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EFFICACY OF ANTIVIRAL CHEMOTHERAPY FOR RETROVIRUS-INFECTED CATS

What does the current literature tell us?

Katrin Hartmann

Retroviral infections and the indication for antiviral chemotherapy

Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) are among the most common infectious agents of cats.[1–5] Retroviral tests diagnose only infection, and not clinical disease,[1,2] and cats infected with FeLV or FIV can live for many years.[6,7] Therefore, a decision regarding treatment or euthanasia should never be based solely on the presence of a retrovirus infection.[8] FIV- and FeLV-infected cats suffer from the same diseases that occur in cats free of retrovirus infections and, as such, the clinical signs in an individual cat might not be related to retrovirus infection at all.[9,10]

Figure 1 This cat with dual FIV and FeLV infection is in the high risk group of cats with outdoor access and a history of fighting

The retrovirus status of all cats should be known (Figure 1).[8] If a cat is diagnosed with a retrovirus infection in a multi-cat household, all cats in that household need to be tested to determine their retrovirus status.[8] If positive and negative cats are identified in the same household, the owner must be informed of the potential risk to uninfected cats and be advised that the best method of avoiding spread is to isolate the infected cat(s) and prevent them from interacting with housemates.[8] The risk of transmission, however, is not very high for either infection.[3–5]

Retrovirus-infected cats need special management and care, and provided they receive this can live for many years in good health. Most retrovirus-infected cats are well managed with symptomatic therapy.[3–5] Specific treatment recommendations for individual cats are summarised in the boxes on page 926. Immune modulators are commonly used in retrovirus-infected cats. Results of uncontrolled studies sometimes suggest dramatic clinical improvement with these compounds, but these effects are usually not observed in properly designed trials, and clear evidence of efficacy is lacking.[4]

Antiviral chemotherapy is only indicated in exceptional cases of FIV and FeLV infection, due to lack of proven efficacy of many antivirals and also their toxicity.[4] An update on published treatment studies is provided in this review, focusing on those drugs that are available on the market and, thus, could potentially be used in cats.

Global importance: The two feline retroviruses, feline immunodeficiency virus (FIV) and feline leukaemia virus (FeLV), are global and widespread, but differ in their potential to cause disease.
Viral infection – FIV: FIV, a lentivirus that shares many properties with human immunodeficiency virus (HIV), can cause an acquired immune deficiency syndrome, which predisposes cats to other infections, stomatitis, neurological disorders and tumours. Although secondary infections are common, specific opportunistic infections or acquired immunodeficiency virus-defining infections, such as those that occur with HIV, are not commonly reported in FIV-infected cats. In most naturally infected cats, FIV does not cause a severe clinical syndrome; with appropriate care, FIV-infected cats can live many years before succumbing to conditions unrelated to their FIV infection. Thus, overall survival time is not necessarily shorter than in uninfected cats, and quality of life is usually high over many years or lifelong.
Viral infection – FeLV: FeLV, an oncornavirus, is more pathogenic than FIV. Historically, it was considered to account for more disease-related deaths and clinical syndromes in cats than any other infectious agent. Recently, the prevalence and importance of FeLV have been decreasing, mainly because of testing and eradication programmes and the use of FeLV vaccines. Progressive FeLV infection can cause tumours, bone marrow suppression and immunosuppression, as well as neurological and other disorders, and leads to a decrease in life expectancy. However, with appropriate care, many FeLV-infected cats can also live several years with a good quality of life.
Practical relevance: A decision regarding treatment or euthanasia should never be based solely on the presence or absence of a retrovirus infection. Antiviral chemotherapy is of increasing interest in veterinary medicine, but is still not used commonly.
Evidence base: This article reviews the current literature on antiviral chemotherapy in retrovirus-infected cats, focusing on drugs that are currently available on the market and, thus, could potentially be used in cats.

Katrin Hartmann
DrMedVet DrHabil DipECVIM-CA
Medizinische Kleintierklinik,
Ludwig-Maximilians-Universität München,
Veterinärstrasse 13, 80539 Munich, Germany

Email: vorstandsassistenz@
medizinische-kleintierklinik.de

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Management and treatment approach for an FIV-infected cat

If no clinical signs are present

- Don't treat
- Keep the cat strictly indoors

If clinical signs are present

- Always look for underlying diseases first (FIV itself is usually not responsible for the clinical signs)
- Treat underlying disease(s)

Treatment of FIV-infected cats with stomatitis

- Avoid glucocorticoids
- First try zidovudine (5–10 mg/kg PO q12h), antibiotics and feline IFN-ω (1 x 10^6 IU SC q24h)
- If this does not work, removal of all teeth (with radiographic confirmation of root removal) is recommended

Treatment of FIV-infected cats with neurological signs

- Look for any underlying diseases causing the neurological signs
- Treat underlying disease(s)
- If no underlying disease is present (and the neurological signs are assumed to be caused by FIV), treat with zidovudine (5–10 mg/kg PO q12h)

Treatment of FIV-infected cats with recurring infections

- Treat recurring infections aggressively
- Check virus load by quantitative RNA PCR
- Check CD4+ and CD8+ cell count
- If virus load is high and CD4+ cells are low, consider treatment with antivirals; eg, plerixafor (0.5 mg/kg SC q12h) and/or zidovudine (5–10 mg/kg PO q12h)

These recommendations are based on the expert opinion of the author (EBM grade IV – see footnote to Table 1 for explanation)

Management and treatment approach for an FeLV-infected cat

If no clinical signs are present

- Don't treat
- Keep the cat strictly indoors

If clinical signs are present

- Always look for underlying diseases first (FeLV itself might not be responsible for the clinical signs; eg, secondary infections may be present)
- Treat underlying disease(s)

Treatment of FeLV-infected cats with anaemia

- Look for underlying diseases causing the anaemia (eg, *Mycoplasma* species infection)
- Treat underlying disease(s)
- Give blood transfusions if anaemia is severe
- If no underlying disease is present, glucocorticoids might be considered (because anaemia in FeLV-infected cats can have an immune-mediated origin, and some cats respond)

Treatment of FeLV-infected cats with lymphoma

- Use chemotherapeutic drug protocols (eg, COP [cyclophosphamide, vincristine, prednisolone], chlorambucil)
- Inform owners about the more guarded prognosis due to FeLV infection

Treatment of FeLV-infected cats with neurological signs

- Look for underlying diseases causing the neurological signs (eg, lymphoma, *Cryptococcus* species infection, toxoplasmosis)
- Treat underlying disease(s)
- If no underlying disease is present (and the neurological signs are assumed to be caused by FeLV) treat with zidovudine (5 mg/kg PO q12h)

Treatment of FeLV-infected cat with recurring infections

- Treat recurring infections aggressively
- Consider feline IFN-ω (1 x 10^6 IU SC q24h)

These recommendations are based on the expert opinion of the author (EBM grade IV – see footnote to Table 1 for explanation)

Classification of antiviral drugs

Most antivirals used in cats are licensed for humans and are specifically intended for treatment of human immunodeficiency virus (HIV) infection. Some of these drugs can be used to treat FIV infection because most enzymes of FIV and HIV have similar sensitivities to a range of inhibitors. Many drugs, such as nucleoside analogues, are less effective against FeLV,[4] as FeLV is not as closely related to HIV.

Antiviral compounds interfere with the viral replication cycle and can be grouped into different classes depending on the specific step at which they exert their activity.[11–13] These drug classes are summarised in Table 1.

The most common antiretroviral drugs interfere with reverse transcription by inhibiting the retroviral enzyme reverse transcriptase (RT). Three classes of these RT inhibitors can be distinguished: nucleoside analogues (the most widely used antiviral compounds); nucleotide analogue RT inhibitors; and non-nucleoside RT inhibitors.[12] The last are usually highly selective for HIV and, thus, not useful in veterinary medicine.[14,15] Drugs with a broader spectrum inhibit other viral enzymes, such as DNA or RNA polymerases, and thus interfere with virus genome replication or inhibit proteinases that are important for the splitting of precursor proteins during

Table 1 Treatment options (antiviral drugs) for retrovirus-infected cats, with EBM grading of available efficacy data

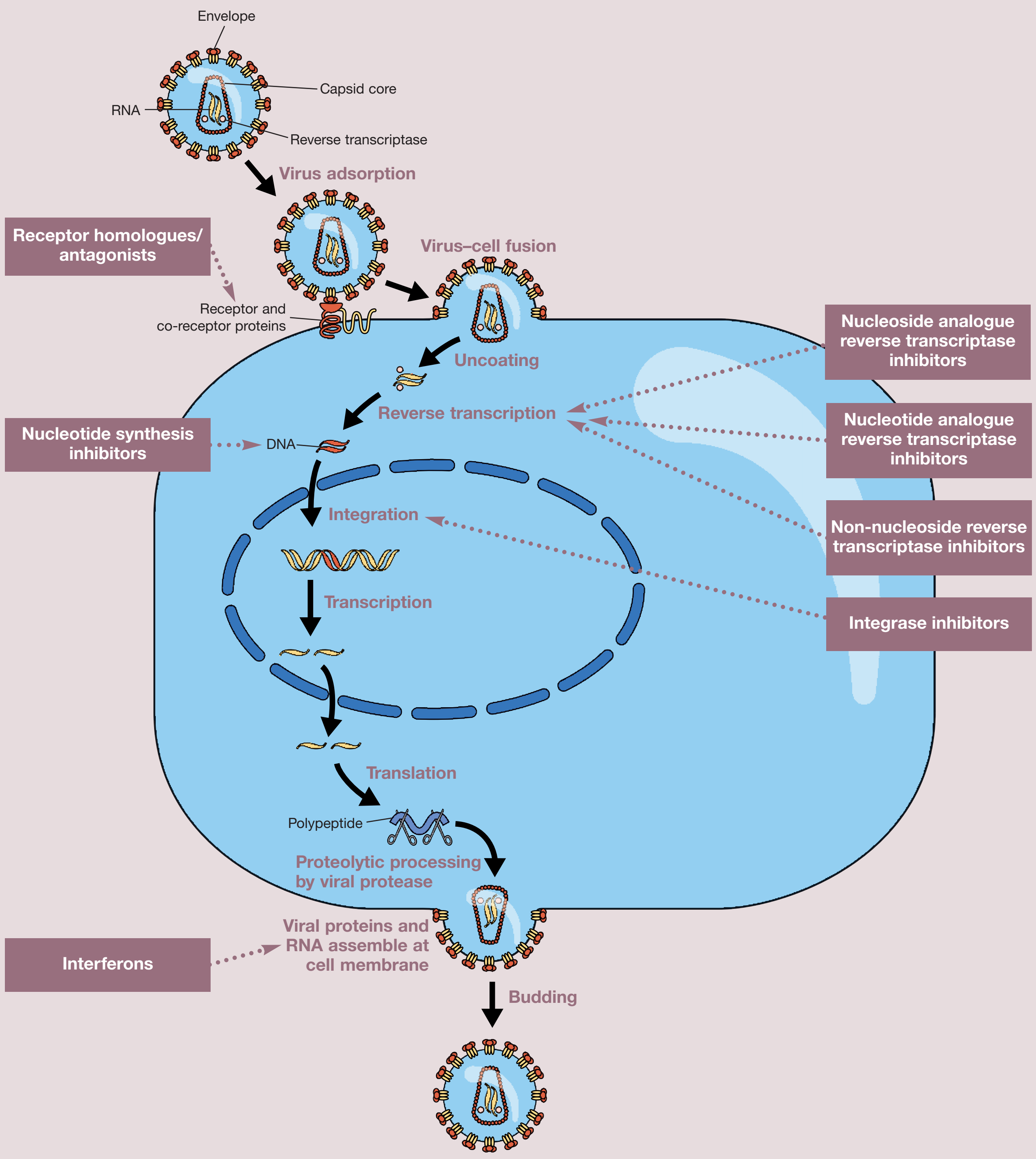
Drug	Infection	Efficacy in vitro	Controlled study in vivo	Efficacy in vivo	Author's personal opinion	EBM grade (I–IV)*
Nucleoside analogue reverse transcriptase inhibitors						
Zidovudine (AZT)	FIV	Yes	Yes	Yes	Effective in some cats (eg, with stomatitis, neurological disorders)	I
	FeLV	Yes	Yes	No	Not very effective	I
Stavudine (d4T)	FIV	Yes	No	ND	Possibly effective, but no data in cats	IV
	FeLV	ND	No	ND	Possibly effective, but no data in cats	IV
Didanosine (ddI)	FIV	Yes	Yes	Yes	Effective in one experimental study, but neurological side effects	II
	FeLV	Yes	No	ND	Possibly effective, but no data in cats	IV
Zalcitabine (ddC)	FIV	Yes	No	ND	Possibly effective, but toxic	IV
	FeLV	Yes	Yes	No	Not very effective, and toxic	II
Lamivudine (3TC)	FIV	Yes	Yes	No	Not very effective, and toxic in high dosages	II
	FeLV	No	No	ND	Possibly effective, but toxic	IV
Nucleotide analogue reverse transcriptase inhibitors						
Adefovir (PMEA)	FIV	Yes	Yes	No	Effective in some cats, but relatively toxic	I
	FeLV	Yes	Yes	No	Poorly effective, and relatively toxic	I
Tenofovir (PMPA)	FIV	Yes	No	ND	Possibly effective, but likely also relatively toxic	IV
	FeLV	Yes	No	ND	Possibly effective, but likely also relatively toxic	IV
Non-nucleoside reverse transcriptase inhibitors						
Suramin	FIV	No	No	ND	Possibly effective, but too toxic	IV
	FeLV	No	No	ND	Weak efficacy in uncontrolled experimental studies	III
Nucleotide synthesis inhibitors						
Foscarnet (PFA)	FIV	Yes	No	ND	Effective in vitro, but too toxic	IV
	FeLV	Yes	No	ND	Effective in vitro, but too toxic	IV
Ribavirin (RTCA)	FIV	Yes	No	ND	Possibly effective, but too toxic	IV
	FeLV	Yes	No	ND	Possibly effective, but too toxic	IV
Receptor homologues/antagonists						
Plerixafor (AMD3100)	FIV	Yes	Yes	Yes	Some effect in a study in privately owned cats; thus, can be considered	I
	FeLV	ND	No	ND	Very likely ineffective	IV
Integrase inhibitors						
Raltegravir	FIV	Yes	No	ND	Possibly effective	IV
	FeLV	Yes	No	ND	Mild effect in one uncontrolled experimental study	III
Interferons						
Human interferon-α (IFN-α)						
SC high dose	FIV	Yes	No	ND	Likely ineffective	IV
	FeLV	Yes	Yes	No	Ineffective	I
PO low dose	FIV	Yes	Yes	Yes	Some effect (more likely on secondary infections)	I
	FeLV	Yes	Yes	No	Ineffective	I
Feline interferon-ω (IFN-ω)						
SC high dose	FIV	Yes	Yes	Yes	Some effect (more likely on secondary infections)	I
	FeLV	Yes	Yes	Yes	Some effect (more likely on secondary infections)	I
PO low dose	FIV	Yes	No	ND	Potentially some effect (more likely on secondary infections)	III
	FeLV	Yes	No	ND	Potentially some effect (more likely on secondary infections)	IV

FIV = feline immunodeficiency virus; FeLV = feline leukaemia virus; ND = not determined; SC = subcutaneous; PO = oral

*EBM grades used according to the European Advisory Board on Cat Diseases (ABCD):

I = Best evidence, comprising data obtained from properly designed, randomised, controlled clinical trials in the target species (cats)
II = Data obtained from properly designed, randomised, controlled studies in the target species (cats) with spontaneous disease in an experimental setting
III = Data based on non-randomised clinical trials, multiple case series, other experimental studies, and dramatic results from uncontrolled studies
IV = Expert opinion, case reports, studies in other species, pathophysiological justification

viral assembly. Other classes of drugs target viral entry by binding to specific receptors that the virus uses for adsorption; by acting as fusion inhibitors, preventing conformational changes by the virus necessary for the fusion process; or by interfering with viral uncoating.[4,11] These various mechanisms of action are illustrated below.



Replication cycle of a retrovirus and mechanism of action of different antiviral agents

Diagram adapted from De Clercq (2009)[12]

Nucleoside analogue reverse transcriptase inhibitors

Nucleoside analogues are similar molecules to the 'true' nucleosides; equally, they have to be phosphorylated intracellularly to become active compounds. Because of their structural similarities, they can bind to the active centre of enzymes (eg, RT, other polymerases) and block enzyme activity. Many of these analogues are also integrated into elongating DNA or RNA strands, but because of small differences in molecular structure, this leads to chain termination or non-functional nucleic acids.[12,16,17] Nucleoside analogues are accepted as false substrates not only by viral enzymes, but also by cellular enzymes, which largely accounts for their toxicity.[18]

✤ **A nucleoside** consists of a nitrogenous base covalently attached to a sugar (ribose in RNA, 2-deoxyribose in DNA)

✤ **A nucleotide** consists of a nitrogenous base, a sugar and a phosphate group

A nucleic acid (RNA and DNA) contains a chain of nucleotides covalently linked together to form a sugar–phosphate backbone with protruding nitrogenous bases. Prior to integration of these nucleotides (or monophosphates) into the nucleic acid, three phosphate groups have to be bound to the nucleoside (triphosphates), two of which are removed, releasing energy during elongation of the nucleic acid chain.[12]

Zidovudine

Zidovudine (3'-azido-2',3'-dideoxythymidine, AZT) was first synthesised in the 1960s[19] as a potential anticancer drug. In 1985 it was shown to be effective against HIV,[20] and 2 years later it was the first drug to be approved for the treatment of HIV infection.[21]

Zidovudine not only inhibits RT, but also cellular polymerases, and this leads to bone marrow suppression. Thus, regular blood cell counts are necessary during zidovudine treatment because non-regenerative anaemia is a common side effect.[22] A complete blood count should be performed weekly for the first month. If values are stable after the first 4 weeks, a monthly recheck is recommended. Cats with bone marrow suppression should not be treated with zidovudine. A study in which FIV-infected cats were treated with zidovudine for 2 years has shown that the drug is well tolerated in most cats.[23] Haematocrit can decline within 3 weeks of initiating treatment to approximately 60% of baseline levels, but recovers in most cases, even without discontinuation of treatment. If the haematocrit drops below 20%, discontinuation is recommended, and anaemia usually resolves within a few days.[23] Other side effects in cats, including vomiting or anorexia, are rare.

✤ **FIV** Zidovudine inhibits FIV replication in vitro[22,24–36] and in vivo;[22,37,38] it reduces plasma viral load, improves the immunological and clinical status of FIV-infected cats, increases quality of life, and prolongs life expectancy.[39] In placebo-controlled trials, zidovudine improved stomatitis (Figure 2) and increased the CD4/CD8 ratio in naturally FIV-infected cats (EBM grade I).[22,23,37] Neurological abnormalities also tend to respond favourably to treatment with zidovudine. In some cats with FIV-associated neurological signs, a marked improvement occurs within the first few days of therapy. As is the case in HIV, evidence exists that FIV can become resistant to nucleoside analogues. Zidovudine-resistant FIV mutants can arise after only 6 months' use, with a single point mutation in the FIV gene being responsible for the resistance.[32]

✤ **FeLV** Zidovudine is effective against FeLV in vitro.[40–45] It has also been shown to be effective in treating cats with early experimental infection. When treated less than 1 week after challenge, cats were protected from bone marrow infection and persistent viraemia (EBM grade II).[45,46] In a study in which cats naturally infected with FeLV were treated with zidovudine for 6 weeks, however, treatment did not lead to a significant improvement in clinical, laboratory, immunological or virological parameters (EBM grade I).[47] Thus, overall therapeutic efficacy of zidovudine is less promising in FeLV-infected cats than in FIV-infected cats.

Stavudine

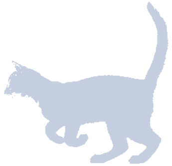
Stavudine (2',3'-didehydro-2',3'-dideoxythymidine, d4T) is another drug with efficacy against HIV,[48–51] and was approved for treatment of HIV infection in 1994.

✤ **FIV** Stavudine is active against FIV in vitro.[28–30,33,36,44,52] Mutants of FIV that are resistant to stavudine and cross-resistant to several other antivirals, including zidovudine, have been detected. Resistance is caused by a single point mutation in the RT-encoding region of the *pol* gene.[36] No in vivo data in FIV-infected cats are available.

✤ **FeLV** The activity of stavudine against FeLV has not been determined.

Figure 2 **Severe stomatitis due to FIV infection. The nucleoside reverse transcriptase inhibitor, zidovudine, has a proven (EBM grade 1) effect on stomatitis in FIV-infected cats**

Nucleoside analogues are accepted as false substrates not only by viral enzymes, but also by cellular enzymes, which causes their toxicity.



Didanosine

Didanosine (2',3'-dideoxyinosine, ddI) is also used to treat HIV infection in humans. It was shown to be active against HIV in 1986,[53] and was the second drug to be approved for treatment of HIV infection. It has been marketed since 1991.[12]

✤ **FIV** Didanosine is active against FIV in vitro.[25,28,30–34,36,54] In one experimental study, FIV replication was significantly suppressed in animals treated with didanosine, but treatment contributed to the development of antiretroviral toxic neuropathy (EBM grade II).[55]

✤ **FeLV** Didanosine is also active against FeLV in vitro,[42,44] but its in vivo efficacy is unknown.

Zalcitabine

Zalcitabine (2',3'-dideoxycytidine, ddC) was previously used to treat HIV infection in humans.[56] It was shown to be active against HIV in 1986,[53] and was approved by the US Food and Drug Administration in 1992. However, it ceased being marketed in 2006. Due to its toxicity, zalcitabine should not be used at concentrations over 5 mg/kg/h by continuous infusion in feline patients.[57]

✤ **FIV** In vitro, antiviral efficacy has been demonstrated against FIV.[25–27,29,31–33,36,54] A mutant of FIV that is resistant to zalcitabine was selected in cell culture and showed cross-resistance to other antiviral compounds.[54] No in vivo data exist demonstrating efficacy in FIV-infected cats.

✤ **FeLV** Zalcitabine is effective against FeLV in vitro and has been used in experimental studies to treat FeLV-infected cats.[44,57–59] It has a very short half-life and, therefore, has been administered via either an intravenous (IV) bolus or controlled-release subcutaneous (SC) implants.[57] Controlled-release delivery of zalcitabine inhibited de novo FeLV replication and delayed the onset of viraemia after experimental infection; however, when treatment was discontinued an equivalent incidence and level of viraemia was established rapidly.[58] In a study evaluating the prophylactic antiviral activity of zalcitabine against FeLV, the drug was administered by continuous IV infusion for 28 days. Higher doses were extremely toxic, causing death in 8/10 cats. Lower doses caused thrombocytopenia. Only 1/10 cats remained FeLV antigen-negative when receiving the low dose, although the onset of viraemia was delayed for several weeks (EBM grade II).[57]

Lamivudine

Lamivudine (2R,cis-4-amino-l-[2-hydroxymethyl-1,3-oxathiolan-5-yl]-[1H]-pyrimidin-2-one, 3TC) is also an approved anti-HIV drug.

✤ **FIV** Lamivudine is active against FIV in vitro.[24,30,38] A combination of zidovudine and lamivudine was shown to have synergistic anti-FIV activities in cell culture.[38] FIV mutants resistant to lamivudine containing a point mutation in the RT gene were selected in vitro and showed cross-resistance to zidovudine.[32] In one in vivo study, cats experimentally infected with FIV were treated with a high dose zidovudine/lamivudine combination.[38] Treatment protected some cats when started before infection, but the zidovudine/lamivudine combination had no anti-FIV activity in chronically infected cats. Severe side effects, including fever, anorexia and marked haematological changes, were observed in some of the cats receiving the high dose dual-drug treatment (EBM II).[38]

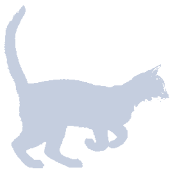
✤ **FeLV** No data on the anti-FeLV activity of lamivudine are available.

Nucleotide analogue reverse transcriptase inhibitors

Nucleotide analogue RT inhibitors interact with the catalytic site of the RT and are incorporated into the elongating proviral DNA strand, subsequently causing strand termination.[12,15] They compete with the natural nucleotides and thus function as competitive substrate inhibitors. In these respects they are similar to nucleoside RT inhibitors. However, in contrast to nucleoside RT inhibitors, nucleotide RT inhibitors contain a phosphate group and therefore need only two intracellular phosphorylation steps to be converted into their active forms.[12] This circumvents the first (and often rate-limiting) phosphorylation step.[15,60]

Adefovir

Adefovir (2-[6-amino-9H-purin-9-yl]-ethoxymethyl-phosphonic acid, PMEA) is active against herpesviruses, hepadnaviruses (hepatitis B) and retroviruses.[61] Adefovir is not licensed as an HIV drug, but is currently



Nucleotide RT inhibitors need only two intracellular phosphorylation steps for conversion into their active form, circumventing the first (and often rate-limiting) phosphorylation step required by nucleoside RT inhibitors.

approved to treat chronic hepatitis B in an orally available form (bis-POM PMEA).

Adefovir belongs to the acyclic nucleoside phosphonates, in which the alkyl side chain of purines and pyrimidines is linked to a modified phosphate moiety and a C-P phosphonate linkage replaces the normal O5'-P phosphate linkage.[60] This phosphonate bond is non-hydrolysable, which makes it more difficult to cleave off these compounds once they have been incorporated at the 3'-terminal end of the elongating proviral DNA strand.[12]

✤ **FIV** Adefovir inhibits FIV replication in vitro.[62] Several studies have investigated the efficacy of adefovir in cats either experimentally or naturally infected with FIV.[10,63–67] Some of these studies have reported some efficacy, but also severe side effects, mainly in the form of non-regenerative anaemia. More recently, adefovir was used in FIV-infected cats in a 6 week placebo-controlled, double-blind clinical trial; 10 cats received the drug (10 mg/kg SC twice weekly) and 10 cats received placebo.[68] There was no decrease in proviral or viral loads in treated cats and they developed a progressive anaemia, which is a common adverse effect of nucleotide analogues (EBM grade I).[68]

✤ **FeLV** Adefovir is active against FeLV in vitro.[69] In a study in experimentally infected cats, adefovir prevented the development of persistent FeLV viraemia if used early in the infection (EBM grade II);[69] but the drug was not effective in a placebo-controlled, double-blind study in naturally infected cats when used for 3 weeks (EBM grade I).[64]

Tenofovir

The antiviral spectrum of tenofovir (2R-1-[6-amino-9H-purin-9-yl]-propan-2-yl-oxy-methyl-phosphonic acid, PMPA) is narrower than that of adefovir, in that it does not extend to herpesviruses, but is confined to hepadnaviruses and retroviruses.[61] Tenofovir is currently the only nucleotide RT inhibitor approved for the treatment of HIV infection; it is marketed as the prodrug tenofovir disoproxil fumarate.[60] Since it was licensed in 2001, it has become one of the most commonly used drugs in HIV therapy.[12,17]

✤ **FIV** Tenofovir is effective against FIV in vitro,[35,70] but in vivo studies have not been published to date.

✤ **FeLV** Tenofovir has also been shown to be effective against FeLV in vitro.[71] However, in vivo data in FeLV-infected cats are likewise not available.

Non-nucleoside reverse transcriptase inhibitors

Most of the non-nucleoside RT inhibitors are highly specific for HIV. Unlike nucleoside and nucleotide RT inhibitors, which bind to the catalytic site of RT, non-nucleoside RT inhibitors interact with an allosteric site of the enzyme[12] and are not incorporated into the proviral DNA strand.[15] They are classified as non-competitive inhibitors of RT and do not require intracellular activation to inhibit the enzyme.[15,16]

Non-nucleoside RT inhibitors are a group of structurally diverse compounds that all bind a single site in the HIV RT enzyme.[72] The interaction with the allosteric site, which is located in close proximity to the catalytic site, leads to a number of conformational changes within the RT.[72,73] Among other effects, these changes cause a decrease in the interaction between the DNA primer and the polymerase domain of the enzyme and, thus, interfere with virus replication.[72,73]

The classical non-nucleoside RT inhibitors are not active against FIV and FeLV; however, there is one old drug, suramin, that can be classified as a non-nucleoside RT inhibitor and has been used in veterinary medicine.

Suramin

Suramin (1-[3-benzamido-4-methylbenzamido]naphthalene-4,6,8-trisulfonic acid sym-3'-urea sodium salt), a sulfated naphthylamine and trypan red derivative, is one of the oldest known antimicrobial agents. It is used as a antitrypanosomal agent as well as for the treatment of some (eg, prostatic) tumours.[74] It also has an inhibitory effect on the RT activity of retroviruses and has been used in patients with HIV infection.[75] Suramin inhibits RT by interacting with the template–primer binding site of the enzyme. It competitively binds to the primer binding site and inhibits the template–primer binding that is necessary for DNA prolongation; thus, suramin can be classified as a non-nucleoside RT inhibitor.[76]

Suramin is associated with a significant number of severe side effects in humans: nausea and anaphylactic shock as immediate reactions during administration; peripheral neuritis leading to palmar–plantar hyperaesthesia, photophobia, skin reactions, agranulocytosis, haemolytic anaemia and destruction of the adrenal cortex as later side effects.[74,75,77–79] Severe side effects have to be expected in cats as well.

Most of the non-nucleoside RT inhibitors are highly specific for HIV. Only an old drug of this class, suramin, has been used in veterinary medicine.

Nucleotide synthesis inhibitors have a broad spectrum of activity against DNA and RNA viruses, but also marked toxicity.

✤ **FIV** The efficacy of suramin against FIV is unknown.

✤ **FeLV** Suramin has not been investigated against FeLV in vitro, but has been used to treat FeLV-infected cats, although only a limited number of cats have been evaluated in uncontrolled studies. In one study, serum viral infectivity ceased transiently in two cats with naturally acquired FeLV infection but returned to high levels approximately 14 days after treatment was stopped (EBM grade III).[80] In another study, six anaemic FeLV-infected cats received suramin and, within 4–14 days, erythropoiesis improved. However, progenitor cells remained infected (EBM grade III).[81]

Nucleotide synthesis inhibitors

Nucleotide synthesis inhibitors interfere with DNA and RNA synthesis, but not by mimicking nucleosides. They usually have a broad spectrum of activity, but also marked toxicity. Foscarnet and ribavirin have been used in veterinary medicine.

Foscarnet

Foscarnet (phosphonoformic acid, PFA) has a wide spectrum of activity against DNA and RNA viruses, including retroviruses. Foscarnet interferes with exchange of pyrophosphate from deoxynucleoside triphosphate during viral replication by binding to a site on RT or DNA polymerase.[82] This drug has only a short effect; after treatment is stopped, viral replication is reactivated. Foscarnet is mostly administered IV by continuous infusion because of its short half-life, a property that has also been demonstrated in cats.[83] Oral application is possible but can cause irritation of mucous membranes and oral bleeding.

Foscarnet has many side effects in humans as well as in cats, such as nephrotoxicity and myelosuppression. It is also toxic to epithelial cells and mucous membranes, and gastrointestinal side effects and ulcerations of genital epithelium can occur. In addition, it chelates cations, such that hypocalcaemia, hypomagnesaemia and hypokalaemia can develop.[84,85]

✤ **FIV** In vitro, foscarnet has been shown to be active against FIV, but foscarnet-resistant FIV strains can develop.[25] No in vivo studies have been published in the literature.

✤ **FeLV** Foscarnet is also active against FeLV in vitro,[86] but no published in vivo data exist.

Ribavirin

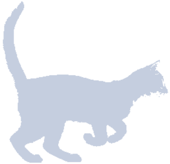
Ribavirin (1-[β-D-ribofuranosyl]-1H-1,2,4-triazole-3-carboxamide, RTCA) has marked in vitro antiviral activity against a variety of DNA and RNA viruses.[87] Ribavirin has multiple effects on virus replication, such as allowing DNA synthesis to occur, but preventing triphosphate synthesis by inhibiting the enzyme inosine monophosphate dehydrogenase (essential for synthesis of nucleotides); it thus prevents nucleotide production.[87]

Systemic application of ribavirin is limited because of side effects.[88] Side effects in cats in several studies (even using low doses) have included haemolysis, which develops as a result of sequestration of the drug in erythrocytes.[89,90] In addition, there is a dose-related toxic effect on bone marrow, primarily on megakaryocytes (resulting in thrombocytopenia and haemorrhage) and erythroid precursors (resulting in non-regenerative anaemia). With prolonged treatment or higher doses, the drug suppresses production of neutrophilic granulocytes. Liver toxicity occurs too. An attempt to decrease the toxicity of ribavirin by incorporating it into lecithin-containing liposomes and giving it at lower doses was not successful.[91]

✤ **FIV and FeLV** Ribavirin is active against many viruses in vitro, including FIV and FeLV.[33,39] No in vivo studies are published. Therapeutic concentrations are difficult to achieve because of its toxicity, and cats are extremely sensitive to the side effects.[90]

Receptor homologues/ antagonists

Receptor homologues/antagonists either bind to the virus or to the cellular receptor and thereby inhibit binding of the virus to the cell surface. Most of these drugs are highly selective for HIV and not useful for veterinary medicine. An exception are the bicyclams (eg, plerixafor), which can be used in cats with FIV infection because of similarity between HIV and FIV with respect to chemokine receptor usage.[92,93] Chemokine receptors belong to a group of seven transmembrane proteins in which signal transmission is afforded through rapid influx of calcium into the cell. They are essential co-receptors for HIV and FIV in the infection of CD4+ lymphocytes.[94] CXCR4 is the major receptor for FIV infection, but other receptors also have been shown to mediate viral binding.[95] By binding to CXCR4, bicyclams prevent interaction of CXCR4 with other ligands, thereby inhibiting the entry of HIV or FIV into the cell.[96–98]



The bicyclams (eg, plerixafor) are novel receptor homologues/ antagonists and have potential application in cats.

Plerixafor

Plerixafor (1,1'-[1,4-phenylenbismethylene]-bis[1,4,8,11-tetraazacyclotetradecane]-octachloride dehydrate, AMD3100) is the prototype compound among the bicyclams. It is not on the market as an anti-HIV drug, but is used in humans for stem cell mobilisation.[99] Plerixafor is administered to cats at a dose of 0.5 mg/kg SC q12h. Magnesium and calcium levels should be monitored regularly during treatment.[68]

✚ **FIV** Plerixafor is active against FIV in vitro.[97] Its efficacy was investigated in naturally FIV-infected cats in a placebo-controlled, double-blind clinical trial.[68] Treatment with plerixafor resulted in a significant decrease in provirus load; a decrease in serum magnesium levels was also recorded, although this did not have any clinical consequences. No development of resistance of FIV isolates to plerixafor was found during treatment (EBM grade I).[68]

✚ **FeLV** Efficacy against FeLV has not been determined, but plerixafor is likely ineffective against this retrovirus due to the different receptors that FeLV uses for cell entry.[100]

Integrase inhibitors

The enzyme integrase catalyses strand transfer (3'-end joining), which inserts both viral DNA ends into a host cell chromosome. The high degree of conservation of integrase-active sites across many retroviruses suggests that FIV and FeLV can be sensitive to integrase inhibitors.[101] The mechanism of action of these drugs is inhibition of integration of the proviral DNA that is produced by reverse transcription of the viral RNA genome.[71]

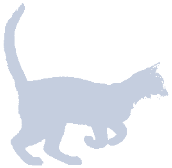
Raltegravir

Raltegravir is used in humans as an anti-HIV compound.

✚ **FIV** Raltegravir is effective against FIV in vitro.[102] No in vivo studies have been published so far.

✚ **FeLV** Raltegravir has recently been shown to be highly effective in vitro in several feline cell lines for inhibition of FeLV.[71,101] The effective concentration of raltegravir had no effect on cell viability and did not induce apoptosis, suggesting that this might also be an effective and safe drug in vivo.[55] However, raltegravir is partly eliminated as glucuronide, via a metabolic pathway that is not very efficient in cats, and this increases the risk of toxicity due to drug accumulation.[99] A very recent study evaluated efficacy and safety of raltegravir in seven cats with experimentally induced progressive FeLV infection.[103] Raltegravir was administered at 40 mg PO q12h for 6.5 weeks and then at 80 mg PO q12h for 2.5 weeks. No control group was included in the study. The treatment was successful in reducing viraemia in each cat, with up to 1 $\log_{10}$ reduction in viral RNA in 4/7 cats; however, viraemia rebounded in all cats after treatment was stopped. The drug reached sufficient plasma concentrations with both doses. It was found to be safe, with no harmful side effects (EBM grade III).[103]

The integrase inhibitor raltegravir has been used safely in cats, but further work is required to determine its potential as an anti-retroviral drug.



Interferons

Interferons (IFNs) are polypeptide molecules with a variety of biological functions.[104] They play an important role in mediating antiviral and antigrowth responses and in modulating the immune response.[105] They can be divided into two major types – type I and type II IFNs – both of which show antiviral properties. Type I IFNs, including IFN-α, IFN-β and IFN-ω, are produced by virus-infected cells.[104,106] Type II IFN, consisting of only IFN-γ, is produced by activated T lymphocytes and natural killer cells in response to their recognition of virus-infected cells.[107]

IFNs act in an autocrine or paracrine fashion,[108] inducing an antiviral state in non-infected cells. IFNs bind to specific cell surface receptors and result in the transcription of IFN-stimulated genes. The products of these genes are proteins with potent antiviral properties which interfere with various stages of viral replication.[108] Several studies suggest that retroviral protein synthesis is not affected by IFNs and conclude that the antiviral activity of IFNs is related to interference with later stages of the viral replication cycle, such as virion assembly and release.[104,109] Interferons also trigger virus-infected cells to undergo apoptosis by activating the expression of genes that contribute to the process of programmed cell death.[107,109] Thereby IFNs prevent the spread of virus from infected cells and aid in the clearance of virus infection.[107]

Human IFNs have been manufactured by recombinant DNA technology and are available commercially. Recombinant feline IFN-ω is on the market in Japan, Australia and European countries, licensed for use in cats and dogs.

Human interferon-α

Recombinant human interferon-α (IFN-α) has antiviral and immunomodulatory activity, and is active against many DNA and RNA viruses.[108] There are two common treatment regimens for use of IFN-α in cats: SC injection of high doses (1×10^4 to 1×10^6 IU/kg q24h) or oral application of low doses (1–50 IU/kg q24h). When given parenterally to cats, human IFN-α becomes ineffective after 3–7 weeks due to the development of neutralising antibodies that limit its activity.[46]

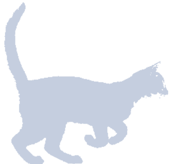
IFN-α can be given orally for a longer period as no antibodies will develop during oral treatment, and it has been used in this manner to treat FIV and FeLV infections. However, given orally, IFN-α is inactivated by gastric acid and destroyed by trypsin and other proteolytic enzymes in the duodenum.[110] Thus, direct antiviral effects are unlikely after oral application, but it still seems to have immunomodulatory activity. After oral application, IFN-α can bind to mucosal receptors in the oral cavity, stimulating the local lymphoid tissue. This leads to cytokine release on lymphatic cells in the oral or pharyngeal area, triggering a cascade of immunological responses that finally act systemically.[111–113]

✤ **FIV** IFN-α is active against FIV in vitro.[114] Although frequently used in the field for treating FIV-infected cats, no controlled studies have evaluated the effect of high dose parenteral IFN-α in FIV-infected cats.

Use of low dose oral IFN-α in sick cats naturally infected with FIV (50 IU/kg on the oral mucosa q24h for 7 days on alternating weeks for 6 months, followed by a 2 month break, and then repetition of the 6 month treatment) resulted in improvement of clinical signs in a placebo-controlled, double-blind study.[115]

✤ **FeLV** Several studies have been conducted on the use of IFN-α in FeLV-infected cats. In vitro, FeLV replication is inhibited by IFN-α.[116] One study evaluated the therapeutic efficacy of high dose IFN-α (1.6×10^4 to 1.6×10^6 IU/kg SC q24h) in experimentally FeLV-infected cats with persistently high levels of antigenaemia.[46] Treatment resulted in a significant decrease in circulating FeLV antigen beginning 2 weeks after the initiation of therapy (EBM grade II).[46] However, because of anti-IFN-α antibody development, cats became refractory to therapy 3 or 7 weeks after starting treatment.[46] In a placebo-controlled, double-blind study in naturally FeLV-infected cats using a similar high dose regimen, treatment with IFN-α (1×10^5 IU/kg SC q24h for 6 weeks) did not lead to a significant improvement in clinical, laboratory, immunological or virological parameters (EBM grade I).[47]

Low dose oral IFN-α was used in a placebo-controlled study in experimentally induced FeLV infection; 0.5 IU/cat (eight cats) or 5 IU/cat (five cats) was given (following experimental challenge) on 7 consecutive days on alternate weeks for a period of 1 month.[111] No difference was found in the development of viraemia between groups; however, treated cats had significantly fewer clinical signs and longer survival times when compared with the placebo group (with a better response in the cats given 0.5 IU/cat) (EBM grade II).[111] Several uncontrolled field studies have also reported a beneficial response in cats when treated with low dose oral IFN-α,[116,117] but they only included a limited number of cats and the findings are impossible to interpret without control groups (EBM grade III). In a larger study, the outcome of 69 FeLV-infected cats with clinical signs that were treated with low dose oral IFN-α (30 IU/kg for 7 consecutive days on a 1 week on/1 week off schedule) was compared with historical controls; significantly longer survival times were reported in the treated cats (EBM grade III).[117] In a placebo-controlled study, treatment of sick client-owned FeLV-infected cats with low dose oral IFN-α (30 IU/cat for 7 consecutive days on a 1 week on/1 week off schedule) did not result in a significant difference in FeLV status, survival time, clinical or haematological parameters, or owners' subjective impression when compared with a placebo group. Thus, this controlled study was not able to demonstrate efficacy (EBM grade I).[118]



Interferons likely have an effect on secondary infections, rather than a direct effect on the retrovirus itself.

Feline interferon-ω

Feline interferon-ω (IFN-ω), the corresponding feline interferon, is licensed as a veterinary medicine in Japan, Australia and European countries. Feline IFN-ω is a recombinant product that is produced by baculoviruses containing the feline sequence for this IFN that replicate in silkworms after infection. Results of studies investigating the efficacy of feline IFN-ω against FIV and FeLV are summarised in the box on page 935.

Future priorities

Unfortunately, the level of efficacy of antiviral chemotherapy is often poor and the duration of treatments used in clinical trials is often inappropriate for infections with such long clinical courses. Additionally, the degree of generalisability between experimental infections in cats kept under laboratory conditions and pet cats infected with field strains is unknown. Therefore, it is very important that more well-designed double-blind, placebo-controlled trials using antivirals in naturally retrovirus-infected cats are undertaken to allow judgement on treatment efficacy and side effects of different antiviral compounds.

Efficacy of veterinary licensed feline interferon-ω

FIV

IFN-ω inhibits FIV replication in vitro.[114] One placebo-controlled, multi-centre study investigated the efficacy of feline IFN-ω against FIV infection in 62 naturally infected cats treated with high dose IFN-ω (1 x 10^6 IU/kg SC q24h) on 5 consecutive days. This study did not find significant changes in survival rate in treated cats compared with a placebo group, although some clinical improvement was noted (EBM grade I).[119] In another study evaluating naturally FIV-infected cats housed in a shelter, some clinical improvement was seen with IFN-ω treatment administered at the above-mentioned high dose, but in this study there was no placebo control.[106] Haematological values remained within reference intervals, and there were no biochemical abnormalities associated with IFN-ω treatment (EBM grade III).[106]

A recent study evaluated use of an orally administered medium-high dose of IFN-ω for the treatment of symptomatic, client-owned, naturally FIV-infected cats.[120] The treatment protocol was 1 x 10^5 IU/cat PO q24h for 90 consecutive days, administered by the cats' owners. A historical group treated subcutaneously with the high dose licensed protocol (1 x 10^6 IU/kg SC q24h) was used as a control for comparison, but no placebo group was included. Treatment resulted in significant improvement of clinical scores post-treatment, compared with pre-treatment values. Furthermore, there was no significant difference between the SC high dose historical control group and the PO medium-high dose group, suggesting that oral administration of IFN-ω in a lower dose could be used as an alternative to the licensed protocol at reduced cost (EBM grade III).[120]

In a recently published study that assessed viraemia, provirus load and blood cytokine profile in naturally FIV-infected cats treated either with oral or subcutaneous feline IFN-ω (in the same dosages described above), but again without placebo control, there was no change in viraemia or in most of the cytokine levels measured (EBM grade III),[121] which questions the efficacy noted in previous clinical trials without placebo control. The fact that virus load remained unchanged in the cats, but some clinical improvement could be observed, invites the conclusion that IFN-ω might have an effect on secondary infections rather than on FIV itself.[104]

> In FIV and FeLV infection, a treatment protocol of 1 x 10^6 IU/kg SC q24h on 5 consecutive days is suggested. No major severe side effects have been reported in cats.[120]

In summary, studies to date on feline IFN-ω in FIV-infected cats have reported differing outcomes, and definitive conclusions cannot be drawn without additional studies incorporating sufficiently high numbers of naturally infected cats that are randomised, placebo-controlled and double-blinded.

FeLV

Feline IFN-ω inhibits FeLV replication in vitro.[122] In a placebo-controlled field study, 48 cats with FeLV infection were treated with high dose IFN-ω at 1 x 10^6 IU/kg q24h SC on 5 consecutive days. This treatment was applied three times, with several treatment-free weeks in-between. There was a significant difference recorded in the survival time of treated vs untreated cats in a 9 month follow-up period (EBM grade I).[119] No virological parameters, however, were measured throughout the study. This supports the hypothesis that the IFN-ω was inhibiting secondary infections rather than having a direct anti-FeLV effect. In another study evaluating FeLV-infected cats housed in a shelter, some clinical improvement was noted with IFN-ω treatment using the same dose as described above, but no placebo group was included, precluding a definitive assessment (EBM grade III).[106]

No studies have been published so far on the oral use of IFN-ω in FeLV-infected cats.

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Conflict of interest

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