availability of susceptible hosts and host cells, and the potential development of compensatory mutations that restore fitness and allow resistant variants to persist or transmit. Propagation dynamics, however, can be very different. Compared with antibacterial resistance, propagation of antiviral resistance in the human population can be very slow or extraordinarily rapid depending on the epidemiology of the virus. Resistant influenza virus, from the time of initial detection, can become 100% dominant globally within a single epidemiological year (8). No antibacterial resistance mechanism has ever made a similar transition. In contrast to influenza and SARS-CoV-2, the spread of antiretroviral resistance in HIV is often slower. However, resistant strains can still emerge rapidly within transmission networks (9), or in the context of widespread use of drugs with low genetic barriers to resistance (10).

Antiviral resistance can also spread in the absence of selective pressure, particularly through highly fit viral variants that retain efficient transmission in spite of the resistance mutation. Adamantane resistance in influenza A viruses is one important example of local selection and ensuing global spread of resistant lineages in the absence of selective pressure (11;12). These

events have rendered adamantanes useless since 2009. Now, some sensitive variants are finally reemerging. A better understanding of resistance mechanisms is crucial for determining effective and targeted prevention and control measures.

“It’s just a viral infection”

Antiviral resistance is not the only part of the virological perspective on AMR. Viral infections are important drivers of antibacterial resistance, and as mentioned in the one-health strategy against AMR, measures to prevent, diagnose and treat viral infections properly can contribute to reducing antibacterial resistance.

Acute viral respiratory tract infections may be mistaken for bacterial infections or lead to secondary bacterial infections, leading to increased and often unnecessary antibacterial treatment. Respiratory tract infections underly the majority of antibiotic prescriptions in primary care (13;14), and upper respiratory tract infections (URIs) are the leading cause of acute disease globally with an estimated 12.8 billion infections in 2021 (15). By force of sheer numbers, improvements in prevention, diagnosis and rational treatment of viral URIs should therefore be expected to reduce prescriptions, decreasing antibiotic exposure and ultimately slowing the development of antibacterial resistance.

Chronic viral infections also drive antibacterial resistance. People living with HIV are at increased risk of infections with resistant bacterial pathogens (16). Opportunistic infections due to uncontrolled HIV infection lead to increased exposure to antibiotics and to resistant microbes in healthcare institutions, and has contributed to the spread of multidrug-resistant tuberculosis (17).

The six strategic goals of the strategy through a virological lens

The national one-health strategy includes six overall goals to address AMR challenges (listed in box 2.1) (2), and several of these goals have important implications for virology. From a virological perspective, some of these goals are directly relevant to the prevention, detection and control of antiviral resistance, while others highlight how improved prevention, diagnosis and treatment of viral infections can contribute to reducing antibacterial resistance. The following sections comment on all six goals, focusing on the strategic goals most relevant to these perspectives.

Box 2.1 The national one-health strategy - six goals to address AMR challenges

1. Strengthen cross-sectoral AMR collaboration
2. Strengthen the prevention of AMR
3. Ensure prudent and responsible use of antimicrobial agents
4. Ensure access to necessary antimicrobial agents
5. Increase and make use of new knowledge regarding AMR
6. Be an active force in the global efforts against AMR

Goal 1: Cross-sectoral collaboration

For viral infections with zoonotic and pandemic potential, effective surveillance and preparedness depend on collaboration across sectors. Goal one of the strategy (box2.1) is to strengthen cross-sectoral collaboration on AMR. The AMR strategy further emphasises that cross-sectoral coordination is important at all levels, from the different departments of government, down to the individual healthcare institutions and laboratories involved in human and animal health and the environment (2).

As an example of cross-sectoral collaboration, the strategy mentions NORM and NORM-VET, underlining the importance of systems for One Health surveillance of antibacterial resistance. Here we would like to put forward as a virological example, the close cooperation between the National Influenza Centre and the Veterinary Institute in the genomic surveillance of influenza strains circulating in animals. This surveillance is important for pandemic preparedness, helping to ensure that we will have effective diagnostics, vaccines and antivirals available for zoonotic events in Norway.

Goal 2: Strengthening the prevention of AMR through surveillance

Surveillance is essential for detecting emerging antiviral resistance and evaluating whether prevention and treatment strategies affect resistance patterns. In line with Goal two (box 2.1) strengthening surveillance is a key measure for management of antiviral resistance. Surveillance systems are crucial for detecting and monitoring emerging resistant variants, and for planning and evaluating targeted interventions.

One example of the importance of viral surveillance is the introduction of pre-exposure prophylaxis (PrEP) against HIV. When PrEP was introduced, the benefits were well documented, but concerns were raised about potential development and spread of resistant HIV strains (4). The concerns were based on the possibility that PrEP would select for mutations associated with resistance to these drugs. The capacity of HIV to develop antiviral resistance is well documented, and it was a relevant question if using the same drugs for both treatment and prevention could compromise the efficacy of first line treatment. Studies have also shown that undiagnosed HIV infection at the onset of PrEP, can rapidly lead to resistance mutations (18). However, six years of systematic surveillance in Norway has shown no increase in the prevalence of PrEP-mutations and instead, indicated a reduced risk of transmission of PrEP- resistant variants. Thus, surveillance data provided critical real world information for guiding further use of PrEP. Monitoring

resistance mutations in HIV remains important to detect any changes and development of resistant strains.

Another example where surveillance is needed is in relation to hepatitis C infection. Ambulatory clinics and testing sites have been introduced in Oslo and other areas, offering free testing and treatment to people with substance use disorders and at high risk for hepatitis C infection (19). These services make it possible to reach a high-risk group that otherwise might remain undiagnosed, and it is important for improving access to treatment. However, it is also important that this is accompanied by follow-up and surveillance to detect potential impact on the development of resistance.

Furthermore, surveillance of antiviral drug resistance plays a central role in preparedness and response to serious cross-border health threats, because resistant pathogens can spread rapidly between countries and undermine both treatment and control measures. Influenza can spread rapidly, both within and across borders. The emergence of a resistant variant may reduce the efficacy of treatment and increase transmission, with consequences at both individual and population levels. Continued surveillance is therefore important to detect such changes and identify development of new resistant strains.

Goal 3: Responsible use is more than reducing consumption

Antiviral resistance is shaped not only by how much antivirals are used, but also by treatment effectiveness, adherence, genetic barriers, viral fitness and transmission dynamics. Goal 3 (box 2.1) addresses the importance of restrictive and responsible use of antimicrobials.

Undertreatment, ineffective treatment and treatment outside of indications are important drivers of both antibacterial and antiviral resistance. However, due to differences in drivers and mechanisms of resistance in bacteria and viruses, public-health guidance emphasises somewhat different control measures. For bacteria, measures against antibacterial resistance focus on limiting total consumption, especially of broad-spectrum antibacterial agents, reducing unnecessary antibiotic exposure, and preventing spread of resistant organisms. For viruses, measures are more closely related to the prevention of undertreatment, adequate adherence and dosing, combination therapy where indicated, genomic surveillance, and detection of variants with reduced susceptibility. Low compliance and low genetic barriers select for resistance.

The One Health perspective is relevant to both bacteria and viruses, but through different mechanisms. Antibacterial agents are used in both human and veterinary medicine, and resistant bacteria can spread and circulate between animals, humans, and the environment through horizontal gene transfer (20). Reducing the overall use of antibacterial agents across sectors is a cornerstone of the efforts to limit the spread of antibacterial resistance. For viruses, however, the One Health perspective is more closely linked to their zoonotic and pandemic potential. As antivirals are primarily used in human healthcare, measures such as vaccination and general infection control play a central role by reducing transmission, the need for antiviral treatment, and consequently also the risk of resistance development.

Antiviral resistance is most likely to emerge during prolonged treatment. In treating chronic viral infections, responsible use of antivirals therefore involves not only limiting unnecessary use, but also ensuring effective treatment through adequate adherence, combination therapy, and the use of drugs with a high genetic barrier to resistance. Incomplete treatment or suboptimal drug regimens may select for resistant variants, making patient follow-up an important component of resistance prevention.

When treatment programs expand, access to viral load monitoring and resistance testing becomes increasingly important for both patient management and surveillance. Limited laboratory capacity and access to diagnostic tools, particularly in resource-limited settings, may hinder the detection of resistant variants and allow their continued spread.

Goal 4: Ensuring access to necessary antiviral agents

Goal 4 (box 2.1) underscores the importance of ensuring access to necessary antimicrobial agents. This remains as a global challenge, especially in resource-limited settings. Maintaining worldwide availability of life-saving antiviral drugs for chronic infections such as HIV, is essential for reducing the global burden of disease, and supporting long-term epidemic control.

Furthermore, we need to secure drug supply chains in the event of a new pandemic. This includes both maintaining the stockpile and ensuring that the antiviral agents still have good effect against the relevant pathogens. It is important to ensure a diverse selection of antiviral drug classes with different targets, particularly for viruses such as influenza which have a pandemic potential. Currently, only neuraminidase inhibitors are available in Norway.

Goals 5 and 6: To increase the knowledge and be an active force against AMR

Goal 5 and 6 (box 2.1) emphasise the importance of increasing knowledge regarding AMR, and of being an active force in the global efforts against AMR, which is relevant for all microbes.

The strategy highlights the importance of improving knowledge on how prevention and treatment of viral infections also can contribute to reducing antibacterial resistance. From a clinical virology perspective, there is also a need for a better understanding of the drivers of antiviral resistance and the measures required to prevent its emergence. Improved knowledge of the mechanisms behind development, propagation and persistence of resistance is important for designing effective and targeted prevention and control measures.

When it comes to being an active force as mentioned in goal 6, Norway has valuable experience to share. High public trust in health authorities, strong uptake of vaccination programmes, and a restrictive approach to antibacterial treatment for probable viral infections contribute to reducing the need for antimicrobial treatment. These experiences may provide valuable lessons for international AMR efforts.

Conclusion

Given that viral infections are drivers of antibiotic use and antibacterial resistance, a comprehensive action plan for prevention of AMR should include measures to improve prevention, diagnosis and treatment of viral infections. Antiviral resistance is a smaller but important component of the overall AMR landscape. In line with the national strategy, efforts should focus on strengthening surveillance, ensuring responsible use of antivirals according to guidelines, improving knowledge, and preventing infections. Through the national surveillance system RAVN, we aim to support these measures by providing systematic surveillance of antiviral resistance and generating evidence to inform clinical practice and public health action.

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Mutagenic antiviral drugs – Can the development of resistance be prevented?

Andreas Christensen

Most antiviral drugs are enzyme inhibitors that target virus-specific enzymes such as polymerases, proteases, integrases, and neuraminidases. This allows efficient inhibition of viral replication while exerting minimal effects on host enzymes. Reverse transcriptase (RT) is one such enzyme. During the late 1990s, a series of highly effective nucleoside analogues targeting RT revolutionized the treatment of HIV infection. It soon became evident that some of these compounds also possess mutagenic properties (1). They were shown to increase the frequency of point mutations in the viral genome, and this increase in mutagenesis was demonstrated to contribute to enhanced antiviral efficacy. These observations sparked considerable interest in mutagenesis as a therapeutic principle. Shortly thereafter, the well-established antiviral drug ribavirin was also found to exert mutagenic effects (2). Since then, two novel antiviral agents whose primary mode of action is mutagenesis – favipiravir and molnupiravir – have been developed (3;4). In this article, I provide a brief overview of the properties of these drugs before examining the risk of antiviral resistance in greater detail.

Antiretroviral nucleoside analogues

It is not surprising that nucleoside analogues may exert mutagenic effects. These compounds mimic natural nucleosides and become incorporated into the viral genome. In many cases, this results in premature termination of viral replication. However, when replication proceeds despite incorporation, the analogue may promote the insertion of incorrect nucleotides into the growing complementary nucleic acid strand (5). This occurs because the nucleoside analogues are capable of forming base pairs that violate the conventional pairing rules whereby adenine pairs with uracil and guanine pairs with cytosine.

All currently approved nucleoside analogues used for the treatment of HIV act by terminating elongation of the viral genome during replication. Therefore, they are often referred to as chain-terminating agents. By preventing the production of the next generation of virions, these drugs render their mutagenic component essentially negligible. In contrast, non-chain-terminating anti-HIV compounds have a much greater potential to increase the viral mutation rate. Such agents are currently confined to experimental research and have not entered clinical practice (6).

Ribavirin

Ribavirin was introduced as early as 1972 and has since been used against a number of viral infections, including respiratory syncytial virus (RSV), hepatitis C virus, hepatitis E virus, influenza A and B virus, and several viral hemorrhagic fever viruses (6). It can be administered orally, parenterally, or by inhalation. Ribavirin exhibits moderate antiviral activity against a broad spectrum of RNA viruses and was, for many years, a cornerstone of hepatitis C therapy until it was superseded by newer and more effective direct-acting antivirals.

For decades, the mechanism of action of ribavirin remained poorly understood, and our knowledge is still incomplete. It is known to inhibit the RNA-dependent RNA polymerase (RdRp) of RNA viruses while also enhancing host cell responses, including interferon induction and apoptosis, in addition to inhibiting nucleotide biosynthesis. As mentioned above, it became clear in 2000 that ribavirin also possesses mutagenic properties. The multiple mechanisms of action of ribavirin have proved difficult to disentangle in both cell culture and animal studies, complicating investigations of this drug. Consequently, during the early years, research into mutagenic antiviral agents focused primarily on antiretroviral compounds.

Mutagenic antiviral agents

Drugs with mutagenic properties may also have the potential to induce mutations in the patient's own genome. This risk must be avoided, and extensive safety studies are therefore required before such compounds can be approved for routine clinical use. On the other hand, they possess considerable therapeutic potential. In theory, they may drive the entire viral population within an infected patient to collapse within a matter of days (1). Some enthusiastic virologists have even suggested that resistance-free antiviral therapy may be achievable if this principle can be exploited correctly. This may sound too good to be true, but the hypothesis is intriguing and certainly merits further investigation.

RNA virus evolution and quasispecies

RNA viruses are characterized by exceptionally high mutation rates—up to 10,000-fold higher than those of cellular organisms. This high mutation rate underlies their remarkable evolutionary flexibility and their ability to adapt rapidly to new hosts or new ecological niches within the host. RNA-viruses ability to recombine also contributes to the variability. Additionally, recombination may rescue defective mutations allowing even higher mutation rates. Extensive genomic diversity provides the substrate for rapid evolution. Within a single infected patient, several thousand distinct genomic variants may coexist (7). These can be viewed as a swarm of related viral variants.

This swarm functions as a cooperative unit in which genes and proteins are effectively shared. Indeed, it can in principle be regarded as a biological individual – albeit one with diffuse boundaries. The term *quasispecies* has become the accepted designation for this phenomenon. It describes the fact that RNA viruses exist as dynamic populations of genetically distinct viral genomes that can complement one another functionally. If one viral gene is damaged, a functional copy may be replaced through recombination with one of the many viral genomes present within the same infected cell.

Collectively, these interactions allow the viral population within a host to maintain a master sequence. This is the most abundant sequence within the population and the one with the highest fitness, and it should not be confused with the more theoretical term “consensus sequence” (8). The presence of a master sequence indicates genetic stability – that selective forces keep the population centered around the fittest variants. Most viral genomes differ only slightly from this master sequence and together ensure the production of sufficient numbers of functional virions.

At the same time, other genomes accumulate mutations relatively freely, thereby generating diversity and exploring new evolutionary trajectories.

A high mutation rate is therefore an important determinant of RNA virus survival. However, there is an upper limit to the amount of genetic variation that a viral population can tolerate. Once the swarm of viral genomes becomes so heterogeneous that a master sequence can no longer be maintained, the population collapses. The viral genome effectively loses its identity and disintegrates as deleterious mutations overwhelm beneficial ones. Under such circumstances, even advantageous mutations – including resistance mutations – cannot become established because they arise in genomes that are no longer replication-competent. In theory, the viral population therefore loses its ability to evolve antiviral resistance. The mutation rate at which a particular viral population collapses is referred to as the *error threshold*. The collapse itself has been termed *error catastrophe*, while the overall phenomenon is known as lethal mutagenesis.

The rationale behind mutagenic antiviral therapy is to push the viral population beyond the *error threshold* and into *error catastrophe*. As long as the population remains above this threshold, resistance should, in principle, be unable to emerge. Most RNA viruses naturally exist close to this threshold, meaning that only a relatively modest increase in mutation frequency may be sufficient to trigger population collapse (9).

Favipiravir

Favipiravir is a mutagenic antiviral agent that has been approved for the treatment of influenza in Japan since 2014 (3). It is administered orally. Animal studies have demonstrated antiviral activity against a wide range of other RNA viruses, including highly pathogenic viruses such as Ebola virus, Lassa virus, Crimean-Congo haemorrhagic fever virus, and some hantaviruses.

Favipiravir is a nucleoside analogue capable of mimicking both guanosine and adenosine. The molecule is incorporated into the viral genome, where it exerts both chain-terminating and mutagenic effects. The latter results from its ability to pair with either uracil or cytosine during viral replication, thereby introducing point mutations into the single-stranded RNA genome. For example, if the active metabolite of favipiravir is incorporated in place of adenosine and subsequently pairs with cytosine, the cytosine will pair with guanine during the next round of replication. The result is an A to G transition mutation (10).

Because incorporation of favipiravir into the viral genome is mediated by the viral polymerase, mutations in the polymerase gene could theoretically confer resistance. This has indeed been demonstrated in both cell culture and animal models of influenza virus infection, and specific resistance mutations have been identified (11). However, resistance has not been documented in treated patients.

Despite its promising antiviral properties, favipiravir has not achieved widespread clinical success. The principal limitation is its poor bioavailability, resulting in drug concentrations that are insufficient in plasma and certain tissues (4). Consequently, there is a marked discrepancy between the antiviral efficacy observed in cell culture and that achieved in humans. Efforts are therefore underway to develop novel favipiravir derivatives with improved bioavailability.

Molnupiravir

Molnupiravir is another orally administered nucleoside analogue. Its mechanism of action is broadly similar to that of favipiravir in that the drug is capable of pairing with two different bases, thereby promoting single-nucleotide substitutions during viral replication (4). Molnupiravir is somewhat more potent than favipiravir but has no direct inhibitory effect on the viral RNA-dependent RNA polymerase (RdRp). It therefore represents the antiviral agent with the most purely mutagenic mechanism of action currently available.

Like favipiravir, molnupiravir exhibits broad-spectrum activity against RNA viruses but has so far been approved only for the treatment of SARS-CoV-2 infection. The drug was introduced during the COVID-19 pandemic and received emergency authorization in several countries in 2021 and 2022, with the restriction that it should be used for patients with mild to moderate COVID-19 when other antiviral therapies were unavailable (12).

Now that the pandemic has subsided, there has been an opportunity to complete the remaining safety studies. The potential mutagenic effects of molnupiravir on host cells remain the primary safety concern, and, to date, toxicological studies have not identified evidence of clinically relevant genotoxicity. Although mutations have been detected in cultured cells exposed to molnupiravir, these findings have not been reproduced in animal studies. During the pandemic, clinical use of molnupiravir remained relatively limited because alternative antiviral agents, particularly nirmatrelvir and remdesivir, demonstrated superior clinical efficacy (6).

Resistance to mutagenic antiviral agents

Mutagenic antiviral agents represent an exciting class of compounds with broad-spectrum antiviral activity and potentially high therapeutic efficacy. They also appear to have a relatively low propensity to select for antiviral resistance. However, this should not be interpreted as resistance-proof therapy. Experimental resistance has been demonstrated for all of the mutagenic antiviral agents discussed above (6). Resistance can be selected by serially passaging viruses in cell culture in the presence of suboptimal drug concentrations. By analogy, tissues in which drug concentrations are comparatively low may also serve as sites where resistant variants emerge in vivo.

Mutations in RdRp may arise in tissues where drug concentrations are insufficient to increase the mutation rate beyond the *error threshold*. Under such conditions, the master sequence is preserved, the viral population remains viable, and the virus continues to explore new evolutionary trajectories despite ongoing antiviral treatment. Resistance may develop either through increased replication fidelity of the RdRp, thereby reducing the mutation rate, or through reduced incorporation of the mutagenic nucleoside analogue into the viral genome (13).

If the *error threshold* is not exceeded, mutations in RdRp can be transmitted to subsequent generations of virus. Such mutations may reduce polymerase efficiency and therefore impose a fitness cost. They would consequently be expected to disappear once drug pressure is removed. However, a clinical study published in 2023 demonstrated transmission of SARS-CoV-2 variants carrying multiple molnupiravir-induced mutations to individuals who had not received molnupiravir treatment (6). This observation may indicate that the fitness cost associated with

these mutations is relatively low, although it may also reflect the hypermutated state itself. High levels of mutagenesis are a double-edged sword. Unlikely combinations of mutations may arise when millions of parallel replication events occur under strong selective pressure. The crucial question is therefore which process predominates: viral population collapse or the emergence of resistance.

One should therefore remain cautious and monitor patients receiving mutagenic therapy. At the same time, it is important to emphasize that this study did not demonstrate resistance to molnupiravir itself, only the transmission of molnupiravir-induced mutations. At present, the clinical significance of this finding remains uncertain. Moreover, the study had several important limitations. It did not estimate the fitness costs associated with the observed mutations, nor did it include measurements of drug concentrations. Studies specifically addressing these questions are currently underway.

In animal models, resistance has been demonstrated for ribavirin (poliovirus), mutagenic antiretroviral nucleoside analogues (HIV), and favipiravir (influenza virus), whereas resistance to molnupiravir has not yet been demonstrated (SARS-CoV-2) (6). To minimize the risk of resistance, drug doses must be sufficiently high to drive the viral mutation rate beyond the *error threshold* in all infected tissues, preferably by a substantial margin. Adequate bioavailability is therefore essential. At the same time, it is equally important to ensure that such doses remain well tolerated by patients.

Many questions concerning mutagenic antiviral agents and antiviral resistance remain unanswered. Nevertheless, it is noteworthy that neither favipiravir nor molnupiravir resistance has been documented in humans so far. Clinical studies evaluating combination regimens that include mutagenic antiviral agents are also underway, and such strategies may further reduce the risk of resistance development.

For several reasons, the new generation of mutagenic antiviral agents is not yet fully mature for routine clinical use. Nevertheless, these compounds hold considerable promise, and their potential against highly pathogenic RNA viruses – including filoviruses, bunyaviruses, arenaviruses, alphaviruses, and hantaviruses – are highly compelling.

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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 products/pharmaceuticals 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 2011 to 2025 (Figure 3.1 and Figure 3.2 respectively), although the sales measured in number of DDDs was slightly reduced during the SARS-CoV-2 pandemic period 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 are treated with single tablet regimens, the number of pharmaceuticals can be reduced despite an increase in number of users.

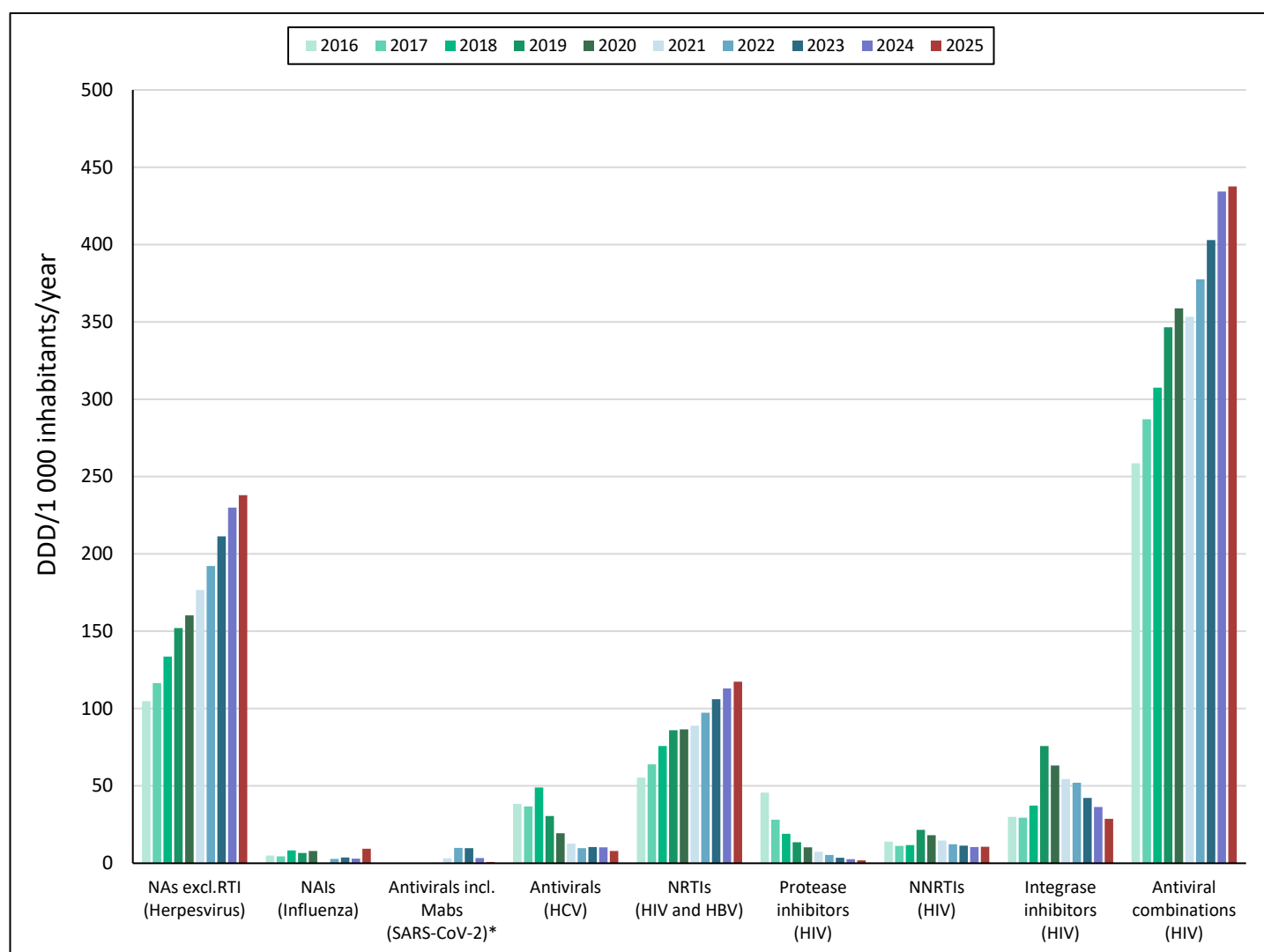


Figure 3.1 Sales of direct acting antiviral drugs for systemic use (ATC group J05A) for 2016-2025 (1).

The figure shows the sales of direct acting antiviral groups over time according to the Norwegian drug wholesales statistics database. The numbers are given as defined daily doses (DDDs) per 1000 inhabitants per year. NAs excl. RTI: Nucleo(s)tide-analogues excluding reverse transcriptase inhibitors (J05AB); NAIs: Neuraminidase inhibitors (J05AH); SARS-CoV-2 treatment remdesivir, favipiravir, molnupiravir, nirmatrelvir and ritonavir, sotrovimab, casirivimab and imdevimab; Antivirals for treatment of HCV infections (J05AP); NRTIs: Nucleo(s)tideanalogue reverse transcriptase inhibitors (J05AF); Protease inhibitors (J05AE); NNRTIs: Non- nucleo(s)tide-analogue reverse transcriptase inhibitors (J05AG); Integrase inhibitors (J05AJ); Antiviral combinations, HIV: Antivirals for treatment of HIV infections, combinations (J05AR). Due to low numbers phosphonic acid derivatives (J05AD) used against herpesviruses and other antivirals (J05AX); are not indicated in the plot. Drugs included in wholesale data are not necessarily used in 2025 it could be stored in pharmacies or in hospitals. * For SARS-CoV-2 monoclonal antibodies mAbs are included in the figure.

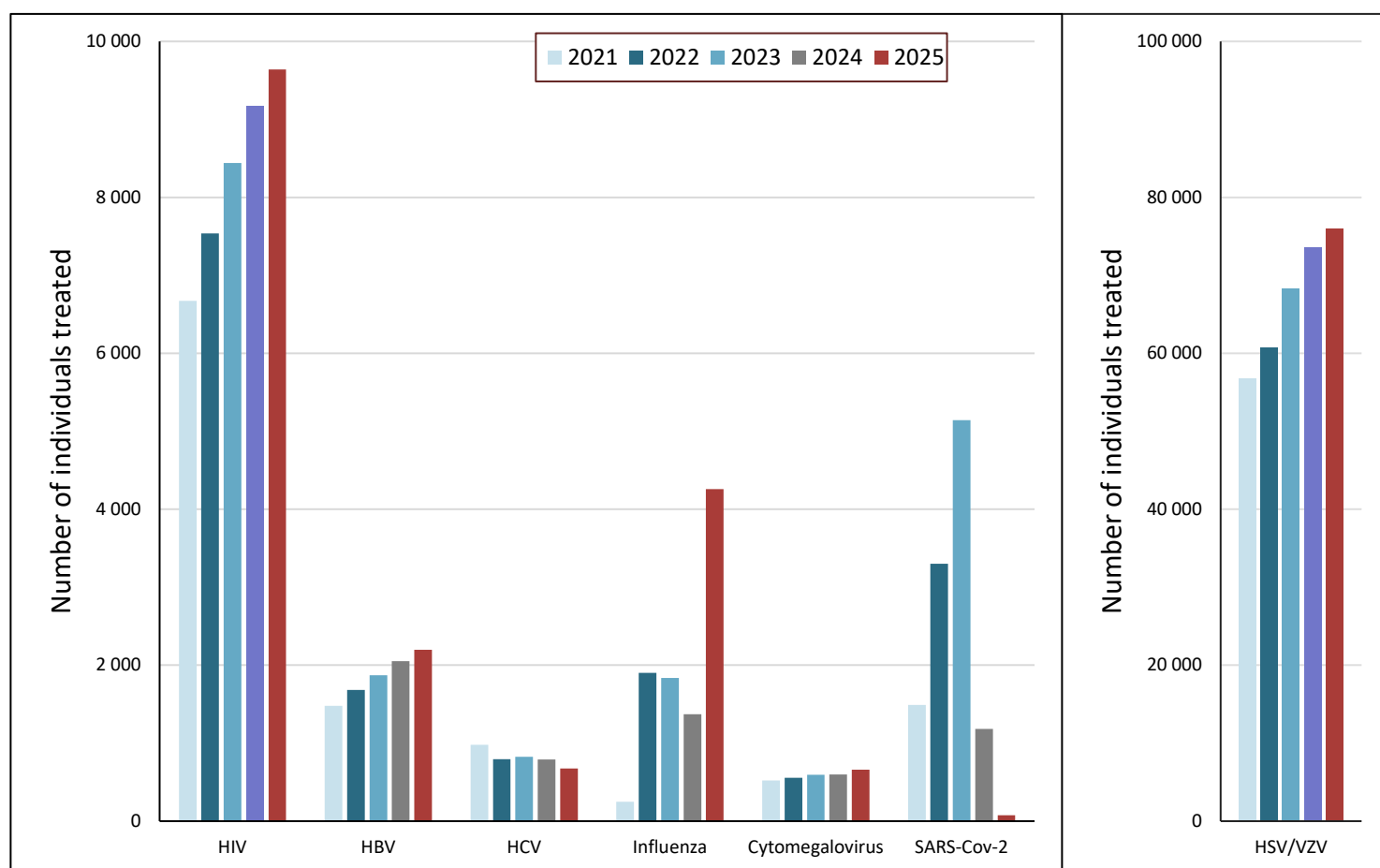


Figure 3.2 Trends in the use of direct acting antiviral drugs for systemic use (ATC group J05A) grouped by virus for 2021-2025 (1).

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. Efavir® (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 2021, while the number of individuals treated for HCV has decreased. The use of DAA against influenza varies from year to year as described below. The number treated for cytomegalovirus infection is relatively stable, but slowly increasing (Figure 3.2).

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 against 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 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.

The number of vaccines sold has increased substantially during the last couple of years and sales made a jump in the first year of the covid-19 pandemic. 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.

Oseltamivir is available as oral treatment and is the therapy used for prevention in primary care. Zanamivir is indicated for complicated and potentially life-threatening influenza type A and B and is only available as an infusion. It is seldom used; 252 packages were sold in 2025.

Table 3.1 Number of individuals with at least one prescription of neuraminidase inhibitor per year (1).

	2021	2022	2023	2024	2025
Oseltamivir	250	1 901	1 835	1 371	4 257

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 usage is decreasing. In 2023, 5077 individuals purchased Paxlovid® compared to only 74 individuals in 2025 (Table 3.2).

Table 3.2 Number of individuals with at least one prescription of nirmatrelvir and ritonavir (Paxlovid®) per year (1).

	2021*	2022*	2023	2024	2025
Nirmatrelvir and ritonavir	0	615	5 077	1 181	74

**In 2021 and 2022, the influenza drug Favipiravir was used for treatment of SARS-CoV-2 (2;3).*

Parenteral antiviral treatment of COVID-19 in Norway is only given in hospitals. In Norway, remdesivir has been approved for use against SARS-CoV-2 since November 2020. This use is decreasing and in 2025, 960 DDDs were used in Norwegian hospitals compared to 2 008 DDD in 2024. Likewise, 3 120 DDDs of Paxlovid® (nirmatrelvir and ritonavir), were used in hospitals in 2025 compared to 7 860 DDDs in 2024 according to the hospital pharmacies drug statistics database (Sykehusapotekenes Legemiddelstatistikk).

The use of monoclonal antibodies for (Mabs) the treatment of SARS-CoV-2 has been limited in Norway.

Human immunodeficiency virus

There are currently 36 drugs or combination drugs in Norway that are used for treatment of HIV. The use of the different drugs has shifted in the last five-year period. During the whole period, nearly 99% of persons treated received products/pharmaceuticals containing more than one active substance. 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 three different types of drugs: complete single tablet regimens; other fixed dose combination drugs (combinations of two or more substances used with other drugs or as PrEP); 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 in Figure 3.3. 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.

When looking at complete ART regimens, combinations containing integrase inhibitors are widely used, which is also in accordance with the Norwegian guidelines (4). 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), has an impact on the choice of drugs for treatment of HIV (5). The combination of the two single ingredient injections; cabotegravir and rilpivirin, was approved as complete dual therapy in December 2020. This is the first long-acting injectable treatment for HIV-1 infection (6). The sales of these injections were limited in 2021 but have since then increased. The use measured in number of DDD was twice as high in 2025 as in 2023 (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 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.

The fixed combination of emtricitabine and tenofovir disoproxil (FTC/TDF) has been the most used combination drug in recent years. Although it is not possible from the drug statistics to separate the proportion of PrEP nor PEP from the total use of these drugs, the increase since 2016 is most probably related to its use at pre-exposure prophylaxis (PrEP) in risk groups, with full reimbursement of the costs since 2016. The use of FTC/TDF increased almost 47% from 2018 to 2019, and a yearly increase has continued steadily, except during the pandemic years 2019 to 2021 (2). In 2025 the increase has levelled off, and the number of people receiving FTC/TDF was at the same level as in 2024.

Another prodrug of tenofovir, tenofovir alafenamide (TAF), with a greater bioavailability, is available in various fixed dose combinations with emtricitabine (4). 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 2025 1034 packs were sold (wholesales data)(7).

For post exposure prophylaxis (PEP), the previous recommendation was to use FTC/TDF in combination with the integrase inhibitor raltegravir. From 2025, the recommended first choice for PEP is the fixed combination of bictegravir and FTC/TAF. This could explain the observed reduction in number of prescriptions for raltegravir from 2024 to 2025.

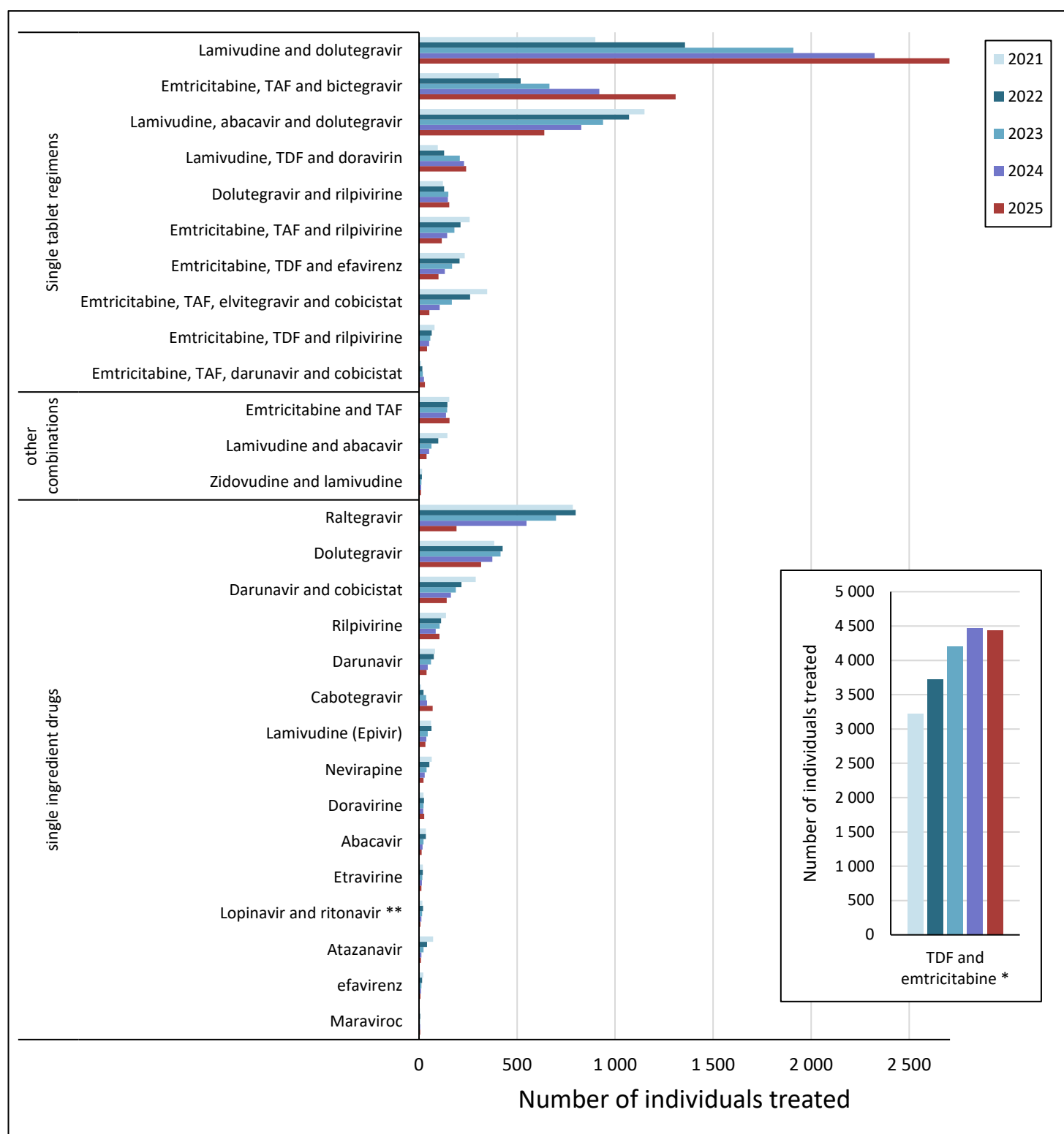


Figure 3.3 Trends in the use of antiviral drugs for treatment of HIV in the periods 2021-2025 (1).

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 2025 are excluded (J05AF01-zidovudine; J05AR09 emtricitabine, TDF, elvitegravir and cobicistat; J05AR15 atazanavir and cobicistat). Ritonavir is also excluded. *Includes PrEP. **Protease inhibitor boosted with ritonavir, considered single ingredient drug.

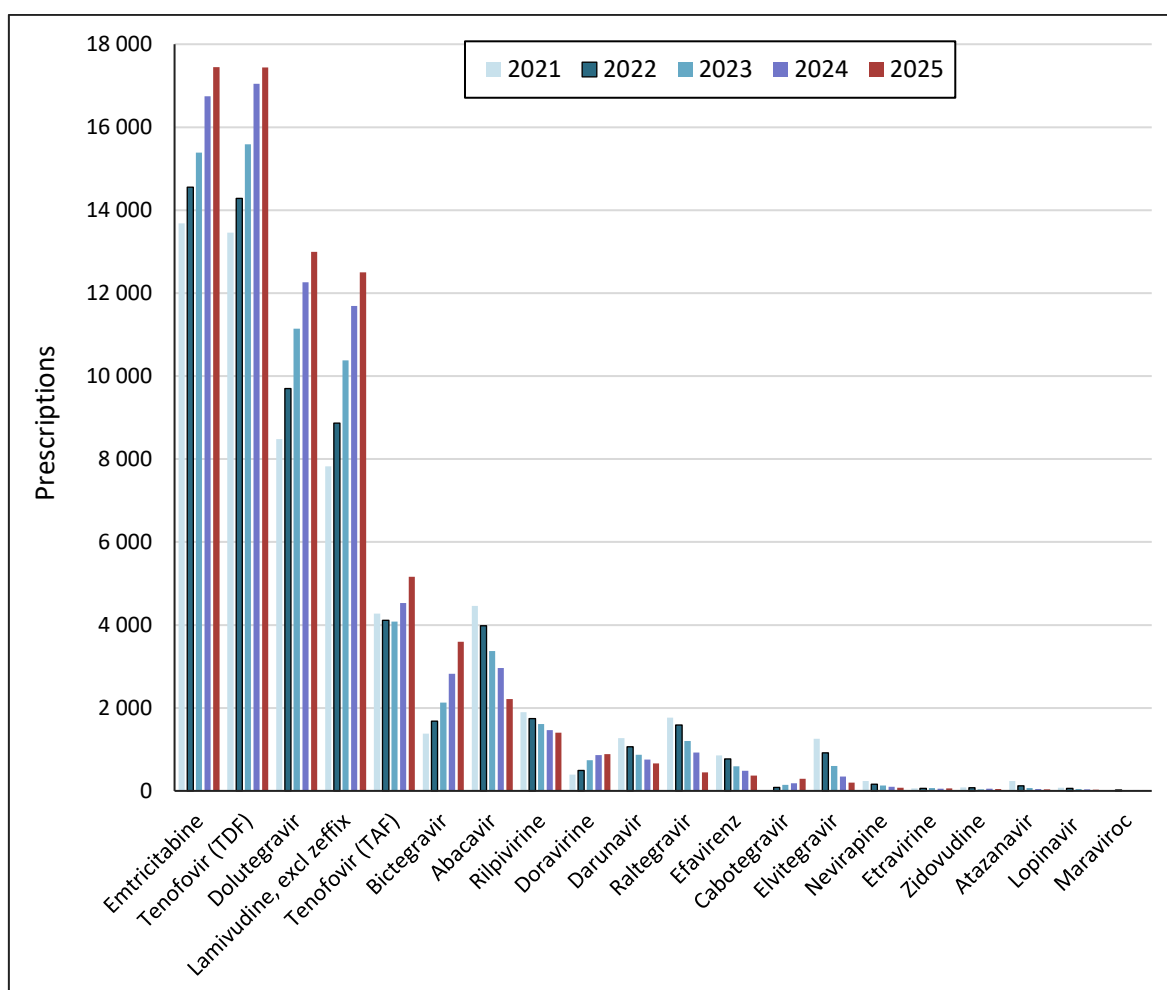


Figure 3.4 Number of prescriptions per active ingredient for HIV drugs (1).

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. Cobicistat and ritonavir, which are used as boosters to other drugs, have been omitted from the figure.

Hepatitis B and D 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 2021-2025. 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 were however no registered sales of bulevirtide until 2025 when 17 individuals were treated.

The annual number of persons treated for HBV has increased considerably during the last five years, by 49% since 2021. 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 2025. From April 2025, tenofovir has replaced entecavir as the preferred drug according to procurement recommendations from The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF) (8). This may explain the increase in the use of Entecavir from 2021.

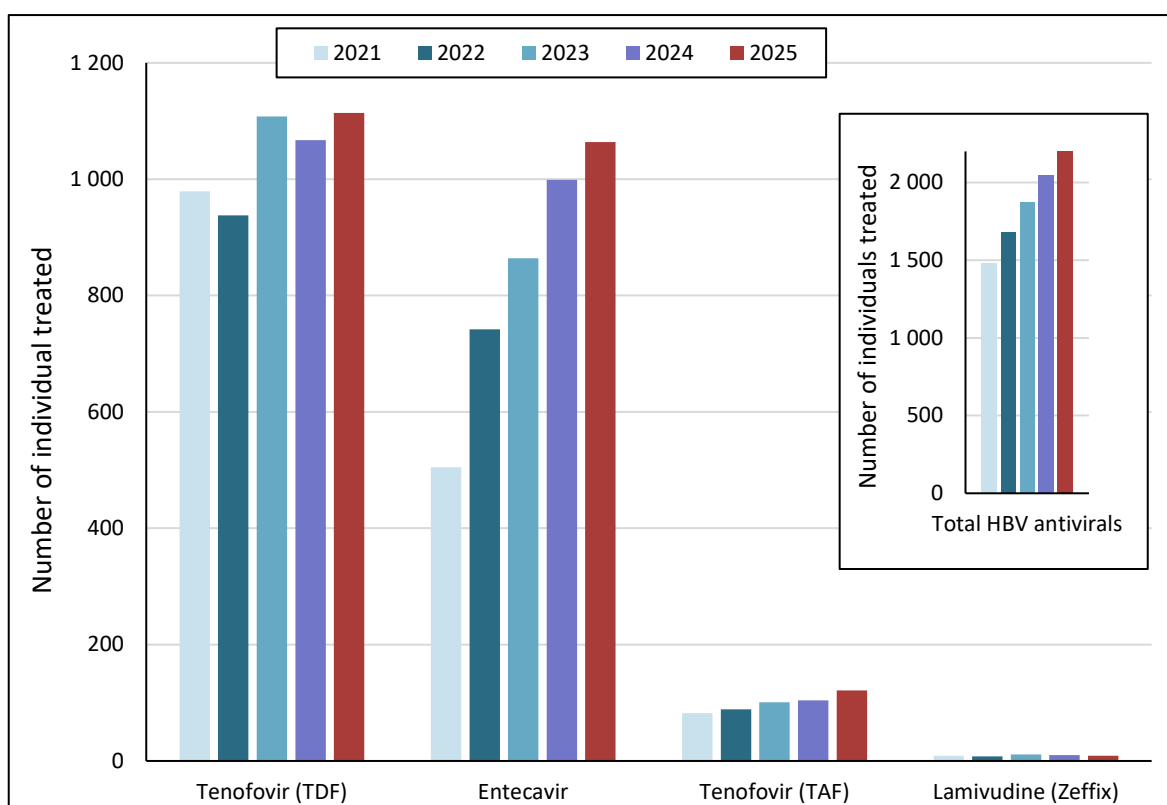


Figure 3.5 Trends in the use of antivirals for treatment of HBV for the period 2021-2025 (1).

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.

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. The number of persons who received at least one prescription for a HCV drug (except interferons) was 674 in 2025, a reduction by 70% since 2019. Fixed combinations of two or more active ingredients have almost completely replaced older regimens with single component drugs and ribavirin as shown in Figure 3.6.

Trends in the use of antivirals against HCV (Figure 3.6) reflect both changes in the NMA-treatment guidelines (9), and recommendations from The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF) (10). Since spring 2025, the Norwegian national recommendations have followed the recommendations of the Norwegian Hospital Procurement Trust, which recommend glecaprevir/pibrentasvir as the preferred treatment for all HCV genotypes in patients without cirrhosis (9).

"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 (11). The strategy is currently under revision. The status report from 2023 states that although the goal of no serious illness caused by HCV in Norway was not achieved by 2023, the number of HCV-related deaths in 2021 was far below WHO targets(12).

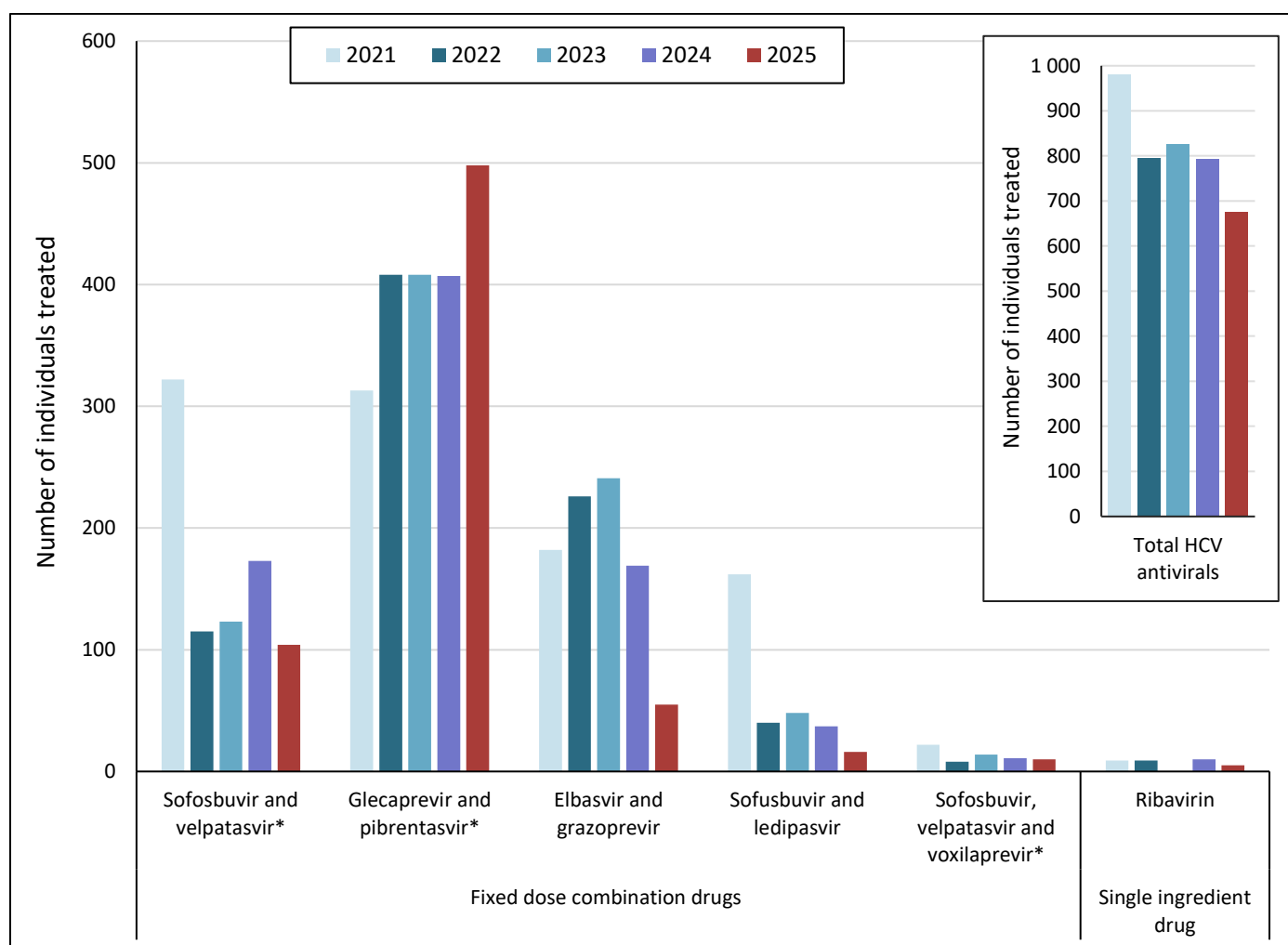


Figure 3.6 Trends in the use of antivirals for treatment of HCV for the period 2021-2025 (1).

*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. *Pangenotypic drugs.*

Cytomegalovirus

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

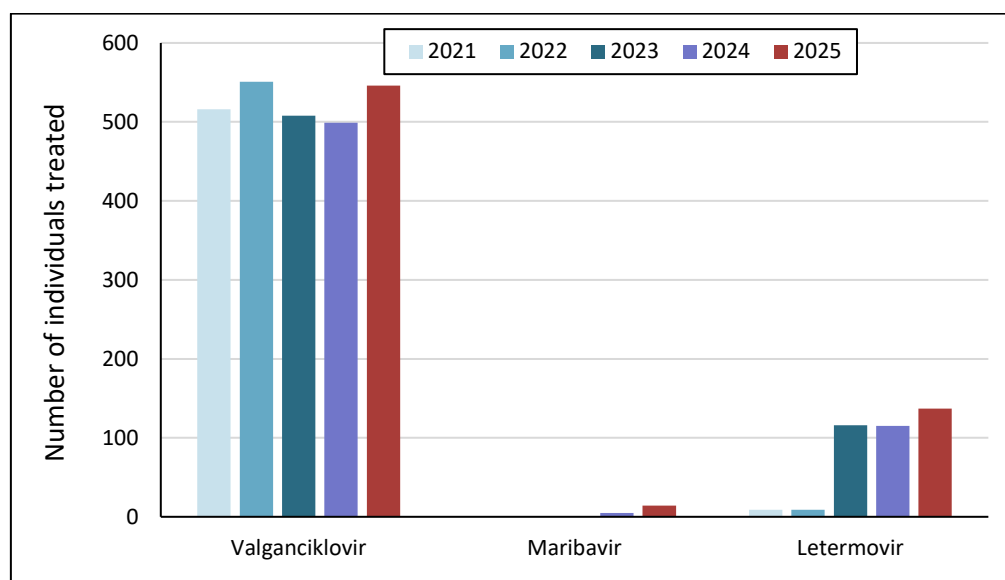


Figure 3.7 Trends in the use of systemic antivirals prescribed for cytomegalovirus infection for the period 2020-2025 (1).

This figure shows the trends in direct acting antivirals used 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 and foscarnet were rarely prescribed and are not included in the figure.

Herpes simplex and varicella zoster virus

Figure 3.8 shows the prescribed drugs for systemic use for human herpesvirus infections over the last five years. Valaciclovir is the most commonly prescribed substance and there has been an increase of more than 64% in the number of individuals treated with this antiviral since 2019. The use of aciclovir has been stable, but in 2025 the use increased, probably due to a shortage of valaciclovir lasting a few months towards the end of 2025. In 2025, 81378 persons were treated with systemic antivirals for herpesvirus infections.

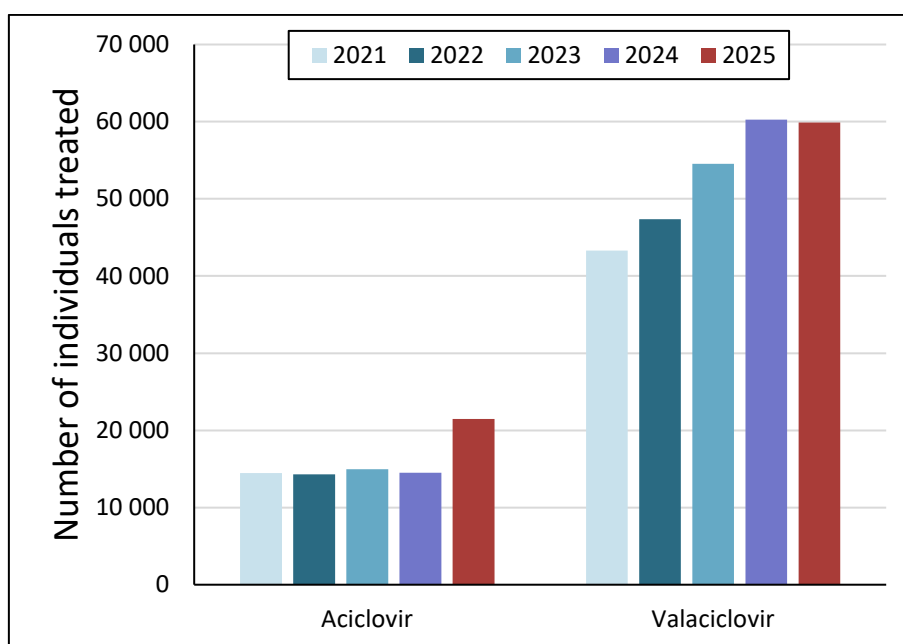


Figure 3.8 Trends in the use of antivirals for treatment of human herpesvirus infection for the period 2021-2025 (1).

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 is 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 3.3). Today all products in this group are available without prescription.

Table 3.3 Sold packages of topical antivirals containing aciclovir, penciclovir and aciclovir in combination with hydrocortisone (1).

	2021	2022	2023	2024	2025
Aciclovir	176013	174756	191192	170443	171208
Penciclovir	14054	10272	8906	8196	8128
Aciclovir, combinations*	45996	40585	55562	53047	61108

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.*

Aciclovir and ganciclovir are also available as eye cream for treatment of herpes simplex keratitis. In 2025, around 3600 packs were sold.

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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.
Clinical 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	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 using samples from sentinel physicians and medical microbiology laboratories. Surveillance supports assessment of the match between vaccine components and circulating viruses, viral evolution, virus characteristics and antiviral susceptibility. Samples from patients includes both untreated and treated individuals.

The NIC reports typing and subtyping data as well as genetic characterisation and relevant mutations to the European Centre for Disease Prevention and Control (ECDC) and the WHO, this data is also included in NIPH's bi-weekly respiratory virus surveillance reports, submissions to GISAID and the Register for antiviral resistance in viruses in Norway (RAVN). Alongside these reports the NRL publishes the Influenza genomic surveillance data on statistikk.fhi.no.

For the analysis of resistance-associated substitutions, whole-genome sequences are screened for mutations in the neuraminidase (NA) gene associated with reduced susceptibility to neuraminidase inhibitors such as oseltamivir, in the M2 ion-channel gene associated with resistance to adamantanes, and in the polymerase acidic (PA) gene associated with reduced

susceptibility to baloxavir. Lists of relevant substitutions are compiled and curated by WHO (1). However, uncertainty remains regarding the magnitude of reduced susceptibility and the clinical relevance of some genotypic markers. Wherever possible, genotypic findings are followed up with phenotypic susceptibility testing (MUNANA) to confirm reduced antiviral susceptibility and to investigate substitutions with a potential impact on antiviral sensitivity.

Surveillance data influenza season 2025-26

The outbreak began very early, reaching a 10% positivity rate by week 46/2025 in comprehensive surveillance and week 47/2025 in sentinel surveillance. In comprehensive surveillance, positivity peaked at 29.5% in week 51/2025, whereas sentinel surveillance peaked at 50% in week 52/2025. Overall intensity was lower than in previous seasons. Positivity rates fell below the 10% threshold in week 10/2026 in both comprehensive and sentinel surveillance.

Influenza A(H3N2) was the main driver of the season, but A(H1N1) viruses were detected throughout the season in substantial numbers, indicating co-circulation of both subtypes. B/Victoria-lineage viruses were detected only towards the end of the season, with numbers suggesting limited circulation.

Influenza antiviral resistance

Among 836 influenza viruses tested for neuraminidase inhibitor susceptibility during the 2025/26 season, four A(H1N1) viruses carried substitutions associated with reduced oseltamivir sensitivity. Three viruses carried the previously identified S247N + I223V substitution combination (2) and were detected in weeks 17 and 18/2026. One A(H1N1) virus carried the I223R substitution, which is associated with reduced sensitivity to both oseltamivir and zanamivir; this virus was detected in week 38/2025 (3). Treatment history was unknown for all four cases. All other tested viruses were sensitive to oseltamivir, zanamivir and baloxavir marboxil.

Seasonal influenza A viruses have generally carried adamantane resistance substitutions since the 2009 A(H1N1)pdm09 pandemic, and adamantanes are therefore not used for treatment in Norway. This season, however, one A(H1N1) virus and three A(H3N2) viruses lacked known adamantane resistance substitutions.

Table 3.1. Norwegian influenza viruses with resistance mutations to the neuraminidase inhibitors oseltamivir and zanamivir and adamantanes, during the influenza seasons 2016/17 through 2025/26 (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
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
2025/26	4/329	0/436	0/71	1/329	0/436	0/71	0/306	0/414	0/62	339/340	440/443	NR

Conclusions

Antiviral resistance among influenza viruses remained rare in Norway during the 2025/26 season. Only four A(H1N1) viruses carried substitutions associated with reduced neuraminidase inhibitor sensitivity, corresponding to 0.5% of all influenza viruses analysed for neuraminidase inhibitor susceptibility. Continued monitoring remains important, as resistance-associated substitutions can emerge and spread globally within a short period (2;4). This is particularly relevant in Norway, where antiviral treatment options are limited and oseltamivir is the only orally administered option.

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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 gene	Protease (NSP5) RNA-dependent RNA polymerase (RdRp) Spike
Clinical indication for resistance testing	None
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 2025, surveillance of SARS-CoV-2 followed a protocol similar to influenza monitoring and was carried out by the national reference laboratory (NRL) for coronaviruses with serious outbreak potential at the National Institute of Public Health (NIPH). The surveillance programme uses whole genome sequencing to assess variant prevalence, analyse virus characteristics and identify drug resistance-associated substitutions.

For the analysis of resistance-associated substitutions, whole genome sequences are examined for mutations in the protease gene NSP5, related to nirmatrelvir, and the RNA-dependent RNA polymerase gene, related to remdesivir. The substitutions are curated using lists provided by the Stanford Coronavirus Antiviral & Resistance Database (1;2), which is regularly updated to reflect findings from publications and clinical trials. In the absence of an internationally recognised 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 NRL reports Pango lineages and relevant mutations to the European Centre for Disease Prevention and Control (ECDC), this data is also included in NIPH's bi-weekly respiratory virus surveillance reports and submissions to GISAID and the Register for antiviral resistance in viruses in Norway (RAVN). Alongside these reports the NRL publishes the SARS-CoV-2 genomic surveillance data on statistikk.fhi.no.

Surveillance data 2025

In 2025, SARS-CoV-2 infections increased from week 19, with positivity rates crossing the 10% threshold in week 34, which also represented the seasonal peak, with a positivity rate of 10.9%. The recombinant XEC variant was the most frequently detected variant at the start of the year, together with BA.2.86. In March 2025, NB.1.8.1 was first detected, followed in April 2025 by detection of the newly identified recombinant XFG.

Both of these new variants increased in proportion over the following months, with XFG becoming dominant in August and NB.1.8.1 accounting for 10–15% of all detections between August and November. In December, BA.3.2 was first detected in Norway. This represents a further developed version of Omicron BA.3.

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 SARS-CoV-2 transmission.

SARS-CoV-2 antiviral resistance

Overall, in 2025, 678 SARS-CoV-2 surveillance samples were analysed for resistance, and no sequences showed mutations conferring significantly reduced sensitivity to nirmatrelvir or remdesivir.

After the emergence of Omicron, virtually all SARS-CoV-2 variants were resistant to neutralisation by the monoclonal antibodies available in Norway, and prescription declined (3;4). As SARS-CoV-2 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 2025 (n=678)

Pango lineage	Number of samples	Percent of samples
B.1.1.529	1	0.2
BA.2.86	182	26.8
BA.3.2	15	2.1
NB.1.8.1	104	15.3
XBB.1.5	1	0.2
XEC	65	9.6
XFG	255	37.6
Others	55	8.1

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. For a more detailed overview on SARS-CoV-2 variants please visit <https://statistikk.fhi.no/ngs/Pd-QnwX6YWyeIQYG-F4z8O6lissjqCHKNO2kuQuj000>).

Conclusions

No mutations that confer resistance to antiviral drugs in SARS-CoV-2 viruses were detected in Norway during 2025. Continued genomic surveillance of SARS-CoV-2 is important, as the rapid fluctuation in dominant variants illustrates how a potentially 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)
Clinical 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. There is no official list of SDRM of integrase, although in 2020, a group of experts suggested candidate surveillance mutations (3)

Surveillance data 2025

A total of 79 samples from newly diagnosed cases of HIV-1 in Norway were analysed for primary HIV-1 drug resistance in 2025. This corresponds to 38% of the 208 cases notified to MSIS (4). Of the 79 samples submitted for resistance testing, 23% were from female patients, and 77% were from males.

The methods used for resistance testing also provide information on HIV subtypes, and the results are shown in Figure 6.1. Subtype B remains the most prevalent subtype among patients infected in Norway, but it is worth noting the increase in the proportion of transmitted subtype A in 2025. Distribution of subtypes in samples from patients infected abroad is more diverse, mostly reflecting the prevalence of various subtypes in the country of transmission.

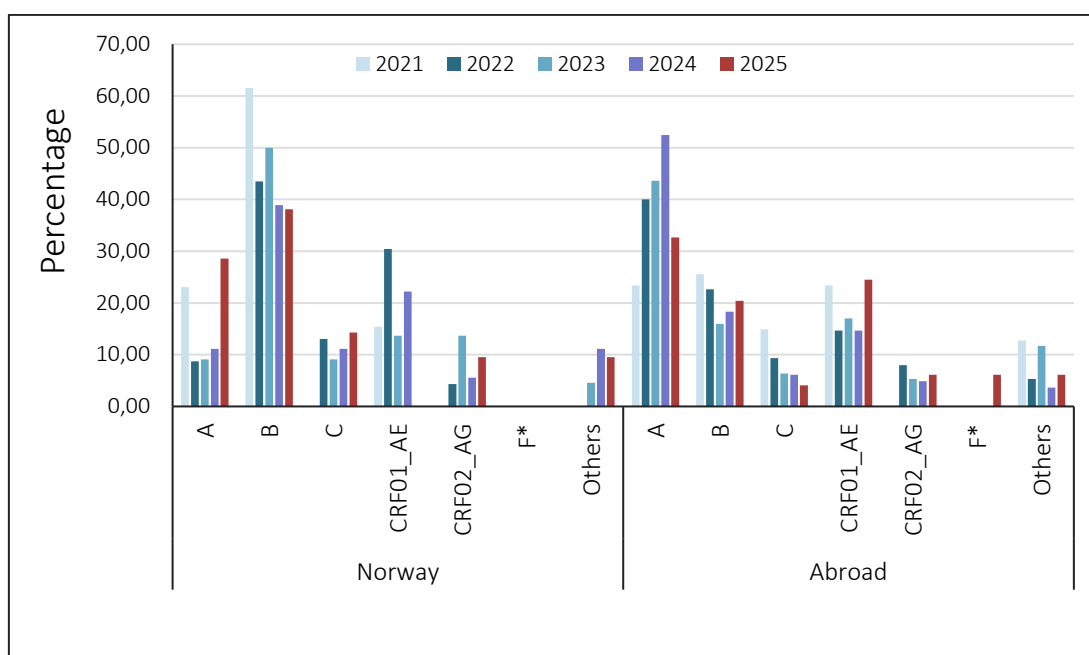


Figure 6.1. Distribution of the most common HIV subtypes detected in 2021-2025 by country of transmission, shown as percentage of subtypes.

The five most frequent subtypes are shown. The group of others includes the circulating recombinant form (CRF) CRF06_cpx, subtypes D, G, and H as well as single cases of other recombinants. *Subgroup F is only shown for 2025 as the number of samples was below 5 previous years.

Cases tested for drug resistance were cross-referenced to epidemiological cases in MSIS to provide information on both route of transmission and country of infection (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 2025 compared to new cases reported to MSIS in 2025.

Route of transmission	Samples tested for resistance 2025	Cases reported to MSIS 2025	Coverage
Male, infected through sexual contact with men	32	60	53%
Male, infected through sexual contact with women	19	29	66%
Male, unspecified sexual transmission	1	8	13%
Female, sexual transmission	13	41	32%
Injection drug use	2	9	22%
Other blood exposure	2	7	29%
Mother to child	-	5	-
Unknown	10	49	20%
Total	79	208	38%

Table 6.2. Coverage of resistance testing by country of transmission, compared to new cases reported to MSIS in 2025.

Country of transmission	Samples tested for resistance 2025	Cases reported to MSIS 2025	Coverage
Infected in Norway	21	24	88%
Infected abroad	49	177	28%
-Infected abroad, before arrival to Norway	25	134	19%
-Infected abroad, residing in Norway	23	32	72%
-Infected abroad, unknown residency	1	11	9%
Unknown	9	7	-
Total	79	208	38 %

Only 21 (27%) of the samples submitted to RAVN were from patients infected in Norway, while 49 (62%) were infected abroad. For 9 samples (1%), country of transmission was unknown. Similar to previous years, the coverage of baseline resistance testing for patients infected in Norway was almost complete (88%). 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 72%.

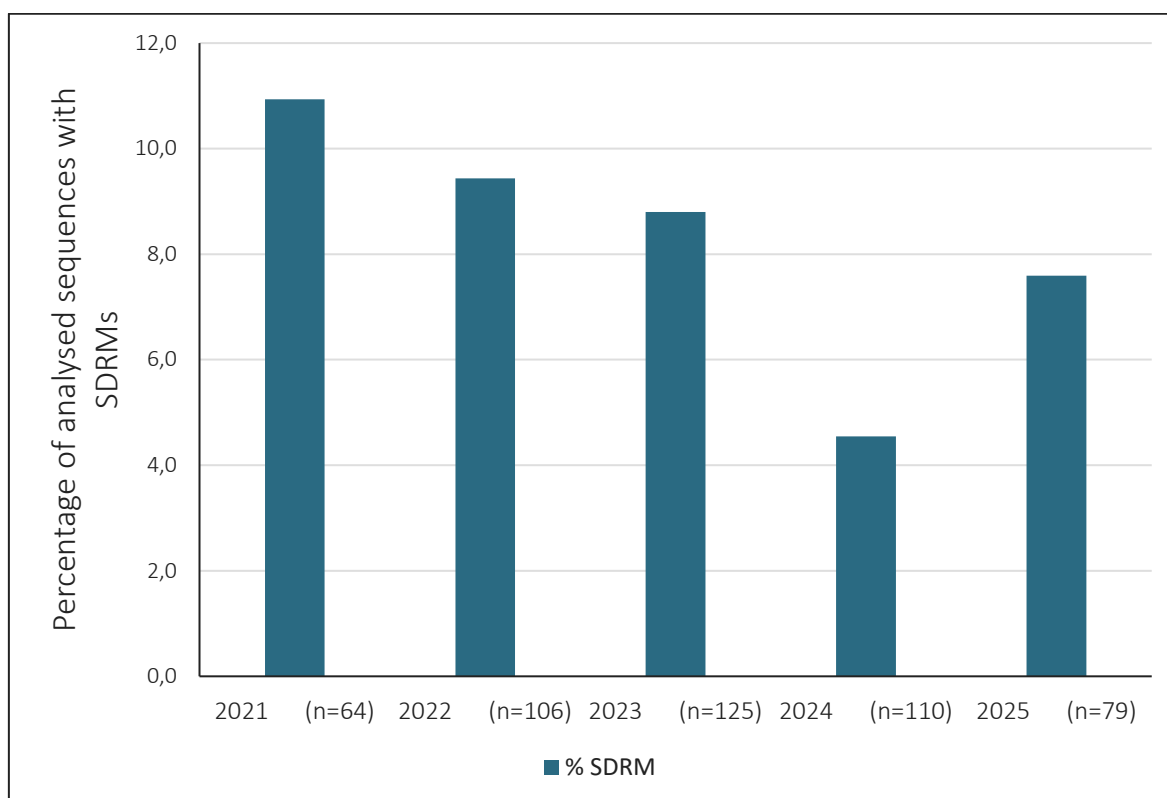


Figure 6.2. Percentage of analysed sequences with detected surveillance drug resistance mutations (SDRMs).

Percentages of the analysed sequences containing one or more SDRMs through the years 2021-2025 are shown as blue columns. There may be several SDRMs per sequence. n = number of sequences analysed for pre-treatment resistance.

In 2025, mutations classified as SDRMs were detected in six samples (7.6%), as shown in Figure 6.2. The individual substitutions detected are listed in table 6.3. Out of the six samples with detected mutations, five samples had mutations associated with resistance to reverse transcriptase inhibitors. Figure 6.3 shows the frequency of SDRMs for each of the drug classes, comparing results for the last ten years of surveillance. In 2025, the proportion of sequences with SDRMs associated with each of the main drug classes was 3.8% for NNRTI, 5.1% for NRTI, and 2.5% for protease inhibitors.

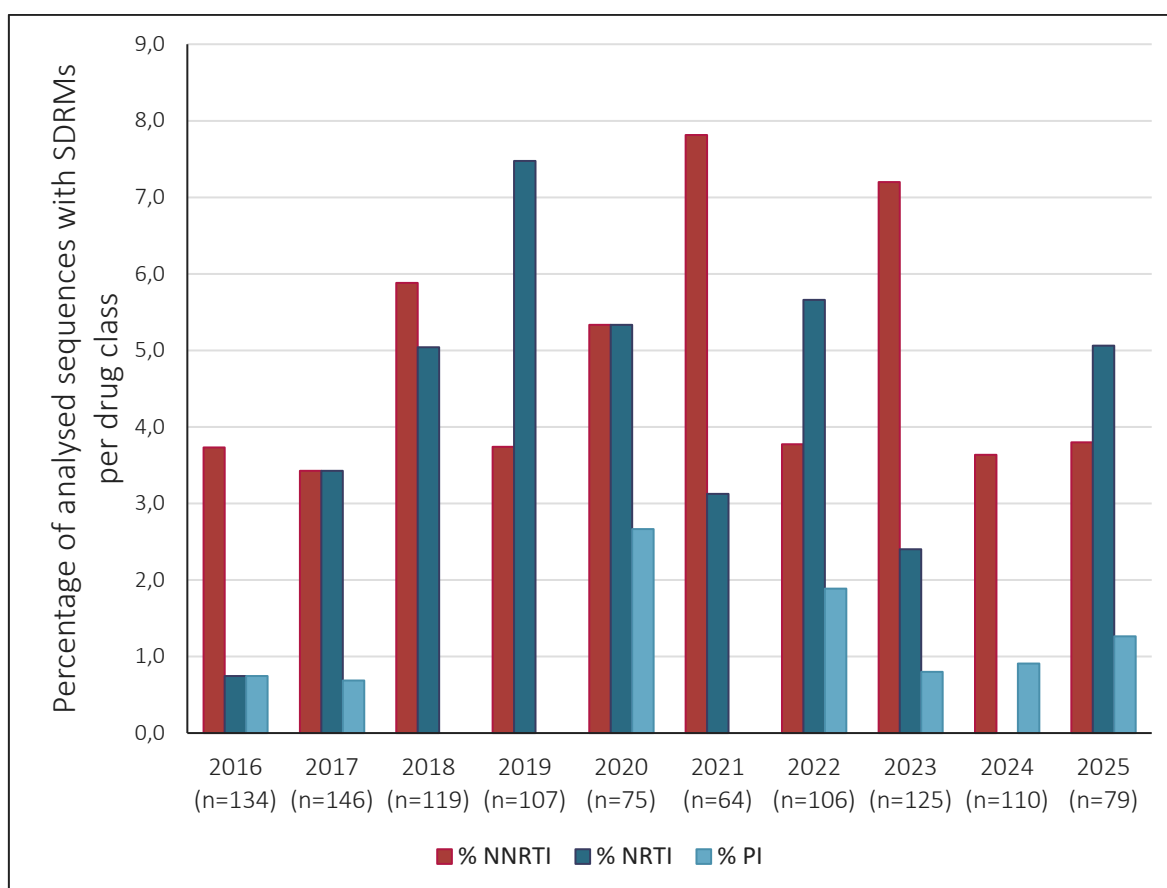


Figure 6.3: Percentage of analysed sequences with detected SDRMs per drug class.

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.

All six of the patients with detected SDRMs were infected abroad. Three cases had mutations associated with reduced susceptibility to NNRTI, two of which had additional mutations affecting NRTI. Additional two cases harboured the substitution M184I/V causing resistance to the NRTIs lamivudine and emtricitabine (5). The sole substitution (M46I) in the protease gene detected in two of the samples 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 polymorphic NNRTI resistance-substitution E138A in a total of five samples, and one case of the non-polymorphic accessory substitution E138G. Two of the cases were infected in Norway, and four were infected abroad. Both mutations are associated with slightly reduced susceptibility to etravirine and rilpivirine, especially when detected in combination with other NNRTI mutations.

Table 6.3. Specification of the surveillance drug resistance mutations (SDRMs) detected in 2025, according to corresponding drug class

Sequence	NRTI	NNRTI	PI	INSTI	Place of transmission
1	T215E	K103N	None	None	Abroad
2	None	None	M46I	None	Abroad
3	None	K103N	None	None	Abroad
4	M184V	None	None	None	Abroad
5	M184I/V	None	None	None	Abroad
6	T215S	K101E, G190A	None	None	Abroad

No major resistance mutations to integrase inhibitors (INSTI) were detected, but four of the samples had accessory substitutions as shown in Table 6.4. All of the detected substitutions are common polymorphisms that are previously reported to have a prevalence of 1-4% among newly diagnosed patients (6-8). 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. Two of the cases with detected integrase substitutions were infected in Norway, and two were infected abroad.

Table 6.4. Substitutions associated with reduced susceptibility to integrase strand transfer inhibitors (INSTI) detected in 2025

INSTI substitution	Mutation type	Drug	n	Percentage of analysed sequences
E157Q	Accessory	RAL, EVG	3	4%
L74I/M	Accessory	RAL, EVG	1	1%

RAL: raltegravir; EVG: elvitegravir

Table 6.5 shows a summary of all SDRMs detected during the last ten years of systematic surveillance of antiretroviral drug resistance in Norway and presented in the yearly RAVN reports. In the two years we have had INSTI surveillance no clinically relevant resistance substitutions has been detected.

Tabell 6.5: HIV drug resistance substitutions detected in the surveillance during the years 2016-2025

Substitution	Number of detections 2016-2025
NRTI	
M41 L	15
T215 E/S/D/V/I/C/Y	13
M184 V/I	10
K219Q/N/E	6
D67 N/G, K70 R	4
V75 M	2
T69 D	1
NNRTI	
K103 N/S	25
G190 A/S	11
K101 E	9
Y181 C	5
Y188L	3
P225 H, V106 M	2
PI	
M46 I/L	9
150 V	1

Discussion

The surveillance data is based on resistance testing of samples collected from patients who had their HIV-1 infection confirmed in Norway in 2025, and where a sample was sent to the National reference laboratory for HIV for resistance testing.

Cross-referencing of sequence data to epidemiological data from MSIS enables detailed analysis of transmitted drug resistance in Norway in different subgroups, such as risk groups or place of transmission.

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, all of the mutations detected in 2025 were found in samples from patients infected abroad, and the mutations were mainly 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. There were two cases where the NRTI mutation M184V was detected, known to confer high level antiviral resistance to lamivudine and emtricitabine that are commonly included in first line regimens. The NRTI substitution T215S detected in two samples is not considered to be clinically relevant according to the International AIDS Society list 2022 (9;10) and is frequently found in treatment naive individuals.

The E138A is not an SDRM, but is nevertheless monitored in the surveillance as it may reduce susceptibility to NNRTIs that are currently in use such as rilpivirine. The substitution was only detected in samples from patients infected abroad, but further monitoring of this substitution over the next years might be of importance.

During the years 2022-2024, there were no detections of any mutations associated with reduced susceptibility to the drugs emtricitabine or tenofovir that are used in pre-exposure prophylaxis (PrEP). Since PrEP was introduced with full reimbursement of the costs in 2016, there has been sporadic detections of the substitution M184V, causing high level resistance to emtricitabine (11). In 2025, the substitution M184V, was detected in two samples. Both samples were from patients infected abroad, and the surveillance data supports that PrEP is still effective in preventing new cases of HIV infection in Norway. Nevertheless, continued monitoring of relevant mutations will be of importance.

The summary of surveillance data for the last ten years, shows that the mutations most frequently detected in recent surveillance are largely consistent with those most observed across the ten-year dataset. The resistance mutations detected during this period primarily affect susceptibility to older antiretroviral drug classes. Common NNRTI substitutions, such as K103N/S, confer high-level resistance to first-generation NNRTIs, which are now largely avoided in current first-line regimens. Nevertheless, over the years, patients infected abroad are identified with resistance to these older drugs. They are mostly well treated and with low risk of transmission, but there may be an accumulation of archived resistance of unknown significance in the community. NRTI mutations, including M184V/I and thymidine analogue mutations, may reduce the activity of backbone drugs but can often be managed by using agents with a higher genetic barrier to resistance, including integrase inhibitors.

Conclusions

The prevalence of transmitted drug resistance remains low in Norway, and most drug resistance mutations were detected in samples from patients infected abroad. For integrase inhibitors, no resistance mutations of clinical importance were found in the surveillance. PrEP is expected to be effective in preventing new cases of infection in Norway.

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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
Clinical 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;

- samples submitted for drug resistance testing primarily in relation to treatment failure (acquired resistance)
- samples submitted for HBV genotyping in the course of diagnostic investigations, usually prior to treatment. Monitoring of this population can therefore be regarded as surveillance of primary resistance.

Mutations resulting in resistance associated substitutions are identified by the geno2pheno (version 2.0) resistance database from Max Planck Institute of Informatics.

Surveillance data 2025

In 2025, a total of 149 samples were analysed for both HBV drug resistance associated substitutions and genotype.

Out of the 149 samples analysed, 128 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 21 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 two of these samples (Table 7.1), both patients were treated with entecavir at the time of sampling. A substitution at position M204I/V was detected in both samples. On its own, M204I/V is associated with *partial* resistance to entecavir, and an additional

substitution, e.g M250V or S202G, is required for resistance to entecavir. The impact of M250L is not known, so for sample 1 intermediate resistance or complete resistance may apply, whereas in sample 2 resistance to entecavir was detected. Sample 1 also showed the substitution A181T, which is not associated with entecavir resistance.

Table 7.1: Resistance associated substitutions detected in samples from 2025 and the drug resistance they confer

Sample	Genotype	Resistance associated substitutions detected	Treatment*	Resistance				
				LAM	LDT	ETV	ADV	TDF/TAF
1	D	V173L;A181T;M204I;M250L	ETV	R	R	I	R	S
2	B	L180M;S202G;M204V	ETV	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.

An overview of the resistance mutations detected in Norway between 2021 and 2025 is presented in Table 7.2. Overall, only around 20 samples are received for resistance testing every year, except in 2024 with a peak of 33 samples. Of the 109 samples analysed over the five-year period, approximately 17 % (19 samples) showed mutations associated with resistance. Among these 19 samples, 9 were submitted due to not obtaining viral suppression on treatment, 8 due to virological breakthrough on treatment, 1 prior to re-treatment and 1 without any treatment information.

Table 7.2: Resistance associated substitutions in samples submitted for HBV drug resistance testing in 2021 - 2025

HBV-variants resistant to antivirals	Drug resistance	2021	2022	2023	2024	2025
Total analysed		17	18	21	33	21
M204V + (I169T ∨ S202G ∨ T184A/S ∨ M250V) ±L180M	LAM (R), LDT (R), ETV (R)	3	3	3	4	1
A181V/T + M204I/V ± L180M	LAM (R), LDT (R), ETV (I), ADV (R)	2				1
M204I/V + L180M ± L80V	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, whereas in 2025 the number is again comparable to previous years with around 20 samples per year. Among 21 samples submitted in 2025, only two samples had mutations associated with resistance.

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 gene	NS3–NS4A (protease) NS5A (replication and assembly factor) NS5B (polymerase)
Clinical indication for resistance testing	-Virological failure during treatment. -Cirrhosis and increased risk of virological failure.
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 a subset 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 2025

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 2025, a total of 120 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 34 (28%) of the analysed samples in 2025 (Table 8.1).

Table 8.1. Descriptive characteristics of analysed surveillance samples in 2025 (n=120)

	Samples	Samples with any RAS to drugs currently in use	Samples that have RAS category I* to drugs currently in use**
	n(%)		
Route of transmission			
Sexual	7 (5.8)	6 (7.7)	3 (8.8)
Injection drug use	36 (30.0)	22 (28.2)	8 (23.5)
Blood/transpl	5 (4.2)	5 (6.4)	4 (11.8)
Mother to child	2 (1.7)	2 (2.6)	2 (5.9)
Unknown	70 (58.3)	43 (55.1)	17 (50.0)
Place of infection			
Norway	31 (25.8)	16(20.5)	5 (14.7)
Abroad	29 (24.2)	23 (29.5)	12(35.3)
Unknown	60 (50.0)	39 (50.0)	17 (50.0)
Total	120 (100.0)	78 (100.0)	34 (100.0)

*Presence of category I resistance to one or several drugs according to HCV-Glue

** Active substances that were in use in 2025 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 2025 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 2023 and 2024, for comparison.

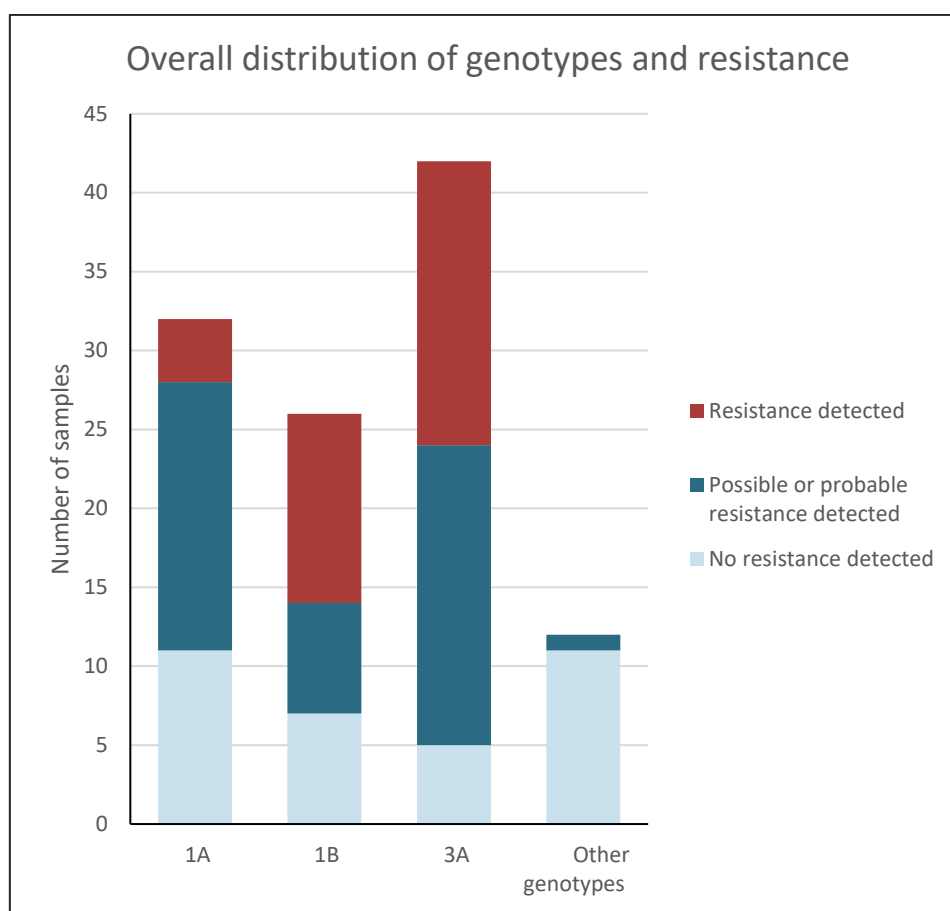


Figure 8.1. Overall distribution of genotypes and resistance in samples analysed for surveillance in 2025 (n=120).

Unknown genotypes are not included. Resistance is shown for active substances that were in use in Norway in 2025: glecaprevir, grazoprevir, voxilaprevir, elbasvir, ledipasvir, pibrentasvir, velpatasvir and sofosbuvir.

Among the DAAs that were prescribed in Norway during 2023-25 (Figure 3.6), a prevalence of resistance above 10% was only detected for sofosbuvir and elbasvir in 2025. For sofosbuvir, the prevalence of resistance for genotype 1B and 3A decreased compared to 2025 (from 54% to 42% for 1B and 57% to 36% for 3A), and for elbasvir the prevalence of resistance for genotype 1B was 19%. For other active substances, prevalence of resistance remained low, and notably, concurrent resistance against all substances in currently registered combination drugs was very rare ($\leq 5\%$ for all genotypes) (Figure 8.3).

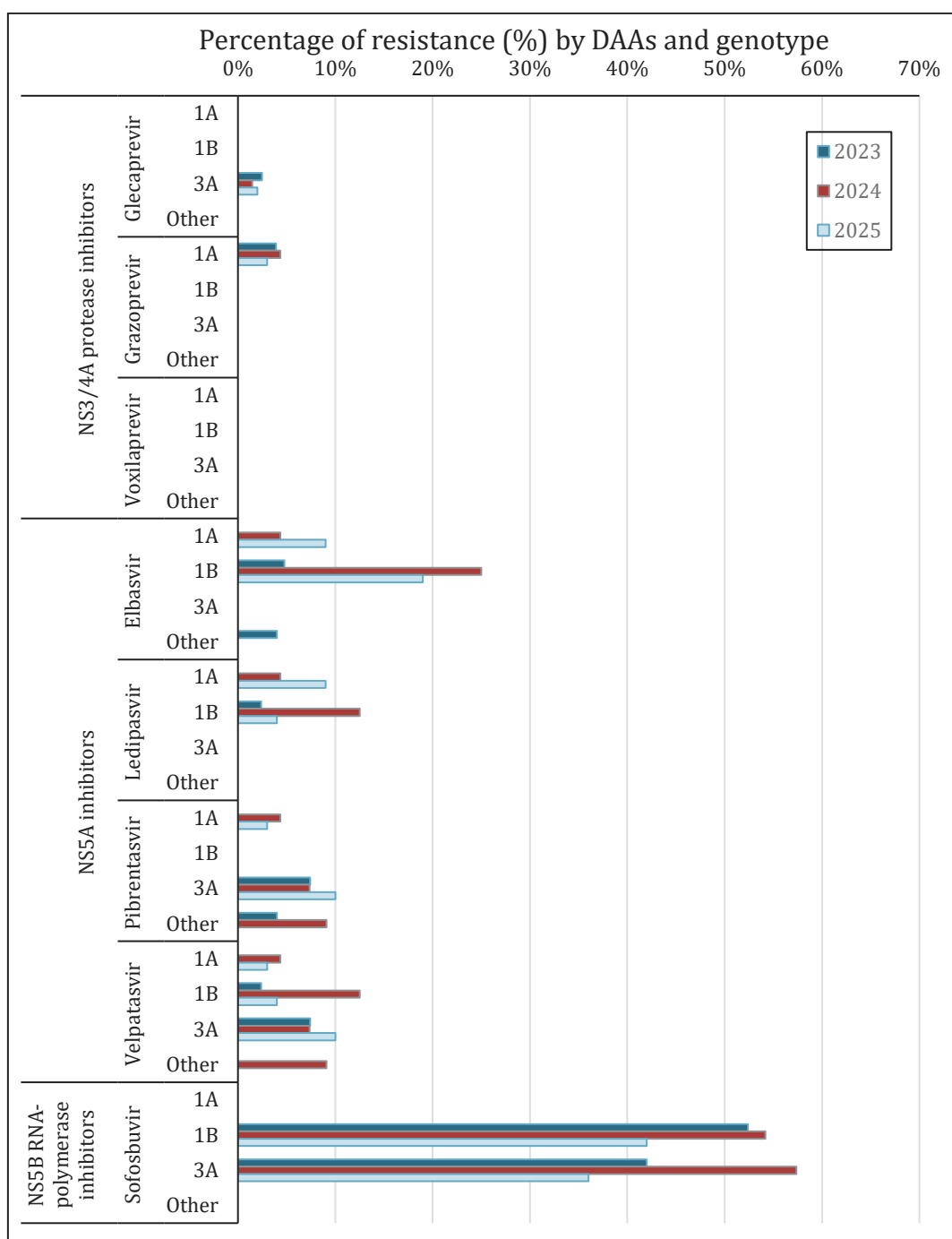


Figure 8.2. Percentage of samples with category I resistance (%) by DAAs and genotype.

The figure presents prevalence of resistance by DAA (only drugs currently in use) and genotype among analysed surveillance samples in 2023 (n=199), 2024 (n=130) and 2025 (n=120), 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.

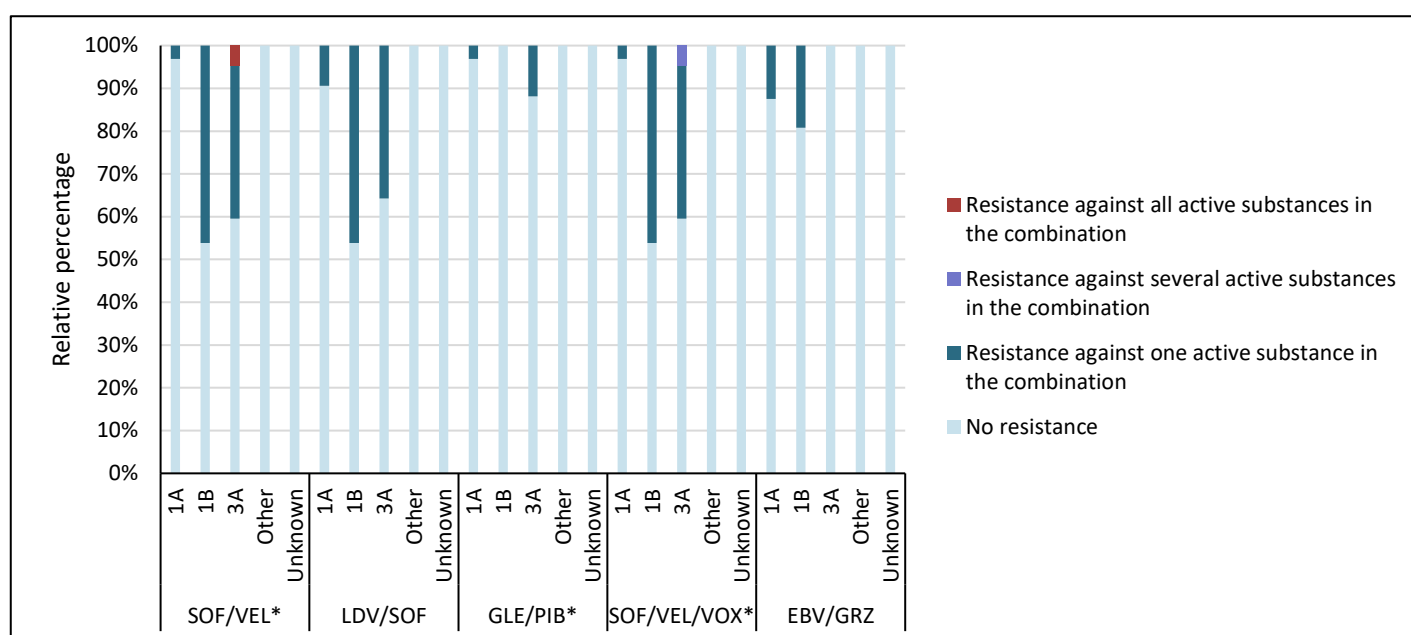


Figure 8.3. Prevalence of resistance (%) against the currently registered combination drugs in Norway in 2025.

The figure presents prevalence of resistance by combination drug and genotype among analysed surveillance samples in 2025 (n=120). The percentage of samples within each genotype with detected resistance against either one or two active substances in the combination are shown per main genotype. The total distribution of genotypes was 1A (n=32), 1B (n=26), 3A (n=42), Other (n=12). "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; GRZ: 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. The percentage of samples analysed for surveillance which were from patients infected in Norway has decreased between 2022 and 2025: 47% – 36% – 35% – 26%. A similar trend can be seen among overall notified cases to MSIS in the same period: 39% – 29% – 28% – 24%. In 2025, the majority of patients (54%) born outside of Norway were born in Ukraine (3).

Among the DAAs that were prescribed in Norway during 2023-25 (Figure 3.6), a prevalence of resistance above 15% was only detected for sofosbuvir and elbasvir. For sofosbuvir, prevalence of resistance decreased in 2025, although still high at around 40% for genotypes 1B and 3A. Resistance against elbasvir was most prevalent (19%) for genotype 1B, although this was a decrease after a marked increase in 2024. For other active substances, prevalence of resistance remained low (Figure 8.2).

Five drug combinations were registered for use in Norway in 2025. The updated recommendations from The Norwegian Hospital Procurement Trust (4), 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 if liver transplantation is not an option (5). 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, only detected for sofosbuvir/velpatasvir in 2/42 (5%) of genotype 3A samples (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) compared to patients without RAS, while the absolute probability of achieving SVR may still be high (6). 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 still a high, but decreasing, prevalence of RASs affecting sofosbuvir, and to a lesser degree elbasvir (deregistered in 2025). 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 emerging resistance patterns affecting multiple components of currently recommended DAA regimens. Although the clinical impact of such patterns is often limited by the high efficacy of modern retreatment regimens, their detection may help identify emerging threats to treatment effectiveness and inform future treatment recommendations.

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9 CYTOMEGALOVIRUS

Fact box: Human cytomegalovirus (CMV) drug resistance	
Treatment	Mono therapy is standard. Unless there are contraindications, the first choice is the nucleoside analogue ganciclovir/valganciclovir. In cases with contraindications or resistance, alternative drugs are nucleotide analogues cidofovir and foscarnet, and the UL-97 kinase inhibitor maribavir. The CMV terminase complex inhibitor letermovir is approved for prophylaxis in stem cell transplanted patients.
Resistance testing method	Genotypic assays based on Sanger sequencing. The sequences are analysed for amino acid substitutions associated with drug resistance. In Norway, all CMV drug resistance tests are performed at the National Reference laboratory for CMV at the Department of Microbiology at the Oslo University Hospital, Rikshospitalet.
Target gene	CMV kinase (UL97), DNA polymerase (UL54), and CMV terminase complex (UL56).
Clinical 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 characterised by comparing phenotypic and genotypic test results. For routine testing only genotypic tests, looking for known resistance mutations, are applicable. Resistance to ganciclovir develops by mutations in the viral kinase CMV UL97 and/or the DNA polymerase CMV UL54 gene. Normally resistance mutations in the CMV UL97 gene precede mutations in the CMV UL54 gene, as ganciclovir is first choice of treatment, and the fitness cost of mutations in CMV UL54 is higher. Therefore, as a standard, the UL97 gene is investigated first. Maribavir resistance mutations are also located 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 2025

In 2025, 18 samples from 16 patients were analysed for CMV antiviral drug resistance. Out of the 18 samples, relevant resistance mutations were detected in two samples (Table 9.1). In 2025, five samples were analysed for mutations in the UL54 gene, and one sample was analysed for mutations in the UL56 gene. 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 2021 - 2025

CMV-variants resistant to antivirals	2021	2022	2023	2024	2025
Total samples analysed	19	24	17*	23**	18***
Number of samples with CMV resistance mutations	5	5	1	3	2
Samples with UL97 mutations	5	5	1	3	2
Samples with UL54 mutations	1	1	1	1	0
Samples with UL56 mutations	-	-	0	0	0

*17 samples from 14 patients were analysed. **23 samples from 18 patients were analysed. ***18 samples from 16 patients were analysed.

Table 9.2: CMV resistance mutations in samples tested in 2025

Case	UL97 substitutions	UL54 substitutions	Resistance
1	C592G	NA*	Ganciclovir low; Maribavir sensitive
2	M460I		Ganciclovir moderate; Maribavir sensitive

*Not analysed due to insufficient DNA

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 categorised 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.

Tabell 9.3: CMV resistance associated substitutions and deletions in samples tested in 2015-2025

Substitution/deletion	Number of samples
UL97	
L595S	17
A594V	11
C603W, H520Q, L595W	4
M460I, M460V	3
C592G, Deletion codon 599-603.	2
A594P, C607Y, C630Q, Deletion codon 597-599, K599R, L959S, T409M	1
UL54	
P522S	3
D588N, E756EK, K513N	2
A505V, A809V, A987R, E745D, E756D, L501I, L545S, T503I	1

Conclusions

Despite an increase in the use of ganciclovir for therapeutic and prophylactic treatment of CMV-infections, drug resistance mutations are 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.

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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).
Clinical 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. Varicella zoster virus samples from Norway are also submitted to Sahlgrenska University Hospital for drug resistance testing. However, a very small number of samples have been submitted for analysis and no resistance was detected.

Surveillance data 2025

In 2025, a total of 10 samples from 8 patients were submitted for HSV drug resistance. Among the 8 patient samples, resistance mutations that conferred resistance to aciclovir were detected in 3 (38%) of the samples (Table 10.1). One of these samples had additional resistance against other HSV antiviral drugs, while another had a mutation of unknown relevance (D163G) (1). In addition, one sample contained a known polymorphism (G985A), that is most likely without clinical significance.

Table 10.1. HSV resistance associated substitutions/truncations detected in 2025

Patient sample	HSV-type	Sample material	TK substitutions/truncations	DNA pol substitutions	Resistance
1	HSV-1	Secretion	L315S		Aciclovir resistance, Brivudin resistance, Penciclovir resistance
2	HSV-2	Secretion	R177W, D163G		Aciclovir resistance
3	HSV-2	Other	D229stop		Aciclovir resistance
4	HSV-1	Vesicle		G985A	

Conclusions

Surveillance of drug-resistant HSV remains limited in Norway, and the number of patient samples submitted for resistance testing in 2025 was slightly lower than in 2024. Among the 8 samples analysed, 38% harboured mutations associated with resistance to aciclovir. However, the limited number and highly selected nature of the samples make it impossible to accurately determine the true prevalence of HSV drug resistance in this patient population in Norway. Resistance may be underreported in immunocompromised patients with HSV reactivation due to limited resistance testing.

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