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Review article

Viral integration into host genomes and virus–virus interactions: Implications for epidemiology, disease prevention, and therapeutic strategies

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Abstract

Genetic interactions among viruses, including recombination, reassortment, pseudotyping, and genomic integration, are central to the epidemiology of poultry diseases. These mechanisms promote the emergence of novel viral strains and influence host-pathogen relationships. Virus–virus interactions, such as recombination and reassortment, rapidly generate genetic diversity during co-infection. In contrast, the integration of viral sequences into the host genome constitutes a distinct pathway for long-term viral persistence. Integration may occur via retroviral mechanisms or non-homologous end-joining, as observed in DNA viruses such as avian herpesviruses. These events can result in latency, vertical transmission, or oncogenic transformation, thereby affecting viral maintenance and the potential for outbreaks in poultry populations. Additionally, such genomic changes may facilitate zoonotic transmission, increasing risks to human health. Elucidating the relationship between stable genomic integration and transient genetic exchange is essential for improving surveillance, biosecurity, and the development of advanced vaccines. Exploring genetic resistance to viral integration within the chicken genome represents a promising approach to sustainably enhance poultry health and productivity.

Keywords: Epidemiology, Gene therapy, Genetic resistance, Host genome integration, Prevention, Vaccines, Viral integration, Virus–virus interactions

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Introduction

The integration of viral genomes into host chromosomes is a complex process that fundamentally alters the epidemiology of avian diseases. These events involve diverse molecular pathways, including canonical enzymatic insertion and non-homologous end joining, which result in the partial or complete incorporation of viral sequences into the host genome. This genomic association enables long-term persistence, immune evasion, and oncogenesis, while influencing the dynamics of both vertical and horizontal transmission (Boodhoo et al., 2016; McPherson and Delany, 2016). In addition to host-virus integration, virus–virus genetic interactions such as recombination, reassortment, and pseudotyping serve as concurrent drivers of viral evolution and epidemiological change.

In avian virology, genomic integration is characteristic of the family *Retroviridae*. In these viruses, provirus formation constitutes an essential step in replication: viral RNA is reverse-transcribed into complementary DNA (cDNA) and covalently integrated into host chromatin by a virus-encoded integrase (Weiss, 2006). In the case of Avian Leukosis Virus (ALV), this

integration can induce insertional mutagenesis, activate cellular proto-oncogenes, or disrupt regulatory elements, which leads to lymphoproliferative disorders and chronic viremia (Payne and Nair, 2012).

In contrast, large DNA viruses employ distinct mechanisms for integration. Marek's Disease Virus (MDV), an oncogenic alphaherpesvirus within the Herpesviridae family, establishes latency by integrating its genome into the telomeric repeats (TMRs) of host lymphocytes (Parcells et al., 2001). Unlike retroviruses, MDV integration is not necessary for replication but is critical for pathogenesis and maintenance of latency, ultimately resulting in rapid-onset T-cell lymphomas.

Reticuloendotheliosis Virus (REV) further exemplifies the complexity of these interactions. Although REV commonly integrates into the host genome to induce neoplastic disease (Witter and Fadly, 2003), its sequences are also frequently identified within the genomes of other large DNA viruses, including Fowlpox Virus (FPV) and MDV. These virus-in-virus events represent horizontal gene transfer between viral lineages rather than traditional host-cell integration and often result in altered virulence or interference with vaccine efficacy.

These events have significant epidemiological consequences. Integrated viral sequences act as stable reservoirs within flocks, facilitating vertical transmission and complicating eradication strategies. Additionally, the ability of integrated viruses to recombine with exogenous strains accelerates the emergence of novel variants. Therefore, distinguishing between true genomic integration and transient genetic exchange is essential for understanding viral ontogeny.

This review elucidates the molecular mechanisms underlying viral integration and virus–virus interactions in poultry, with a primary focus on MDV, ALV, and REV. The impact of these events on pathogenesis and transmission dynamics is examined, along with their implications for next-generation vaccines, biosecurity, and the development of genetic resistance in avian populations.

Viral genome integration versus transient genetic interactions

Differentiating stable genomic integration from transient genetic interactions is essential for elucidating viral ontogeny. Although both processes contribute to viral evolution, they are fundamentally distinct in their molecular mechanisms and patterns of heritability.

Genomic integration and viral insertion

Viral integration is defined as the covalent insertion of viral genetic material into the chromosome of a host cell. In retroviruses, this process produces a provirus via a specialized integrase enzyme, resulting in the permanent incorporation of viral sequences into the host's germline or somatic lineage. In certain DNA viruses, such as hepatitis B virus (HBV) or MDV, integration may occur via non-homologous end joining (NHEJ) or at specific chromosomal loci, such as telomeric repeats. This often leads to viral latency or oncogenic transformation (Wagner and Krug, 2026).

A distinctive feature of avian virology is virus-in-virus integration, in which the genetic material of a retrovirus, such as REV, becomes incorporated into the genome of a large DNA virus, such as FPV or MDV. Unlike integration into the host genome, these events represent inter-viral recombination, resulting in chimeric viral lineages with modified virulence and enhanced environmental stability.

Genetic exchange: Reassortment and recombination

In contrast to the physical integration of viral genomes, reassortment and recombination enable the exchange of genetic information during co-infection without establishing a permanent proviral state.

i) Reassortment occurs exclusively in segmented viruses, such as those in the Orthomyxoviridae and Birnaviridae families, and involves the exchange of the entire genomic segments. Avian Influenza Virus (AIV) employs reassortment to facilitate rapid antigenic shifts, thereby achieving significant evolutionary changes without requiring integration into the host genome (White and Lowen, 2017).

ii) Recombination, primarily observed in non-segmented RNA viruses and DNA viruses, involves template switching by viral polymerases. This process generates chimeric sequences derived from two parental strains and is essential for the diversification of Coronaviruses and certain poultry DNA viruses (McDonald et al., 2016).

iii) Pseudotyping is a non-genomic interaction in which viral progeny acquires the envelope

glycoproteins of a co-infecting heterologous virus. This leads to a temporary alteration in cell tropism and host range, as observed when vesicular stomatitis virus (VSV) incorporates REV glycoproteins, without modifying the underlying viral genome (Chen and Lamb, 2007). Since the genetic material remains unchanged, these phenotypic modifications are not heritable beyond the initial infection cycle, distinguishing pseudotyping from the permanent changes resulting from integration or recombination.

Mechanisms of viral integration

Viral integration involves the covalent insertion of viral genetic material into host chromosomes, a process that varies fundamentally across viral families in terms of necessity, mechanism, and site-specificity.

Retroviral integration is considered the model for this process. In avian species, Avian Sarcoma–Leukosis Virus (ASLV) employs a conserved, integrase-mediated strand-transfer mechanism. ASLV demonstrates a near-random integration profile, in contrast to the pronounced preference for transcriptionally active regions observed in lentiviruses (Barr et al., 2005; McPherson and Delany, 2016). Integration events are categorized into three primary biological contexts:

Mandatory (obligatory) integration

In Retroviridae and related long terminal repeat (LTR) retroelements, such as Pseudoviridae, integration is an essential step in the viral replication cycle. After reverse transcription, the viral cDNA becomes permanently integrated into the host genome as a provirus (Weiss, 2006). This process results in: i) Viral persistence and latency: The integrated viral genome remains stable within the host cell lineage and frequently evades immune detection through transcriptional silencing. ii) Vertical transmission: When integration occurs in germ cells, the virus may be inherited as an endogenous genomic element. iii) Oncogenesis: In poultry, Avian Leukosis Virus (ALV) often induces neoplastic transformation through insertional mutagenesis, most commonly by activating proto-oncogenes such as c-myc.

It is important to distinguish this mechanism from that of Herpesviridae. Although early studies proposed that MDV induced tumors solely through episomal maintenance (Fuller and Perez-Romero, 2002), recent molecular evidence demonstrates that MDV integration into host telomeric repeats (TMRs) is essential for T-cell transformation and lymphomagenesis (McPherson and Delany, 2016; Rohrmann, 2019).

Conditional (facultative) integration

Certain viruses integrate into host genomes only under specific physiological or environmental conditions. Temperate bacteriophages exemplify this, employing site-specific recombinases (phage integrases) to form prophages. This integration is often reversible and may result in lysogenic conversion, during which phage-encoded genes, such as toxins or fitness factors, modify the host phenotype and pathogenicity (Fortier and Sekulovic, 2013).

Endogenous viral elements (EVEs) Endogenous viral elements (EVEs) represent molecular fossils of ancestral viral integration events that have become fixed within the host germline. i) Endogenous retroviruses (ERVs): Originating from ancient retroviral infections, ERVs are inherited according to Mendelian principles. Although most are defective, some retain the ability to be expressed and can modulate host immunity or interfere with exogenous viral infections (Jarosz and Halo, 2024). ii) Non-retroviral EVEs: Genomic fragments from *Circoviridae* and *Geminiviridae* have been identified in diverse host genomes (Bejarano et al., 1996). In the absence of a dedicated integrase, these viruses likely rely on host-mediated DNA repair pathways, such as non-homologous end-joining (NHEJ) or microhomology-mediated recombination, to integrate randomly into host DNA.

Mechanisms of viral genome integration in poultry

Viral genome integration in poultry occurs through several distinct biological mechanisms, such as true proviral integration, episomal persistence with chromosomal association, and interviral recombination events that generate chimeric viral genomes. These processes collectively drive viral evolution, oncogenesis, persistence, and vertical transmission in avian species (Table 1).

Retroviral integration mechanisms

ALV, a member of the genus Alpharetrovirus within the family *Retroviridae*, possesses a dimeric positive-sense single-stranded RNA

genome of approximately 7.8 kb. This genome contains three main coding regions: gag, pol, and env, which encode structural proteins, viral enzymes, and envelope glycoproteins, respectively. ALV strains are divided into 11 subgroups (A–K) according to host range, envelope interference, and cross-neutralization characteristics. Of these, subgroups A, B, C, D, J, and K are exogenous and circulate within naturally infected poultry populations (Payne and Nair, 2012).

A defining feature of retroviruses is the integration of reverse-transcribed viral DNA into the host genome, resulting in stable proviruses that can persist in somatic cells or be vertically transmitted as EVEs. The ALV replication cycle consists of six stages: viral attachment and entry, uncoating, reverse transcription, proviral integration, protein synthesis and assembly, and viral budding. Throughout these stages, ALV engages extensively with host cellular machinery via protein–protein, protein–RNA, and protein–DNA interactions. Host factors such as cellular proteins, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) regulate essential molecular events in viral replication and pathogenesis (Tang et al., 2022).

Following reverse transcription, ALV integrates into host chromosomal DNA, leading to long-term proviral persistence in somatic cells and, in some cases, germline-associated cells. These integration events may activate proto-oncogenes such as c-myc or disrupt normal host gene regulation, thereby facilitating tumorigenesis and persistent infection (Payne and Nair, 2012; Lin et al., 2013; Rawson et al., 2018).

In poultry, retroviral integration is fundamental to viral persistence, oncogenesis, and retroviral evolution. Integration of ALV-derived proviral DNA into the chicken genome supports chronic infection, enables vertical transmission, and leads to the formation of ERVs. Additionally, recombination between endogenous retroviral sequences and exogenous ALV strains is a significant factor in the emergence of novel viral variants with altered pathogenicity or host range (Mason et al., 2020).

Endogenous retroviruses (ERVs) in poultry

Endogenous retroviral sequences related to ALV, such as EAV-HP elements, are present in chicken genomes and can affect genetic diversity, host gene regulation, and disease susceptibility (Mason et al., 2020). Recombination between endogenous retroviral sequences and exogenous ALV strains has facilitated the emergence of novel viral subgroups, including ALV-J (Sacco et al., 2000).

ERVs arise from the stable integration of exogenous retroviruses into host germline DNA, a process that involves four main stages. First, viral attachment and entry occur when the viral envelope surface subunit (SU) binds to specific receptors on the host cell membrane. This binding trigger conformational changes in the SU–transmembrane (TM) complex, exposing the fusion peptide within the TM subunit and enabling membrane fusion and release of the viral core into the cytoplasm (Prasad et al., 2022). Second, reverse transcription takes place as the viral RNA genome is reverse-transcribed into complementary DNA by reverse transcriptase. A negative-strand DNA intermediate is synthesized initially, followed by the formation of double-stranded proviral DNA (Jehad et al., 2025). Due to the lack of proofreading activity in reverse transcriptase, this process is associated with a high mutation rate, contributing to retroviral genetic variability (Peck and Lauring, 2018). Third, nuclear trafficking of proviral DNA occurs when newly synthesized proviral DNA associates with viral integrase and host proteins to form the pre-integration complex (PIC). Depending on the retroviral genus and host cell status, the PIC enters the nucleus either via active nuclear transport or during mitosis after nuclear envelope breakdown (Chen et al., 2019). Fourth, chromosomal integration is mediated by the viral integrase enzyme, resulting in covalent insertion of proviral DNA into the host genome. Integration site selection is not entirely random and varies among retroviral genera. For example, lentiviruses preferentially integrate into actively transcribed genes, while γ-retroviruses often target promoter-rich regions and transcriptional regulatory elements. These preferences are shaped by interactions between viral integrases and host chromatin-associated cofactors, such as LEDGF/p75 and bromodomain and extraterminal domain (BET) proteins. After strand transfer, host DNA repair pathways complete gap repair and ligation, producing stable proviral integration within the chromosome (Sultana et al., 2017).

Recent studies suggest that ERV amplification

is not exclusively reliant on exogenous reinfection. Several endogenous mechanisms may also contribute to ERV proliferation, although these processes typically occur at low frequencies. These mechanisms include reinfection-mediated amplification, cis-mediated retrotransposition, trans-mediated retrotransposition, and LINE-mediated retrotransposition (Jiang et al., 2025). These processes have been primarily described in mammalian endogenous retroviral systems and serve as representative models for understanding ERV amplification dynamics.

Marek's disease virus (MDV)

MDV (Gallid herpesvirus 2) does not require classical proviral integration for productive replication or latency. Instead, latent infection is established primarily as an episomal genome in T lymphocytes, with a strong association between the viral genome and telomeric regions of host chromosomes. During latency, the viral genome persists as circular DNA and replicates in coordination with host chromatin, without obligatory permanent integration. Viral DNA can become physically associated with telomeres through telomeric repeat-like sequences present within the viral genome. This telomere-associated persistence contributes to viral latency, immunosuppression, and lymphoma development in infected chickens (Mason et al., 2020; Emad et al., 2024).

MDV latency is associated with integration of viral DNA into host telomeric regions, particularly in CD4+ T lymphocytes. In this state, the viral genome persists within host cells and is replicated alongside cellular DNA. Current evidence does not support vertical transmission as a major epidemiological route for MDV under natural conditions, and the role of germline integration remains uncertain.

Following infection, the linear MDV genome can integrate into host telomeric regions, an event associated with the establishment of latency and malignant transformation leading to lymphomas. This process is facilitated by telomere-like repeat arrays within the MDV genome, specifically multiple telomeric repeat arrays (mTMRs), which are important for efficient chromosomal integration and maintenance within host cells. Integrated MDV (iMDV) genomes frequently exhibit a conserved orientation, likely resulting from homology-directed recombination, with the unique long (UL) region oriented toward the telomere and the unique short (US) region positioned closer to the centromere (Greco et al., 2014; Denesvre et al., 2024). Integrated viral genomes are consistently detected in MDV-induced lymphomas, supporting the significance of telomeric integration in MDV oncogenesis and pathogenesis (McPherson and Delany, 2016).

Reticuloendotheliosis virus (REV)

REV, a gammaretrovirus, integrates its proviral DNA into the host chicken genome and has also been identified within the genomes of large DNA viruses, including FPV and MDV, through inter-viral genetic incorporation events (Emad et al., 2024; Chacón et al., 2025). Insertion of REV-derived long terminal repeat (LTR) sequences into the MDV genome has been documented; however, this does not result in the generation of infectious REV particles (Emad et al., 2024; Chacón et al., 2025). REV therefore exhibits two distinct biological contexts of genetic interaction: (i) classical retroviral integration into the chicken genome, and (ii) incorporation of REV-derived sequences into the genomes of large DNA viruses such as FPV and MDV. This second process represents non-canonical inter-viral genetic exchange, resulting in chimeric viral genomes. REV is therefore capable of two biologically distinct processes: (i) classical retroviral integration into the chicken genome, and (ii) genetic incorporation into the genomes of other DNA viruses such as FPV and MDV. This second process represents non-canonical inter-viral recombination or sequence acquisition, resulting in chimeric viral genomes. Such viral chimeras may alter the biological properties of the affected viruses, including virulence and antigenic profile, and have been associated with reduced vaccine efficacy in poultry systems (Emad et al., 2024; Chacón et al., 2025).

Co-infection between retroviruses and other oncogenic viruses; It was reported that co-infection between retroviruses and other oncogenic viruses can increase tumor incidence or alter disease outcomes, especially when one agent provides conditions that favor integration, transformation, or recombination with endogenous loci. A specific example in chickens shows that endogenous ALV combined with MDV can boost the incidence of lymphoid leukosis–like bursal lymphomas in susceptible chickens. (Mays et al., 2019).

Table 1: Poultry viruses and integration sites.

Virus Type	Virus	Integration site	Primary outcome
Retrovirus	ALV, REV, EAV-HP	Host chromosomes	Mandatory replication; vertical transmission
Herpesvirus	MDV	Host telomeres	Latency; tumor formation (lymphomas)
Chimeric	REV in MDV	Other viral genomes	Altered virulence; vaccine interference

ALV: Avian leukosis virus. REV: Reticuloendotheliosis virus EAV-HP: Endogenous retrovirus elements in the chicken genome, designated EAV-HP MDV: Marek's disease virus.

Impacts of viral integrations in poultry

Epidemiological impacts

Viral integration is a critical determinant of disease dynamics in poultry, especially for viruses that stably incorporate their genetic material into the host genome. Following integration, viral DNA becomes a permanent or long-term element of host chromosomal DNA, which allows infection to persist beyond periods of active virion production (Crittenden et al., 1987). This integrated state enables immune evasion and sustained maintenance of viral genetic material, thereby supporting prolonged infection cycles. In germline-associated cells, integrated viral sequences are transmitted vertically to offspring, ensuring the propagation of viral genomes across generations.

From an epidemiological perspective, viral integration creates persistent infection reservoirs by stabilizing viral genomes even without active replication. This persistence enables long-term circulation within breeding systems and makes vertical transmission a primary mechanism for viral maintenance. As a result, integrated viral genomes continuously re-seed infection in poultry populations, complicating eradication compared to infections caused solely by lytic viruses. Additionally, integration-induced disruptions of host genomic regulation, such as proto-oncogene activation or altered gene expression, contribute to oncogenesis in viruses like ALV and MDV, thereby increasing the population-level disease burden (Witter and Fadly, 2003).

Vaccine escape of integrated viruses

Integrated or latency-capable viruses, such as MDV and REV, are major avian pathogens that persist through genomic integration or stable latency, allowing continued circulation despite vaccination (Gimeno, 2008; Zhu et al., 2024). The evolution of vaccine-escape mechanisms under immune pressure is a key factor in their persistence.

MDV impairs innate immunity by antagonizing pattern recognition receptor (PRR)-mediated signaling, including cGAS–STING, MDA5/MAVS, and TLR-associated pathways, which leads to reduced type I interferon responses (Zhu et al., 2024). MDV also downregulates MHC class I expression during lytic replication, thereby impairing $CD8^+$ T-cell recognition (McPherson et al., 2016). Current MDV vaccines provide non-sterilizing (leaky) immunity, so vaccinated birds remain susceptible to infection and viral shedding. This situation generates selective pressure that favors the emergence of more virulent strains (Hagag et al., 2020).

REV promotes immune evasion by disrupting signaling pathways, resulting in diminished interferon-mediated antiviral responses (Wu et al., 2023). Additionally, REV can integrate into large DNA viruses such as FPV and herpesvirus of turkeys (HVT), generating chimeric viral genomes that alter pathogenicity and compromise the stability of vaccine vectors (Read et al., 2015). REV may also use exosomal packaging to shield viral antigens from neutralizing antibodies (Su et al., 2021).

The role of viral integration in poultry vaccination

Pathogens such as MDV and REV persist through stable genomic integration or latent

infection, facilitating long-term maintenance despite vaccine-induced selective pressure (Gimeno, 2008; Zhu et al., 2024). Integration-associated persistence allows infected cells to act as permanent reservoirs, sustaining viral genomes independently of active replication. Consequently, vaccinated birds may still become infected and shed virus, sustaining population-level circulation and selection pressure. Viral integration also contributes to indirect immune evasion. Latent or integrated viral genomes reduce antigen presentation, limiting immune recognition and preventing the development of sterilizing immunity. In MDV, this process involves suppression of innate sensing pathways such as cGAS–STING and TLR signaling, as well as downregulation of MHC class I, which impairs $CD8^+$ T-cell recognition (McPherson et al., 2016; Zhu et al., 2024). Similarly, REV infection interferes with interferon-mediated antiviral responses, further supporting viral persistence in vaccinated flocks (Wu et al., 2023). Current poultry vaccines, especially those targeting MDV, often provide non-sterilizing or "leaky" immunity. This partial protection permits continued viral replication and the emergence of more virulent strains under selection pressure (Hagag et al., 2020; Bailey et al., 2020). Over time, these conditions favor viral survival strategies associated with integration and latency, highlighting their epidemiological importance in poultry viral ecology. Recombinant vectors, specifically FPV and Herpesvirus of Turkeys HVT, are widely utilized for their ability to carry heterologous antigens (Romanutti et al., 2020).

Table 2: Impact of viral integration on vaccine design, efficacy, and immune evasion.

Aspect	Mechanism/action	Impact on vaccination	References
Vaccine design	• Integrational safety vs. oncogenesis: Risk of insertional mutagenesis in classical retrovectors.	• Necessitates development of non-integrating platforms like IDLVs.	Kennedy et al. (2020); Mouzakis et al. (2025)
	• Latency targeting: Integrated viruses establish transcriptionally silent reservoirs.	• Requires "shock-and-kill" or CTL-stimulating strategies to clear reservoirs.	Kennedy et al. (2020)
	• Envelope effects: Retroviral envelope proteins can be inherently immunosuppressive.	• Reduces vaccine-induced cellular immunity and cross-protection.	Mouzakis et al. (2025)
Vaccine efficacy	• Reservoir establishment: Persistence in memory T-cells or germline.	• Enables long-term viral maintenance despite high flock antibody titers.	Hafiz et al. (2022)
	• Immune waning: Constant presence of integrated viral antigens drives exhaustion.	• Reduces the long-term durability of vaccine protection.	Villanueva-Flores et al. (2025)
	• Leaky Immunity: Vaccines reduce clinical symptoms but not infection or shedding.	• Drives selection pressure for more virulent strains (e.g., vvMDV).	Gimeno (2008); Hafiz et al. (2022)
Immune evasion	• Antigenic variation: High mutation rates in persistent integrated genomes.	• Promotes vaccine escape by reducing neutralizing antibody affinity.	Maltseva et al. (2024)
	• MHC-I downregulation: Viral interference with host antigen presentation.	• Impairs $CD8^+$ T-cell recognition of cells harboring integrated DNA.	Bachmann et al. (2025)
	• IFN antagonism: Inhibition of cGAS–STING and JAK–STAT signaling.	• Weakens innate immune priming and early antiviral responses.	Maltseva et al. (2024)

Strategies targeting viral integration

Antiviral drugs and gene-based therapeutic

Integrase Strand Transfer Inhibitors (INSTIs) represent the primary class of antiviral drugs that target viral integration. These compounds are specifically developed to inhibit viruses that require stable integration of viral DNA into the host genome, a process most notably observed in retroviruses such as HIV. INSTIs act by targeting viral enzyme integrase, which facilitates the insertion of viral DNA into host chromosomal DNA (Peng et al., 2022). By binding to the active site of integrase, INSTIs block the strand transfer step, thereby preventing the covalent linkage between viral and host DNA and halting provirus establishment. Consequently, viral genomes remain episomal and cannot support productive transcription or replication, which effectively suppresses long-term infection (Lou et al., 2014; Kausar et al., 2021). Table 3 lists antiviral drugs that target viral integration.

Table 3: Antiviral drugs targeting viral integration (Peng et al., 2022).

Drug Name	Generation	Mode of action
Raltegravir	First	The first integrase inhibitor approved for clinical use; highly potent and well-tolerated
Elvitegravir	First	Often used as part of a fixed-dose combination (e.g., Stribild)
Dolutegravir	Second	Advanced second-generation inhibitor with high potency, once-daily dosing, and low cross-resistance with earlier drugs
Bictegravir	Second	Used in potent combination therapies like Biktarvy
Cabotegravir	Second	Available as a long-acting injectable for both treatment and prevention (PrEP)

Gene therapy vectors and CRISPR/Cas systems for targeting viral integration

Gene therapy seeks to treat disease by introducing exogenous genetic material (transgenes) into cells, most often through viral vectors that utilize natural viral entry mechanisms (Li et al., 2023; Ghosh et al., 2020). Since the 1970s, viral vectors have become central to gene delivery because of their high efficiency (Ginn et al., 2018). The primary platforms are adenovirus (Ad), adeno-associated virus (AAV), retrovirus (RV), lentivirus (LV), and herpes simplex virus (HSV). DNA viral vectors such as Ad, AAV, and HSV typically remain episomal, whereas retroviral and lentiviral vectors integrate into host genomes, resulting in stable but potentially genotoxic expression (Ghosh et al., 2020). These vector systems vary in payload capacity, tropism, and immunogenicity, with packaging limits ranging from approximately 36 kb for Ad to 3–4 kb for AAV (Zhao et al., 2021). Safe, effective vector designs and the use of tissue-specific promoters to minimize the risk of insertional mutagenesis (Hacein-Bey-Abina et al., 2008). CRISPR/Cas systems represent a complementary approach for directly targeting viral integration. Cas9 can be engineered to recognize and cleave integrated viral DNA (proviruses), facilitating the disruption or excision of persistent genomes such as HIV (Bayat et al., 2018; Baddeley and Isalan, 2021). This strategy offers the potential for a functional cure by eliminating latent viral reservoirs that evade conventional therapies (Hussein et al., 2023). Advanced techniques, including base and prime editing, enable precise modification of viral sequences without inducing double-strand breaks, thereby reducing genomic instability. Delivery remains a significant challenge, with AAV vectors and lipid nanoparticles currently serving as the primary platforms (Nouri et al., 2025). Despite these promising antiviral applications, limitations persist, including incomplete targeting of infected cells, off-target effects, and the emergence of viral escape mutations (Aubert et al., 2024).

Future perspectives

Current situation and future: Improved mechanistic understanding of virus–host interactions has enabled next-generation vectors that reduce many earlier risks (e.g., self-inactivating LVs, engineered AAV capsids, depleted viral proteins). Although vivo gene delivery still faces substantial challenges (safety, immunogenicity, payload limits, and durable expression), iterative improvements continue to expand viable clinical applications for monogenic diseases, cancer immunotherapy, and other indications (Cox et al., 2015; Ghosh et al., 2020).

Engineered Non-Retroviral Integration Systems. Multiple experimental systems enable stable and targeted integration of DNA into host genomes without requiring complete viral replication: i) Retroviral Integrase-Based Systems: Minimalist retroviral vectors or purified integrase enzymes can mediate precise insertion of therapeutic transgenes using LTR recognition sequences while removing viral virulence components (Yoder et al., 2021; Jaballah et al., 2025; Chiang et al., 2020). ii) Engineered Transposases (DNA-Transposition): Systems such as Sleeping Beauty utilize a cut-and-paste

mechanism to achieve stable DNA integration in the absence of viral structural proteins (Wilber et al., 2011). iii) RNA-Guided Transposases (CRISPR-Associated Transposons, CASTs): CAST systems integrate CRISPR-based targeting with transposase machinery to insert DNA at specified genomic loci without inducing double-strand breaks (Gelsinger et al., 2024; VanDieren and Barrick, 2025). iv) Controlled Retroviral Vectors with Insulators: Self-inactivating (SIN) vectors and chromatin insulators (e.g., cHS4) reduce off-target effects and insertional mutagenesis (Hanawa et al., 2009; Uchida et al., 2013). v) Targeted Retroviral Transduction: Fusing integrase with specific DNA-binding domains can redirect integration to safe genomic loci; however, further optimization is required (Tan et al., 2004; Lim et al., 2010).

This approach aligns with the One Health concept, recognizing that human and avian health are interconnected, particularly regarding shared viruses like influenza, which can cross species barriers. Leveraging human medical studies is highly relevant because many viruses, including metapneumoviruses, share conserved genomic architectures in both human and avian hosts. Human studies often provide more advanced molecular data, offering insights into viral pathogenesis, immunology, and vaccine development (e.g., VLPs) that can inform veterinary practices, particularly for significant poultry pathogens like AIV, NDV, and IBV (Ellwanger et al., 2021).

Conclusion

Both virus-to-virus integration and virus-to-host genome integration are critical determinants of poultry disease epidemiology. These processes drive the emergence of novel viral strains, modify host-virus interactions, and affect disease outcomes. A comprehensive understanding of the mechanisms and consequences of viral integration is essential for the development of effective control and prevention strategies. Vaccine production remains a central element of viral control in poultry, providing targeted protection and mitigating the effects of integrated and evolving viral pathogens. Ongoing research into viral integration and transmission is required to optimize disease management and sustain poultry health and productivity. For breeding programs, the most promising future direction is an integrated genomic strategy by combining immune-locus selection (e.g., MHC and resistance QTL) with ERV-aware genomic profiling to identify candidate loci associated with resistance to viruses, followed by rigorous validation through controlled challenge and multi-generation evaluation to develop resilient flocks.

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