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Review Article

Host-Pathogen Interactions in Immunocompromised States: A Comparative Study of Veterinary and HIV/AIDS Microbiology

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ABSTRACT

The purpose of this study is to compare the host–pathogen interactions in immunocompromised conditions, particularly human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and veterinary lentiviral infections, such as feline immunodeficiency virus (FIV) and simian immunodeficiency virus (SIV). We adopted the Damage-Response Framework as the main paradigm to investigate immune vulnerabilities, evasion strategies of pathogens, clinical disease manifestation, and treatment approaches across species. Our review highlights a "mucosal catastrophe" with selective depletion of cluster of differentiation 4-positive T helper 17 and T helper 22 cells in gut-associated lymphoid tissue, resulting in gut barrier disruption, translocation of bacteria, and systemic chronic inflammation. Pathogens have sophisticated evasion strategies, including latent reservoir establishment, antigenic drift, restriction factor evasion, and immune checkpoint subversion. Zoonotic opportunistic pathogens (Cryptosporidium species, Toxoplasma gondii, Mycobacterium avium, Rhodococcus equi) are a serious concern for vulnerable human populations. The study is limited by the veterinary literature for non-lentiviral diseases and variable designs, which preclude quantitative meta-analysis. We conclude that veterinary models have been directly translated into human therapies, such as tenofovir and the feline immunodeficiency virus vaccine. Implications include integrated One Health surveillance networks, translational therapeutic studies, and the breakdown of academic silos between human and veterinary medicine to improve global public health and outcomes for immunocompromised hosts.

Keywords: Host-Pathogen Interactions, Immunocompromised States, HIV/AIDS, Feline Immunodeficiency Virus (FIV), One Health.

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INTRODUCTION

Numerous biological factors help human immunodeficiency virus (HIV) to develop into acquired immunodeficiency syndrome (AIDS), and opportunistic infections (OIs) are some of the most important contributors to morbidity (Stump & Vande Woude, 2007). AIDS is clinically characterized by severe immunodeficiency, which causes an increased occurrence of these OIs and other malignancies. Nearly identical to this in veterinary medicine is the feline immunodeficiency virus (FIV), a lentivirus with properties similar to HIV that, in feline hosts, predisposes them to secondary infections and neurological diseases (Silva *et al*., 2025). Moreover, the infection of simian immunodeficiency virus (SIV) in macaques is a leading model of human AIDS as it recapitulates the loss of CD4+ T cells and the resulting development of opportunistic diseases that are life-threatening (Kumar, 2025). Most of the OIs common among human HIV/AIDS patients are known to be natural zoonoses that vertebrates are known to transmit to humans either through direct contact, vectors, or contaminated food and water (Russotto, 2022).

The intricate interaction can be most effectively described by the Damage-Response Framework (DRF), which views microbial pathogenesis as the emergent consequence of interaction between a particular host and a particular microbe, rather than as a single characteristic of (Kimball *et al*., 2026). The DRF underlines that clinical disease occurs only when the extent of host damage, be it by the pathogen, immune response by the host, or both, alters normal physiological homeostasis. It is necessary to consider the inclusion of veterinary microbiology into the investigation of human immunocompromised states because most of the emerging diseases have a zoonotic background and exhibit similar pathogenesis in other species (Chauhan *et al*., 2025). The epidemiological information gained through veterinary study of animal-related infections by pathogens like Toxoplasma gondii, Cryptosporidium, and Mycobacterium Bovis is critical in controlling immunocompromised human populations. Finally, de-academicizing animal and human health will enable a one-disease framework to understand the changing epidemiology and microbiology of global infectious threats (Devi *et al*., 2021).
This review aims to:

- Compare immunological responses of host-pathogen interactions in major veterinary immunocompromized states and HIV/AIDS.
- Determine typical opportunistic pathogens and their avoidance mechanisms.
- Test cross-species translational knowledge on therapeutic and preventive interventions.
- Suggest an integrated management approach to one-health.

METHODS AND MATERIALS

Search Strategy and Information Sources

This comparative review was prepared according to the recommendations for narrative and "systematic-like" reviews in microbiology and immunology. We conducted a very thorough search of electronic databases such as PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The date range for the search was January 2000 to March 2026, to capture both seminal and recent lentiviral research. Furthermore, the bibliographies of obtained articles were searched for additional sources.

Search Terms and Keywords

The keywords used included, with Boolean operators (AND, OR): "host-pathogen interactions," "immunocompromised states, "HIV/AIDS," feline immunodeficiency virus" OR "FIV," "simian immunodeficiency virus" OR "SIV," "opportunistic infections," "microbial translocation," "Th17 depletion," "mucosal catastrophe," "latent reservoir," "zoonotic pathogens," "One Health," and "veterinary lentivirus". Search terms were modified to suit each database using the controlled vocabulary (such as Medical Subject Headings for PubMed).

Inclusion and Exclusion Criteria

Inclusion criteria included: (i) original research, clinical trials, and peer-reviewed reviews; (ii) references to mechanisms of susceptibility (e.g., CD4+ T cell depletion, mucosal barrier dysfunction); (iii) descriptions of pathogen evasion strategies in human or veterinary lentiviruses; (iv) Information about clinical presentation, diagnostics, and treatments; and (v) English language

publications. Articles were excluded if they: (i) were not peer-reviewed, were editorials, or conference abstracts without data; (ii) reported on non-lentiviral immunocompromized conditions (e.g., chemotherapy-induced immunosuppression) without comparisons to HIV/FIV/SIV; and (iii) did not provide sufficient details of their methods.

Data Extraction and Synthesis

Data from selected articles were extracted by two independent reviewers (M.Y. and R.S.) on an extraction form. The information extracted was authors, publication year, study design, host species, pathogen type, immunological outcomes, evasion strategies, and clinical or therapeutic outcomes. Any discrepancies were discussed or referred to a third reviewer (M.R.) We undertook a qualitative synthesis using a comparative thematic approach, grouping information into five broad themes: immunological basis of susceptibility, evasion mechanisms, clinical presentation, therapeutic insights, and zoonotic One Health implications. The Damage-Response Framework was used as the conceptual framework to understand pathogenesis in different species.

THEORETICAL BUILDUP

Immunological Basis of Susceptibility in Immunocompromised Hosts

Host immunocompromised hosts are best considered in the Damage-Response Framework (DRF), according to which microbial pathogenesis is an emergent product of host-pathogen interactions but not a fixed microbial property. Disease in this framework is observed when physiological homeostasis is disturbed due to host damage as a result of a weak or over-strong immune response (Cribbs et al., 2020). The gradual loss of CD4+ T lymphocytes is the general hallmark of this vulnerability in not only human HIV/AIDS, but also the models of Feline Immunodeficiency Virus (FIV) and Simian Immunodeficiency Virus (SIV) (Teer *et al*., 2025). These cells are key orchestrators of the immune system; their loss in terms of both quantity and quality results in a severe deficiency in the ability to generate effective responses, both cellular and humoral, to opportunistic challenges (Mukherjee & Mishra, 2026).

Figure 1

Mechanism of Intestinal Barrier Breakdown

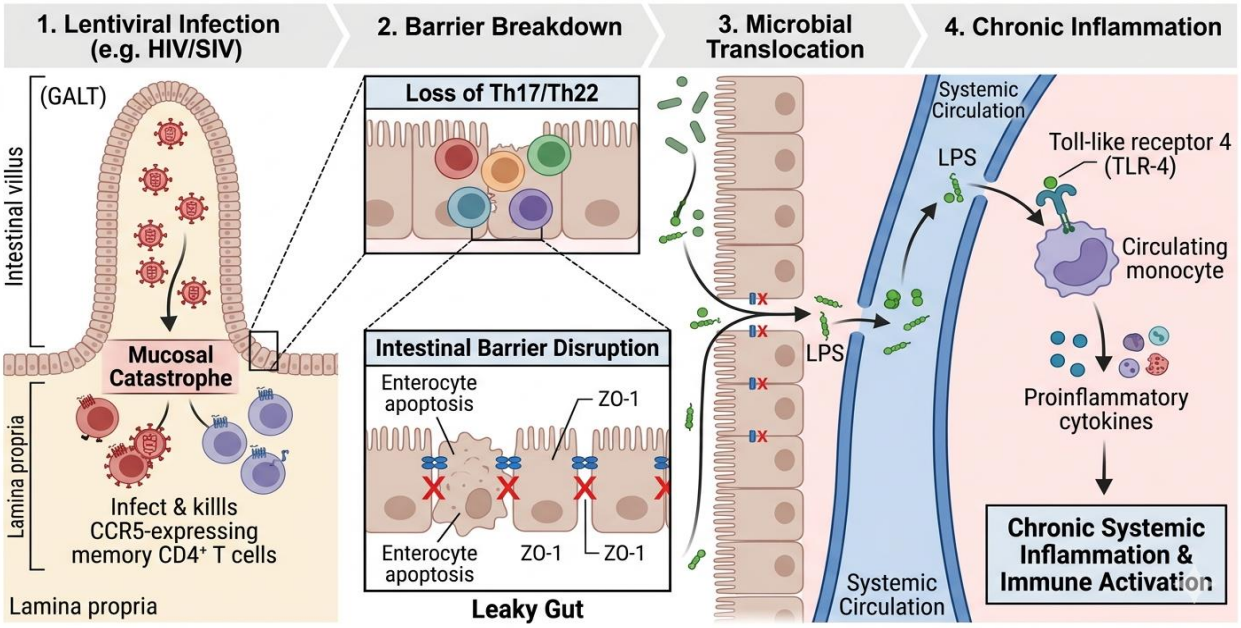

Figure 1: Sequential progression from lentiviral infection (e.g., HIV/SIV) in gut-associated lymphoid tissue (GALT) to chronic inflammation. (1) Selective infection of CCR5+ memory T cells by the virus (red dots). (2) Depletion of critical Th17/Th22 subsets disrupt epithelial homeostasis and tight junction proteins (ZO-1, marked with red 'X's). (3) The resulting leaky gut allows the systemic translocation of microbial products, including lipopolysaccharide (LPS). (4) Translocated LPS activates Toll-like receptor 4 (TLR-4) on circulating monocytes, driving chronic systemic immune activation and persistent inflammation, a stronger predictor of disease progression than viremia.

One of the key early events of this process is the "mucosal catastrophe" that takes place in the gut-associated lymphoid tissue (GALT) (Chen, 2023). The virus specifically infects and kills CCR5-expressing memory CD4+ T cells that are numerous in the intestinal mucosa. In particular, the depletion of Th17 and Th22 subsets is catastrophic because these cells play a crucial role in the preservation of the intestinal epithelial barrier and the generation of antimicrobial peptides. They are depleted and cause enterocyte apoptosis and tight junction disruption, causing a leaky gut (Alexandrova *et al*., 2022). This anatomical defect promotes microbial translocation, in which intestinal luminal microbial products like lipopolysaccharide (LPS) are translocated into systemic circulation. LPS then causes Toll-like receptor 4 (TLR-4) and leads to chronic systemic immune activation and chronic inflammation, which are typically more reliable indicators of disease progression than viremia itself (Mu et al., 2024). The mechanisms of cell death also make immunopathology complicated. Although direct viral lysis does take place, about 95 percent of CD4+ T cell loss in lymphoid tissues is caused by pyroptosis, which is a very inflammatory type of programmed cell death that is brought about by abortive infection (Lionakis *et al*., 2023). This forms a vicious cycle that kills cells and releases proinflammatory cytokines, which attract and activate new target cells, creating new viral replication and tissue destruction. Moreover, the host experiences T cell exhaustion, a functional impairment caused by ongoing exposure to the antigen and characterized by an increase in inhibitory receptors such as PD-1 and CTLA-4 (Yang *et al*., 2020). This fatigue restrains the proliferative ability of the effector cells, making the host incapable of eliminating the pathogen in a manner that a healthy system can deal with easily.

Moreover, Th1 to Th2 cytokine switch compromises cell-mediated immunity against intracellular infections, like Mycobacterium avium, and facilitates dysregulated B cell activation. Finally, the immunological pathogenesis is not an immunodeficiency but a complicated, dysregulated inflammation and immune senescence (Lv *et al*., 2021). In order to supplement the discussion on the Immunological Basis of Susceptibility in Immunocompromised Hosts, the next table provides an overview of the key mechanisms observed in the sources that contribute to disease progression and susceptibility to opportunistic threats in HIV and veterinary lentiviral models.

Table 1

Key Immunological Mechanisms of Susceptibility in HIV and Veterinary Lentiviral Models (Chauvin & Sauce, 2022; Chen et al., 2023; Yan et al., 2023; Balendran et al., 2024)

Mechanism	Description	Primary Markers/Cell Types Involved	Pathological Impact
CD4+ T Cell Depletion	Quantitative and qualitative loss of central immune coordinators.	CD4+ T lymphocytes	Hallmark of immunodeficiency: increased OIs and malignancy.
Mucosal Catastrophe	Rapid elimination of memory T cells in the gut during primary infection.	CCR5+ memory CD4+ T cells	Early structural damage to the gut-associated lymphoid tissue (GALT).
Th17 and Th22 Loss	Depletion of subsets is vital for maintaining mucosal integrity and antimicrobial peptides.	Th17 and Th22 cells; IL-17, IL-22	Impaired barrier repair and loss of mucosal antimicrobial defense.

Intestinal Barrier Disruption	Disruption of epithelial tight junctions and enterocyte apoptosis.	ZO-1 tight junction protein	Development of "leaky gut," allowing systemic pathogen entry.
Microbial Translocation	Systemic escape of microbial products (e.g., LPS) from the intestinal lumen.	Lipopolysaccharide (LPS); sCD14	Chronic systemic immune activation and persistent inflammation.
T Cell Exhaustion	State of functional impairment due to persistent antigen exposure.	PD-1, CTLA-4, Tim-3	Reduced proliferative capacity and failure to clear viral/opportunistic threats.
Cytokine Shift	Imbalance favoring regulatory or humoral responses over cell-mediated immunity.	Th1 to Th2 shift; TGF-β, IL-10	Impaired response against intracellular pathogens like M. avium.
Pyroptosis	Highly inflammatory programmed cell death triggered by abortive infection.	Caspase-1; IL-1β	Vicious cycle of inflammatory cell recruitment and tissue damage.

This immunological environment depicts that susceptibility is not simply a deficiency of immune response, but of chronic, dysregulated inflammation and structural breakdown at the mucosal surfaces. Inability to replace these particular mucosal subsets together with the functions of barriers despite suppressive antiretroviral treatment has been one of the most pressing issues in clinical treatment.

Pathogen Evasion Strategies across Host Species

To overcome host defense, pathogens have developed a rich repertoire of strategies, and this is most productively described in the Damage-Response Framework (DRF), where the pathogenesis is an emergent property of host-microbe interactions instead of a fixed microbial characteristic (Obeagu & Obeagu, 2024). One of the main mechanisms common to human and veterinary lentiviruses is the creation of latent reservoirs, most frequently in the resting memory CD4+ T lymphocytes and lymphoid tissues. In human HIV-1 and feline immunodeficiency virus (FIV), transcriptionally silent proviruses are integrated into the host genome, and this enables them to be undetectable by cytolytic effectors and forms a permanent shield against elimination (Gunawan *et al.*, 2026). Moreover, these viruses take advantage of anatomic niches like the central nervous system (CNS), the gastrointestinal tract (GIT), and B cell follicles, wherein ineffective drug penetration and limited immune surveillance allow autonomous viral evolution and survival.

Antigenic variation is an important mechanism of escape, especially for viruses with high mutation rates. HIV-1 constantly produces the so-called decoy proteins and viral mutations in order to counteract the earlier antibody and cytotoxic T lymphocyte (CTL) responses (Ding *et al.*, 2026). Equally, equine infectious anemia virus (EIAV) employs sequence variation in its Rev protein to limit the expression of structural genes at times of clinical quiescence, thus causing an evasion of the host immune system (Su *et al.*, 2022). In addition to viruses, Cryptosporidium species have a great deal of intraspecific variation in their sub-telomeric genes, such as the MEDLE, insulinase-like proteins (INS), and SKSR families. These putative virulence factors genomic islands enable the parasite to evolve into host species and tune immune responses (Bashiardes *et al.*, 2026).

Pathogens also synthesize certain proteins to resist host restriction factors, which are proteins in the innate cell that are meant to prevent viral replication. HIV-1 Vif protein causes the degradation of human APOBEC3G to avoid disastrous G-to-A

hypermutations in the viral genome (He *et al*., 2025). HIV-1 and HIV-2 also use Vpu and Env to antagonize tetherin, which is a protein that inhibits the release of nascent virions of the host cell, respectively. In veterinary systems, the simian immunodeficiency virus (SIV) inverses SAMHD1 through the expression of a protein called Vpx, which is an accessory protein that allows the virus to infect non-dividing macrophages and dendritic cells; a process that is absent in HIV-1 (Jasinska *et al*., 2022). Also, HIV and SIV viral Nef proteins selectively suppress MHC-I molecules to prevent the expression of viral epitopes to the adaptive immune system (Aldhalmi & Al-hadrawi, 2022).

Intracellular opportunistic pathogens use structural and behavioral adaptations to survive in immunocompromised conditions. According to the Amoeboid Predator-Animal Virulence Hypothesis, such pathogens as Mycobacterium avium and Legionella pneumophila use environmental amoeba as a bootcamp to develop resistance to mammalian macrophages (Navasardyan *et al*., 2023). Such pre-adaptation enables them to use host phagocytes as protective niches.

Talaromyces Marneffei employs thermal dimorphism to convert a mold into a pathological phase of a yeast, which enables it to endure endothermic hosts. It also alters the immune microenvironment through M2 macrophage polarization and programmed death-ligand 1 (PD-L1) upregulation, which basically transforms host cells into Trojan horses to be disseminated throughout the system without being detected by the immune system (Augello *et al*., 2023). Similarly, Cryptosporidium sporozoites develop a secure niche at the host epithelial apex, creating a parasitophorous vacuole and a specialized feeder organelle to scavenge nutrients but are not a part of the host cytosol. Lastly, the capability of pathogens such as Cryptosporidium to resist the environment is augmented by the formation of thick-walled oocysts, which are highly resistant to chemical and physical adversities (Obeagu & Obeagu, 2026).

Table 2

Comparative Pathogen Evasion Strategies in Human and Veterinary Microbiology (Scaglioni, 2025; Le Hingrat et al., 2021; Wang et al., 2021; Jiménez et al., 2023; Tokarev et al., 2022)

Evasion Strategy	Mechanism	Examples (Human/Veterinary)
Latent Reservoirs	Integration into the host genome in resting memory cells.	HIV-1, FIV, SIV (Resting memory CD4+ T cells)
Anatomic Sanctuaries	Persistence in sites with poor drug penetration (CNS, GALT).	HIV-1, FIV, SIV
Antigenic Variation	Rapid mutation of surface glycoproteins and regulatory proteins.	HIV-1 (Env), EIAV (Rev), Cryptosporidium (gp60)
Restriction Factor Counteraction	Degradation or antagonism of innate cellular blocks.	HIV-1 (Vif vs APOBEC3G; Vpu vs Tetherin); SIV (Vpx vs SAMHD1)
Antigen Presentation Interference	Downregulation of MHC-I to avoid CTL detection.	HIV-1 (Nef), Veterinary Lentiviruses
Host Cell Polarization	Induction of M2 macrophage phenotype for safe residence.	Talaromyces marneffei, Toxoplasma gondii, M. avium
Immune Checkpoint Manipulation	Upregulation of inhibitory ligands like PD-L1.	Talaromyces marneffei
Structural Protection	Formation of parasitophorous vacuoles or thick-walled oocysts.	Cryptosporidium spp., Microsporidia
Thermal Dimorphism	Phase transition (mold to yeast) to survive at the host body temperature.	Talaromyces marneffei, Histoplasma spp.

Figure 2

Comparative Immune Evasion by Human and Veterinary Pathogens

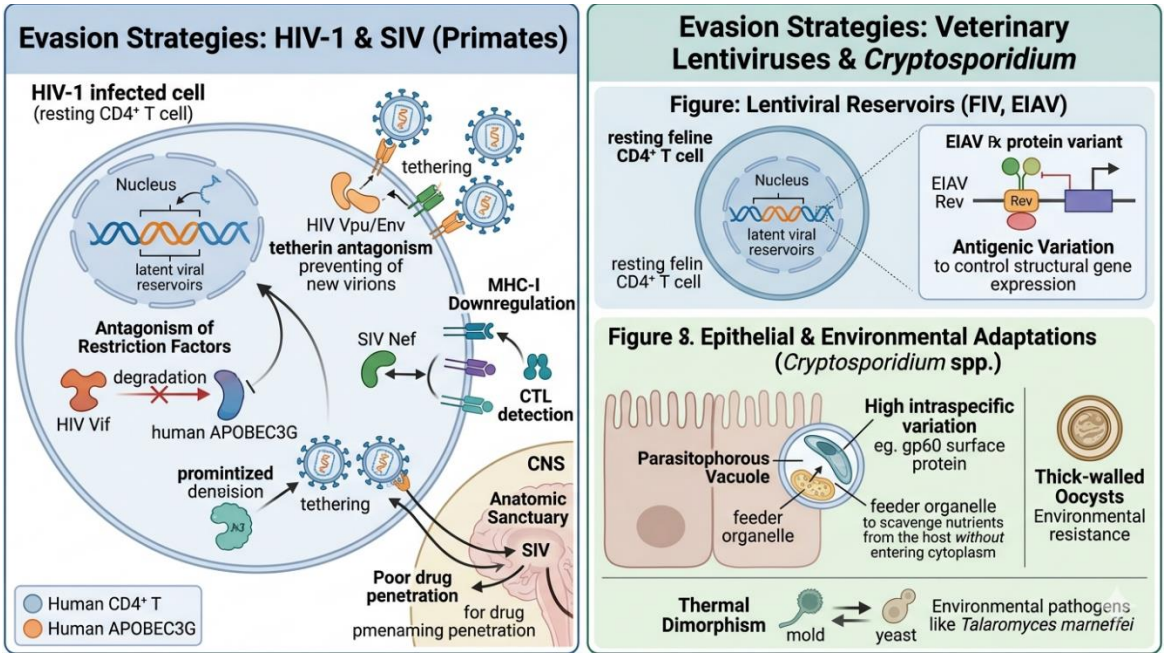

Figure 2: This visual summary illustrates analogies in microbial pathogenesis across species. (Left Panel) Mechanisms observed in HIV-1 and SIV infection, including the establishment of latent viral reservoirs in the nucleus, antagonism of restriction factors (Vif degrading APOBEC3G; Vpu/Env antagonizing tetherin), downregulation of MHC-I to evade CTL detection (Nef), and the use of the CNS as an anatomic sanctuary. (Right Panel) Evasion in veterinary lentiviruses and zoonotic enteric pathogens. Similar reservoirs are formed by FIV; EIAV exhibits high antigenic variation (Rev protein) to control structural gene expression. The diagram of Cryptosporidium shows unique adaptations: developing a distinct parasitophorous vacuole and feeder organelle at the epithelial apex (blue arrows) to survive extracellularly from the cytoplasm, alongside environmental resistance (thick-walled oocysts). A shared mechanism of thermal dimorphism is also visualized for environmental pathogens like Talaromyces marneffei.

Clinical Manifestations and Diagnostic Approaches

Diseases in immunocompromized states are mainly mediated by the progressive loss of CD4+ T lymphocytes, which is the main surrogate endpoint in terms of monitoring disease severity and predicting the overt development of immunodeficiency in humans and veterinary animals. In human HIV infection, this loss results in a shift after an acute phase (which is usually marked by anorexia and lymphadenopathy) into clinical AIDS, which is marked by a CD4 count below 200/mm 3 and the development of opportunistic infections (OIs) and malignancies at high incidence (Okoye & Picker, 2013). This pathology is also well reflected in veterinary medicine by Feline Immunodeficiency Virus (FIV), which has a long period of asymptomatic infection and a symptomatic period with periodic relapsing secondary infections, wasting, and B-cell or T-cell lymphomas (McCune, 2001). Respiratory signs and symptoms constitute a major burden of morbidity in the world. Mycobacterium tuberculosis is the most prevalent significant OI in humans, and it tends to hasten the development of HIV and elevate the rate of mortality. This is similar in veterinary medicine to Rhodococcus equi in horses that causes cavitary, granulomatous pneumonia resembling human tuberculosis (Février *et al*., 2011). Moreover, Pneumocystis jiroveci (PJP) is also a hallmark of human AIDS and FIV-infected cats, and is the major cause of severe pneumonia, which is caused by the destruction of alveolar spaces. Fungal coinfections such as Aspergillus have become significant hazards and commonly complicate cases of previously treated pulmonary tuberculosis by colonizing and forming aspergillomas in the remaining lung cavities (Alimonti *et al*., 2003).

Gastrointestinal involvement is a cross-species finding and is usually associated with severe watery diarrhea and dehydration. E. coli, Cryptosporidium species, and other pathogens result in the major destruction of epithelial tight junctions and the loss of barrier function, and the inability to absorb nutrients. This "mucosal catastrophe" promotes microbial translocation, in which microbial products like lipopolysaccharide (LPS) are released outside the intestinal lumen into the systemic circulation and cause chronic inflammation in both humans and bovine hosts (Vidya Vijayan *et al*., 2017). Salmonella bacteremia that occurs regularly can be identified as an AIDS-defining diagnosis, which indicates the presence of severe underlying immune malfunction. On the same note, Campylobacter Jejuni has been commonly implicated in both human and animal diarrhea, pointing to the commonality in risk factors that contribute to the zoonotic enteric threats (Peng *et al*., 2020). Additional neurological and dermatological manifestations demonstrate the breadth of clinical disease. Neurotropic strains of HIV and FIV infect CNS macrophages, microglial cells, and astrocytes, causing HIV-associated neurocognitive disorders (HAND) in humans or feline neurological abnormalities, including aggressive behavior and delayed reflexes (Brenchley *et al*., 2004). A perfect example of a zoonotic threat is Toxoplasma gondii; cats are the host organisms, oocysts of which can cause deadly encephalitis to humans with weakened immunity. These clinical features are usually accompanied by chronic inflammatory diseases such as stomatitis and gingivitis in cats, which tend to respond to treatment with zidovudine (Beck, 2005).

Diagnostic methods should be multi-modal in distinguishing between active clinical disease and simple infection. Quantitative PCR of viral load and CD4 flow cytometry of CD4 counts are still the gold standard for human HIV. ELISA and Western blot are widely used in veterinary settings to detect lentiviruses, but the best cost and infrastructure frequently restrict access to nested PCR (Tolomeo & Cascio, 2024). In the case of human herpesviruses (HHVs) that are important copathogens, laboratory techniques encompass antigen tests in tumor tissue biopsies as well as RT-PCR of body fluids. Recent developments imply the use of soluble CD14 (sCD14) and I-FABP as biomarkers to determine monocyte activation and enterocyte injury as a result of microbial translocation. Moreover, pathogen screening, such as cryptococcal antigen (CrAg) and interferon-gamma release assays (IGRA), should be used in the initial stages of screening in high-risk groups (Mishra *et al*., 2009). Finally, the key to successful management is to promptly detect these coinfections and avoid the development of immune reconstitution inflammatory syndrome (IRIS) upon the initiation of treatment.

Therapeutic and Preventive Strategies: A Comparative View

The treatment of immunocompromised conditions has undergone a paradigm shift, and diseases such as HIV/AIDS are no longer terminal diagnoses but a manageable chronic illness with the amazing success of Highly Active Antiretroviral Therapy (HAART). This medical advancement finds close reflection in veterinary medicine, in which human antiretroviral drugs have been repackaged to treat lentiviral infections of cats and monkeys, and is an example of a continuity of pharmacological development that can be termed as One Health (Foka & Mufhandu, 2023). The standard of care in humans is a combination regimen, usually two nucleoside reverse transcriptase inhibitors (NRTIs) with an integrase inhibitor or a protease inhibitor, to maintain viral control. This is not only a way to decrease morbidity but also a Treatment as Prevention (TasP), as it is known to decrease the risk of transmission as the infectiousness of the host is minimized (Bakasis & Androutsakos, 2021). Likewise, in feline medicine, zidovudine (AZT) is effective in enhancing the clinical condition of cats with FIV, especially in the treatment of related stomatitis as well as in the correction of CD4/CD8 ratios. Non-species toxicity of the drugs, however, tends to limit their use in veterinary practice, including non-regenerative anemia in cats receiving adefovir (PMEA) or bone marrow suppression with high-dose AZT. Interestingly, the design of human therapies based on Tenofovir was actually influenced by preliminary studies of efficacy in FIV-infected cats (Alemu *et al*., 2022).

Preventative measures are another area of cross-species synergy that is also of major concern, especially in the field of vaccinology. As an efficient human HIV-1 vaccine has not been developed even after decades of intensive research and promising trials, such as RV144, veterinary medicine has made a breakthrough with the commercial launch of a dual-subtype FIV vaccine (Fel-O-Vax FIV) (Kamvuma *et al*., 2026). This inactivated whole-virus vaccine has a global subtype and circulating recombinant prophylaxis, and its efficacy has mainly been credited to the development of strong T-cell immunity. The veterinary

accomplishments offer crucial models to human vaccine development, especially in the discovery of evolutionarily preserved epitopes on proteins such as p24 that may induce cross-protective cellular responses. In addition to vaccines, preventive care includes vigorous screening and prophylaxis against opportunistic infections (OIs) (Sun & Wang, 2024). An example is the use of acyclovir to slow the disease course in HIV/HSV-2 coinfected persons, and the use of trimethoprim-sulfamethoxazole as the basis of prophylaxis against Pneumocystis jirovecii pneumonia.

The contemporary treatment edge has now shifted to destroying latent reservoirs and alleviating chronic inflammation. In human studies, the goal of the "Shock and Kill" approach is to activate the expression of viruses in resting memory CD4+ T cells by administration of latency-reversing agents, namely HDAC inhibitors, and induce their immune clearance. Preclinical testing of these interventions would not be possible without veterinary models, especially the SIV-infected macaque (Miti et al., 2020). Moreover, since ART does not fully heal the mucosal state, researchers are exploring adjunct interventions to treat microbial translocation. Administration of the non-systemic antibiotic rifaximin or probiotics has demonstrated the potential of reducing systemic immune activation in SIV-infected macaques and in HIV-infected humans. Lastly, zoonotic risk reduction should be incorporated in clinical management. In the case of immunocompromised people, this involves observing stringent hygiene protocols when contacting pets, including not feeding animals raw meat and the use of gloves during litter box cleaning to avoid contacting pathogens like Toxoplasma gondii and Salmonella (Saka *et al*., 2023). Treatment then requires a concerted effort between doctors and veterinarians to treat the common microbial habitat of the host.

Zoonotic Dynamics and the One Health Perspective in Immunocompromised Populations

The syndemic model of the clinical manifestation of infectious disease in immunocompromized states is becoming more common, in which the potential of a pathogen is mediated by the interaction between it and other infectious agents and environmental factors. Many life-threatening opportunistic infections (OIs) in human HIV/AIDS patients are known as zoonoses, which are naturally acquired between human beings and vertebrate animals (Ullah, 2026). This fact requires dismantling of academic isolations between human and animal health, and the implementation of the so-called one disease model that has long been a mainstay of veterinary medicine to safeguard human health around the world (Hossain *et a*l., 2025).

Rhodococcus equi, a common veterinary pathogen in horses, is one of the most important bacterial zoonoses, causing cavitary granulomatous pneumonia in immunocompromised humans, which is similar in appearance to pulmonary tuberculosis. Likewise, nontyphoidal Salmonella and Campylobacter jejuni are common isolates of both human and animal enteric infections, and repeated Salmonella bacteremia is a definitive AIDS-defining diagnosis (Wilcox & Steele, 2021). The importance of domestic animals as reservoirs is also found in Bartonella species, including B. henselae (the cause of cat-scratch disease), which may induce bacillary angiomatosis and peliosis hepatis in patients with low CD4 counts. Moreover, protozoal parasites such as Cryptosporidium species have a high genetic diversity and a large host range, frequently having a livestock origin that results in disastrous mucosal catastrophes in humans with long-term systemic inflammation and microbial translocation (Hossain *et al*., 2025).

It is essential to integrate veterinary microbiology into clinical management of humans since studies of animal-related infections with such pathogens as Toxoplasma gondii and Mycobacterium avium offer valuable epidemiological data. Also, the ecological study of environmental pathogens such as Legionella pneumophila proposes an "Amoeboid Predator-Animal Virulence Hypothesis" in which microbes utilize environmental amoeba to pre-adapt to survive in mammalian macrophages. Finally, the immunocompromised need to be informed on how to reduce the risk of zoonotic infections by providing specific hygiene information about handling pets and livestock (Vale, 2022).

Table 3

Comparative Zoonotic Pathogens and Their Veterinary/Human Impact (Ellwanger et al., 2021; Ortiz-Millán, 2025; Overgaauw et al., 2020; Erkyihun & Alemayehu, 2022; Rauf et al., 2023)

Pathogen	Primary Animal Reservoir	Veterinary Manifestation	Human Manifestation in Immunocompromised
Rhodococcus equi	Horses (foals)	Granulomatous pneumonia	Cavitary pneumonia; TB-like disease
Bartonella henselae	Cats	Usually, asymptomatic	Bacillary angiomatosis; peliosis hepatis
Cryptosporidium spp.	Livestock, pets	Scours (watery diarrhea)	Wasting; mucosal catastrophe; "leaky gut"
Toxoplasma gondii	Felines (felids)	Asymptomatic oocyst shedding	Encephalitis; cerebral mass lesions
Mycobacterium avium	Birds, environment	Granulomatous disease	Disseminated infection; Th2 cytokine shift
Salmonella spp.	Livestock, reptiles	Enteritis; septicemia	Recurrent bacteremia; AIDS-defining illness

DISCUSSION

Comparative study of human and veterinary microbiology demonstrates that states of immunocompromised have a common basic pathophysiological structure. Pathogenesis, in the context of the Damage-Response Framework (DRF), is an emergent consequence of the unique interaction of a host and a microbe and not a fixed microbial trait. This paradigm shift shifts the emphasis away, however, to reductionist "virulence factors" to the dynamic imbalance of host homeostasis, in which disease is expressed, either as a consequence of inadequate or excessive immune response (Dunga *et al*., 2025).

One of the key themes that unite all the species is the mucosal catastrophe that occurs early during the infection. The intestinal epithelial barrier is destroyed by the selective depletion of Th17 and Th22 CD4 + T cell subsets in the gut-associated lymphoid tissue (GALT) (Samadi & Hailat, 2021). This structural breakdown results in microbial translocation- the systemic release of microbial products such as lipopolysaccharide (LPS)- a major cause of chronic systemic immune response and chronic inflammation in human HIV/AIDS and veterinary models such as Simian Immunodeficiency Virus (SIV) (Kundu *et al*., 2024).

The essential templates of study of these complex interactions are done using veterinary models, especially Feline Immunodeficiency Virus (FIV) in cats and SIV in macaques. SIV infection in Asian macaques accurately recapitulates the characteristic CD4+ T cell depletion and consequent development of life-threatening opportunistic infections (OIS) and malignancies seen in human AIDS. In addition, a number of these OIs are known zoonoses like Cryptosporidium, Toxoplasma gondii, and Mycobacterium Bovis, which are naturally spread between vertebrate animals and humans (Gado *et al*., 2023). The high rates of these infections, particularly in the developing regions, highlight the importance of the One Health approach that helps in communication between physicians and veterinarians in order to safeguard the health of the entire world. Veterinary research has had a direct clinical influence on human clinical practice, therapeutically. An example is that the original in vivo efficacy of acyclic nucleoside phosphonate analogues in FIV-infected cats was the basis of the development of Tenofovir, now a key component of human HIV treatment. Moreover, the commercial availability of the dual-subtype FIV vaccine (Fel-O-Vax FIV) presents a crucial template to human vaccine development, showing that extensive prophylactic efficacy could be attained by induction of strong, evolutionarily preserved T-cell immunity (Mubareka *et al*., 2023).

With HIV/AIDS becoming a chronic disease extending over multiple decades, clinical attention has shifted away from acute OIs and towards persistent inflammation and non-AIDS comorbidities that are related to premature aging. The elimination of latent reservoirs and restoration of mucosal barriers should be a priority in future research (Hartady *et al*., 2026). New approaches, like mitochondrial rescue through PPARa signaling and probiotics (such as Lactobacillus plantarum), have the potential to heal the intestinal integrity regardless of immune cell regeneration. Finally, it is necessary to disrupt academic barriers to support comparative immunology to gain insight into the changing microbiology of immunocompromised hosts.

CONCLUSION

Immunocompromised states of host-pathogen interactions demonstrate an impressive biological continuum between human HIV/AIDS and veterinary lentiviral infections, especially Feline Immunodeficiency Virus. By utilizing the Damage-Response Framework (DRF), the paradigm shift of reductionist perceptions can be made, with pathogenesis being considered as an emergent, dynamic product of host-microbe interactions in which clinical disease only occurs when damage to homeostasis and physiological processes occurs. One key similarity of species is the early mucosal disaster, in which Th17 and Th22 subsets of CD4+ T cells are selectively depleted to cause intestinal barrier breakdown and microbial translocation. This structural breakdown promotes chronic systemic immune activation, defining human and veterinary lentiviral disease. Translational antiretroviral development, especially with feline and simian models, will continue to rely on veterinary research to develop antiretrovirals such as Tenofovir and develop effective prophylaxis vaccines. Moreover, the high rates of life-threatening zoonotic opportunistic infections, including Cryptosporidium and Toxoplasma gondii, highlight the urgent need for a One Health model, which will help to communicate across sectors. Finally, the shift of HIV/AIDS into a chronic illness necessitates the development of therapeutic measures in the future beyond viral suppression to eliminate latent reservoirs and develop novel repair of mucosal barriers.

LIMITATIONS

There are several limitations to this review. First, the literature on veterinary immunocompromised states (especially BIV and non-lentiviral conditions) is limited in comparison to HIV/AIDS. Second, study designs (case reports versus cohort studies) are heterogeneous, which does not allow direct quantitative comparisons. Third, the majority of veterinary literature does not include immune phenotyping (e.g., CD4:CD8 ratios) that can be standardized to allow meta-analysis. Lastly, the review lacked non-mammalian immunocompromized models (e.g., avian), which can provide further information.

Limitations of the Review Methodology

Meta-analysis was unavailable because of different study designs, species-specific outcome measures, and a lack of consistency in immunophenotyping (e.g., CD4:CD8 ratio in veterinary studies). We did not include grey literature or non-English sources, potentially leading to a language bias.

RECOMMENDATIONS

It is based on this comparative review that the following recommendations are made to improve the clinical management and scientific understanding of immunocompromised hosts:

Integrated Surveillance Networks: Develop cross-sectoral surveillance of opportunistic infections in people and animals, to support a one-disease model to safeguard the world population's health. It is important to monitor the occurrence and distribution of pathogens like Rhodococcus equi, Mycobacterium Bovis, and Salmonella as these are major zoonotic agents to HIV-infected people.

Cross-Species Therapeutic Trials: Test repurposed antiviral and immunomodulatory agents in FIV-positive cats to guide human HIV adjunctive therapies. The effectiveness of feline models to showcase the effectiveness of acyclic nucleoside phosphonates, which was the direct basis of the development of Tenofovir, exemplifies the translational importance of these comparative trials.

Future studies should also focus on immunomodulators with the ability to suppress chronic systemic inflammation, a common hallmark of lentiviral disease.

Diagnostic Accessibility: Work on low-cost point-of-care (POC) PCR and CD4 count diagnostic tests in veterinary clinics, especially in low-resource environments. Use of sensitive diagnostics should be standardized in veterinary medicine because a lot of states associated with animals have immunocompromised states that are currently not researched rigorously enough to allow comparative research.

Public Health Education: Educate people with weakened immunity on zoonotic risk of pets and livestock, and focus on preventive behaviors like hand hygiene, no diets of raw meat in animals, and the use of gloves when cleaning litter boxes. Better interaction between physicians and veterinarians is essential because, in a clinical setting, there is a lack of accurate information on the risks of animal-human bonding.

Comparative Research Funding: Provide specific research funding for comparative immunology and One Health infectious disease programs. The bridging of human and veterinary microbiology longitudinal cohort studies is needed to determine evolutionarily conserved immune targets and to comprehend the intricacies of host-pathogen interactions in immunological failure states.

DECLARATION

Ethical Consideration: This study strictly adhered to the Declaration of Helsinki and relevant national and institutional ethical guidelines. Informed consent was obtained. All procedures performed in this study were consistent with the ethical standards of the Declaration of Helsinki. This review article does not involve primary data collection from human or animal subjects. All cited studies adhered to their respective institutional ethical guidelines.

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Similarity Index/ Plagiarism: The similarity index was checked, and it is well below the threshold value of 19%, whereas each source is less > 5%.

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