An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Recommendation on the Use of Live Attenuated Influenza Vaccine (LAIV) in HIV-Infected Individuals

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada

Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.
    —Public Health Agency of Canada

PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Over the coming years NACI will be refining methodological approaches to include these factors. Not all NACI Statements will require in-depth analyses of all programmatic factors. As NACI works towards full implementation of the expanded mandate, select Statements will include varying degrees of programmatic analyses for public health programs.

PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF THE INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of this statement for details.

1. What

Annual influenza vaccination is recommended for all individuals 6 months of age and older, including those with human immunodeficiency virus (HIV) infection. Prior to this statement, NACI recommended that live attenuated influenza vaccine (LAIV) was contraindicated for all individuals with HIV infection.

2. Who

This statement updates NACI's guidance on the use of LAIV for HIV-infected individuals.

3. How

LAIV may be considered as an option for annual vaccination of children 2–17 years of age with stable HIV infection on highly active antiretroviral therapy (HAART) and with adequate immune function. LAIV remains contraindicated for adults with HIV. LAIV should only be considered in children with HIV who meet the following criteria:

- Receiving HAART for ≥4 months;
- CD4 count ≥500/μL if 2–5 years of age, or ≥200/μL if 6–17 years of age (measured within 100 days before administration of LAIV); and
- HIV plasma RNA <10,000 copies/mL (measured within 100 days before administration of LAIV).

Intramuscular (IM) influenza vaccination still is considered the standard for children living with HIV by NACI and the Canadian Pediatric & Perinatal HIV/AIDS Research Group (CPARG), particularly for those without HIV viral load suppression (i.e. plasma HIV RNA >40 copies/mL). However, if IM vaccination is not accepted by the patient or substitute decision maker, LAIV would be reasonable for children meeting the criteria outlined above.

4. Why

LAIV is considered immunogenic in HIV-infected children 2–17 years of age with stable HIV infection on HAART and with adequate immune function. LAIV has a comparable immunogenicity profile to inactivated influenza vaccine for this population. No concerns regarding safety have been demonstrated, but there is currently insufficient evidence to draw a conclusion on the rate of uncommon, rare, and very rare adverse events (AE) after vaccination with LAIV in individuals with HIV. Intranasal administration of the influenza vaccine may be preferable to intramuscular injection for some children. There is insufficient evidence at this time to recommend LAIV for adults with HIV.

I.   INTRODUCTION

Annual vaccination against influenza is recommended for all individuals 6 months of age and older, including those with human immunodeficiency virus (HIV) infection[1]. Acquired immunodeficiency syndrome is associated with increased influenza-related morbidity and mortality. However, data on the burden of influenza illness in individuals living with HIV who have less severe immunosuppression are sparse and likely influenced by the degree of immunosuppression, effectiveness of antiretroviral therapy, and comorbidities[2-4]. Although data are limited, influenza vaccination is immunogenic and efficacious in a substantial proportion of individuals with HIV[5-7].

Live attenuated influenza vaccine (LAIV) is a type of seasonal influenza vaccine that is administered as an intranasal spray. The influenza viruses contained in LAIV are attenuated so that they do not cause influenza and are cold-adapted and temperature sensitive, so that they replicate in the nasal mucosa rather than the lower respiratory tract. A quadrivalent formulation of LAIV (FluMist® Quadrivalent, AstraZeneca) is currently authorized for use in Canada for individuals 2–59 years of age. There are several LAIV-specific contraindications, including for children and adults with immune compromising conditions. For these populations, inactivated influenza vaccine (IIV) has been recommended. NACI's previous recommendation against LAIV use for individuals with immune compromising conditions was based on expert opinion and the small number of studies in children and adults with mild to moderate immune suppression due to HIV infection and cancer (NACI Recommendation Grade D)[8].

Live vaccines are generally contraindicated in persons with immunodeficiency, out of concern that the live virus may cause disease in the host. However, for infections for which the disease burden is significant and live vaccines are the only option (e.g., measles), criteria have been established to permit vaccination when immune function is not severely impaired. Live attenuated vaccines, such as measles-mumps-rubella (MMR) and varicella vaccines, have been shown to be safe and are recommended for persons with HIV if the infection is controlled and immune function is satisfactory.

An environmental scan of recommendations on LAIV use in HIV-infected individuals from Canadian provinces and territories and from selected high income countries revealed that LAIV is contraindicated for HIV-infected individuals in British Columbia, Alberta, Manitoba, Saskatchewan, New Brunswick and in the United States (US)[1][2][9-14], and for immunocompromised individuals in Ontario, Newfoundland and Labrador, Yukon[15-17]. Some jurisdictions, such as Quebec, the United Kingdom, and France[18-20] and professional organizations including the Infectious Diseases Society of America and the British Children's HIV Association[21-22] state that LAIV may be given to individuals with HIV who meet specific criteria. The product monograph for FluMist® Quadrivalent cautions that the administration of the vaccine to immunosuppressed individuals should be based on careful consideration of potential benefits and risks, but does not explicitly identify this vaccine as being contraindicated for this population[23].

Guidance objective
The objective of this advisory committee statement is to review the efficacy and effectiveness, immunogenicity, and safety evidence on LAIV use in HIV-infected individuals and to provide updated guidance on the use of LAIV in this population.

II.   METHODS

The systematic review's methodology was specified a priori in a written protocol that included review questions, search strategy, inclusion and exclusion criteria, and quality assessment. NACI's Influenza Working Group (IWG) reviewed and approved the protocol.

Research question
What are the efficacy and effectiveness, immunogenicity, and safety of LAIV in HIV-infected individuals?

P (population):	HIV-infected individuals
I (intervention):	Live attenuated influenza vaccine
C (comparison):	Inactivated influenza vaccine or placebo given to HIV-infected individuals, LAIV given to individuals without HIV, or no comparator
O (outcomes):	Efficacy and effectiveness, immunogenicity, safety, and vaccine virus shedding

The search strategy was developed based on the research question and PICO in consultation with a librarian of the Health Library of Health Canada and PHAC (search strategy available upon request). The EMBASE, MEDLINE, Scopus, ProQuest Public Health, ClinicalTrials.gov, and PROSPERO electronic databases were searched for primary research articles and case reports from inception until April 13, 2018, using search terms for LAIV and HIV. Searches were restricted to articles published in English and French. In addition, hand searching of included studies was performed by checking reference lists to identify additional relevant publications. Hand searching of reference lists was also performed for any relevant retrieved secondary research articles. Two reviewers independently screened the records retrieved from database searches for relevance. They were initially screened by title and abstract for potential eligibility. The full-text of records deemed potentially eligible were obtained and further reviewed by both reviewers for potential inclusion in the review. Appendix A shows the PRISMA Flow Diagram. One reviewer extracted data and a second reviewer independently validated the extracted data. Two reviewers independently appraised study's quality using the criteria outlined by Harris et al.[24]. Any disagreements or discrepancies were resolved by discussion and consensus. The knowledge synthesis was performed by two NACI members, DM and ND, and was supervised by NACI's IWG.

Studies were included if they met the following criteria:
1. The study population or subpopulation consisted of HIV-infected individuals; and
2. The study assessed efficacy or effectiveness, immunogenicity, safety (including impact on markers of HIV infection), or vaccine virus shedding following LAIV receipt.

Studies were excluded if they met one or more of the following criteria:
1. The study did not present data on any of: efficacy and effectiveness, immunogenicity, safety or vaccine virus shedding outcomes for LAIV;
2. The study was in a language other than English or French;
3. The study was a non-human or in vitro study;
4. The article was an editorial, opinion, or news report;

5. The study presented only secondary research (e.g., literature review, systematic review, meta-analysis); or

6. The LAIV investigated was not a seasonal LAIV based on the Ann Arbor backbone.

Canadian Adverse Events Following Immunization Surveillance System

AE following immunization are monitored through the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS). A search was performed through CAEFISS to identify reports on AE following vaccination with LAIV in HIV-infected individuals. Reports with a vaccine trade name of FluMist® or FluMist® Quadrivalent and mention of keywords (e.g. HIV, HIV infection, AIDS, etc.) in medical history or supplementary information were returned.

Recommendation Development

Following critical appraisal of individual studies, summary tables with ratings of the quality of evidence using NACI's methodological hierarchy (Tables 3, 4 and 5) were prepared, and proposed recommendations for vaccine use developed. Following thorough review of the evidence, NACI approved the recommendation contained in this statement on June 5, 2019. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the following sections.

III.   USE OF LAIV IN HIV-INFECTED INDIVIDUALS

III.1   LAIV Preparation Authorized for Use in Canada

LAIV is given as an intranasal spray. The influenza viruses contained in LAIV are attenuated so that they do not cause influenza and are cold-adapted and temperature sensitive, so that they replicate in the nasal mucosa, rather than the lower respiratory tract. A quadrivalent LAIV (LAIV4; FluMist® Quadrivalent) is authorized for use in Canada for individuals 2–59 years of age. The trivalent LAIV (LAIV3; FluMist®, AstraZeneca) is no longer available in Canada.

Table 1. Characteristics of FluMist® Quadrivalent influenza vaccine

Route of administration	Dosage	Clinically relevant non-medicinal ingredients
Intranasal	Each 0.2 mL dose contains $10^{6.5-7.5}$ fluorescent focus units of live attenuated reassortants given as 0.1 mL in each nostril.	• Arginine • Egg protein (trace amount) • Gelatin hydrolysate • Gentamicin (trace amount) • Monosodium glutamate • Sucrose

III.2   Vaccine Efficacy and Effectiveness

No studies on the efficacy or effectiveness of LAIV in HIV-infected individuals were identified.

III.3   Vaccine Immunogenicity

III.3.1   Correlates of Protection against Influenza Infection

For hemagglutination inhibition (HI) serological assessments, an HI titre of 1:40 has been suggested to correlate with an efficacy of 50–70% against clinical symptoms of influenza in healthy adults, but may vary, depending on individual characteristics, population, age, and vaccine type[25]. A similar correlate for protection between antibody titre and vaccine efficacy has not been determined for children. The concentration of observed serum HI antibodies is calculated as the geometric mean titre (GMT), which is the mean of the logarithmic values of serum antibody titres. Seroprotection rate is the proportion of subjects achieving an HI titre of ≥1:40 post-vaccination. Seroconversion rate is the proportion of subjects achieving significant increase from pre- to post-vaccination HI titres (≤1:10 to ≥1:40 or ≥4-fold rise in HI titres). Fold rise is the ratio of post- and pre-vaccination HI titres. Correlates of protection against influenza have not been well-established for other assessments of humoral immunity, such as microneutralization (MN) assay[26], and assessments of cell-mediated immunity.

III.3.2   Characteristics of Immunogenicity Studies

Three studies investigated the immunogenicity of LAIV in a total of 191 HIV-infected children and young adults 2–25 years of age[27-29] and one study investigated the immunogenicity in 28 HIV-infected adults 18 years of age and older[30]. All four studies were of good quality according to ratings of Harris et al (2001)[24] . Key study characteristics are summarized in Table 2. Additional details on the studies assessing immunogenicity can be found in Table 7.

Table 2. Characteristics of immunogenicity studies included in the systematic review

Author	Study design (vaccine administered)	Study population	Outcomes
King et al. (2000)[30]	RCT (LAIV3 vs. placebo)	Adults 18–58 years of age with HIV (n=57 total; 28 received LAIV3) and without HIV (n=54 total; 27 received LAIV3) Eligibility criteria for HIV-infected subject: Immune class A1-2, plasma HIV RNA <10,000 copies/mL, and >200 CD4 cells/µL (and if ≤500 CD4 cells/µL, be on stable antiretroviral regimen) within three months prior to vaccination.	HI antibody response
King et al. (2001)[27]	RCT (LAIV3)	Children less than 8 years of age with HIV (n=24) and without HIV (n=25) Eligibility criteria for HIV-infected subject: Immune class N1-2 or A1-2 and plasma HIV RNA <10,000 copies/mL within 100 days prior to enrolment.	HI antibody response
Levin et al. (2008)[28] Weinberg et al. (2010a)[31] Weinberg et al. (2010b)[32]	RCT (LAIV3 vs. IIV3)	Children 5 to less than 18 years of age with HIV (n=243 total; 122 received LAIV3 and 121 received IIV3) Eligibility criteria for HIV-infected subject: Stable HIV on HAART for ≥16 weeks and with HIV-1 plasma HIV RNA <60,000 copies/mL within 60 days prior to vaccination. All subjects had received IIV3 in at least one of the prior two years.	HI and MN antibody response; Salivary mucosal IgA and IgG antibody response; T cell response.
Curtis et al. (2015)[29] Weinberg et al. (2016)[33]	Prospective cohort study (LAIV4)	Children and young adults 2–25 years of age with HIV (n=45) and without HIV (n=55) Eligibility criteria for HIV-infected subject: CD4 >15% or >200 cells/µL on cART, or >25% or >500 cells/µL if not on cART. All subjects had received influenza vaccine in one or more previous seasons.	HI and MN antibody response; Nasal mucosal IgA response; IgA and IgG memory B cell response; T cell response.

Abbreviations: cART, combination antiretroviral therapy; HAART, highly active antiretroviral therapy; HI, hemagglutination inhibition; HIV, human immunodeficiency virus; IgA: immunoglobulin A; IgG: immunoglobulin G; IIV3, trivalent inactivated influenza vaccine; LAIV3, trivalent live attenuated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; MN, Microneutralization; RCT, randomized controlled trial; RNA, ribonucleic acid.

III.3.3 Hemagglutination Inhibition Antibody Response

Three studies looked at HI antibody response to LAIV in HIV-infected children and young adults[27-29] and one looked at the response to LAIV in HIV-infected adults[30].

Response by HIV infection status

The King et al. (2001) RCT on LAIV3 in children with and without HIV found that after one dose of LAIV, 59% of the HIV-infected and 76% of the non-HIV infected children achieved seroprotection against at least one of the three vaccine strains[27]. Seroprotection against at least one of the three vaccine strains increased to 77% for HIV-infected and 83% for non-HIV infected children 28–35 days after administration of the second LAIV dose. There was no statistically significant difference between the rate and magnitude of serologic responses of the HIV-infected and non-HIV infected children.

In the Curtis et al. (2015) prospective cohort study, pre- and post-vaccination seroprotection rates were not statistically different between the HIV-infected and non-HIV infected children and young adults for all four vaccine strains contained in LAIV4[29]. HI antibody responses were modest, such that the proportions of subjects with titres ≥1:40 at 14–21 day post-vaccination did not differ from baseline for A(H1N1), A(H3N2), and B/Victoria in either group. For B/Yamagata, seroprotection rate significantly increased in the HIV-infected group (p=0.03), but not in the non-HIV infected group.

In the King et al. (2000) RCT on LAIV3 vs. placebo in adults with and without HIV, the level of seroprotection before vaccination was high and very few individuals in any group showed a ≥4-fold rise in HI titres after vaccination[30]. GMT pre- and 28–35 days post-vaccination did not differ significantly among trial groups.

Response by vaccine type

The Levin et al. (2008) RCT on LAIV3 vs. trivalent IIV (IIV3) in children with HIV found that the proportions with HI titres ≥1:40 at baseline and at 4 and 24 weeks post-vaccination were similar in the two groups for A(H1N1) and A(H3N2), but higher with IIV3 for influenza B[28] at all three time points. The proportions with a 4-fold increase in titer for A(H1N1) were similar for LAIV3 and IIV3; however, significantly more IIV3 recipients had a 4-fold increase in titer against A(H3N2) and B. GMT after receipt of LAIV3 and IIV3 were similar for A(H1N1), but were significantly higher after receipt of IIV3 for A(H3N2) and B. Multivariate linear regression analyses showed direct relationships between pre- and 4 weeks post-vaccination GMT for all three strains with both LAIV3 and IIV3.

Response to mismatched strains

The Levin et al. (2008) RCT found that HI antibody responses to mismatched A(H3N2) and B strains not contained in the vaccines administered were increased with both LAIV3 and IIV3 at 4 and 24 weeks post-vaccination. However, IIV3 recipients had statistically significantly higher HI titres compared with LAIV3 recipients against the mismatched A(H3N2) and B strains at 4 and 24 weeks post-vaccination (p<0.0003 for the comparisons)[31].

The Curtis et al. (2015) retrospective cohort study looked at HI antibody responses in HIV-infected and non-HIV infected children and young adults following LAIV4 to the A(H1N1) and B/Yamagata vaccine strains, and additionally the drifted circulating A(H1N1) strain for the 2013–2014 season[33]. HI titres significantly increased 14–21 days post-vaccination against all three viruses (p≤0.02) and pre- and post-vaccination titres did not differ by HIV status pre- and post-vaccination and significantly increased 14–21 days post-vaccination against all three viruses (p≤0.02).

III.3.4 Microneutralization Antibody Response

Two studies looked at MN antibody response to LAIV in HIV-infected individuals[28][29].

Response by vaccine type

In the Levin et al. (2008) RCT, the proportion of HIV-infected children with MN titres of ≥1:40 were similar for LAIV3 and IIV3 at baseline and at 4 and 24 weeks post-vaccination for all three vaccine strains[28][31]. At 4 and 24 weeks post-vaccination, there were statistically significant increases in MN titres against all vaccine strains in LAIV3 and IIV3 recipients, but MN titres at 4 weeks post-vaccination were 2–3 fold higher with IIV3 than with LAIV3 ($p \leq 0.002$). In multivariate analysis, only the plasma HIV viral load was inversely associated with MN responses to all three vaccine strains in IIV3 recipients and to A(H1N1) in LAIV3 recipients.

Response to a mismatched strain

MN titres against the vaccine A(H1N1) strain and a mismatched circulating A(H1N1) strain were measured 14-21 days after vaccination with LAIV4. Titres increased significantly for both strains in non-HIV infected children and young adults. However, in HIV-infected children and young adults, the increase was only significant for the mismatched circulating A(H1N1) strain[33].

III.3.5 Mucosal Immunoglobulin A and Immunoglobulin G Antibody Response

Two studies looked at mucosal immunoglobulin A (IgA) antibody response[28][29] and one study looked at mucosal immunoglobulin G (IgG) antibody response[28] in HIV-infected children and young adults. There were no studies that looked at these responses in HIV-infected adults over 25 years of age.

Response by HIV infection status

Nasal IgA antibody concentrations against the vaccine strains contained in LAIV4 were found in the Curtis et al. (2015) study to have significantly increased post-vaccination in HIV-infected and non-infected children and young adults ($p<0.05$). Post-vaccination there was also an increase in antibody concentration against the drifted circulating A(H1N1) strain in HIV-infected children but not in the non-HIV infected group[29][33]. There were no significant differences in nasal IgA concentrations against any strain by HIV status, with the exception of post-vaccination IgA levels for B/Victoria, which were significantly higher in the HIV-infected group. IgA response occurred earlier and, for influenza A strains, persisted longer in the non-HIV infected group compared with the HIV-infected group.

No study looked at mucosal IgG antibody response in HIV-infected individuals compared to non-HIV infected individuals.

Response by vaccine type

In the Levin et al. (2008) RCT, both LAIV3 and IIV3 were found to increase salivary IgG antibodies in HIV-infected children. The increase was significantly higher with IIV3 than with LAIV3 at 4 weeks post-vaccination, but there was no significant difference between the groups at 24 weeks post-vaccination. Multivariate analysis showed that salivary IgG responses at 4 weeks post-vaccination to either vaccine were directly associated with baseline salivary IgG antibody concentrations and inversely associated with baseline plasma HIV viral load[28][31]. Salivary IgA antibody responses were detected only in a minority of participants and therefore no meaningful findings were reported[28][31].

III.3.6 IgA/IgG Memory B Cell Response

Only one study investigated IgA/IgG memory B cell response to LAIV in HIV-infected children and young adults[29]. None of the studies investigated this response in HIV-infected adults aged over 25 years.

Response by HIV infection status
The Curtis et al. (2015) prospective cohort study, supplemented with data from Weinberg at al. (2016), of children and young adults found that HIV status was not associated with any differences in IgG memory B cell pre-LAIV4 vaccination responses to the A(H1N1) and B/Yamagata vaccine strains or to the drifted circulating A(H1N1) strain. There were no significant differences in responses at 14–21 days post-vaccination by HIV status for the A(H1N1) vaccine strain or the A(H1N1) drifted strain; however, IgG memory B cell response for B/Yamagata vaccine strain was lower in the HIV-infected group than in the non-HIV infected group (p=0.04)[33]. Most study subjects did not have detectable IgA memory B cells before or after vaccination for any of the influenza strains, regardless of HIV status[33].

III.3.7 T Cell Response

Two studies investigated T cell response to LAIV in HIV-infected children and young adults[28][29]. None of the studies investigated T cell response to LAIV in HIV-infected adults aged over 25 years.

Response by HIV infection status
HIV-infected children and young adults in the Curtis et al. (2015) study had lower T cell responses than non-HIV infected participants to all vaccine strains contained in LAIV4 pre-vaccination (p≤0.06) and lower responses at 14–21 days post-vaccination to the vaccine and drifted circulating A(H1N1) strains (p≤0.04), but not to B/Yamagata. The fold-rise in T cell responses from pre- to post-vaccination did not differ by HIV status[33].

Response by vaccine type
In a sub-analysis of the Levin et al. (2008) RCT of children with HIV, an unexpected decrease in T cell response was found for both LAIV3 and IIV3. At 4 and 24 weeks post-vaccination, IIV3 resulted in a significantly greater decrease in T cell response for the all influenza strains compared to LAIV3 (p≤0.02). Nonspecific responses to phytohemagglutinin also tended to decrease at 4 weeks after receipt of IIV3 compared with LAIV3 (p=0.07), but rebounded at 24 weeks[32].

III.4   Vaccine Safety

Five studies reported AE following LAIV; three in HIV-infected children and young adults[27-29] and two in HIV-infected adults[30][34]. Effects on HIV infection following receipt of LAIV were assessed in three studies; two in HIV-infected children[27][28] and one in HIV-infected adults[30]. Four of the studies were of good quality, and one was rated as fair. Additional details on the studies assessing vaccine safety can be found in Table 8.

III.4.1 Adverse Events Following Immunization

Adverse events by HIV infection status
A RCT of children with HIV (n=24) and without HIV (n=25) who received two doses of LAIV3 found no significant difference in number or duration of AE, including fever events and influenza-like illness (ILI), by HIV status[27]. There was one episode of ILI after 38 doses of LAIV in children with HIV and two episodes of ILI after 49 doses in children without HIV.

In a prospective cohort study of children and young adults aged 2–25 years with HIV (n=45) or without HIV (n=55) who received LAIV4, muscle aches and decreased energy occurred significantly more frequently in the HIV-infected group compared to the non-HIV infected group (17.8% vs. 3.6%, p=0.04 and 24.4% vs. 5.4%, p=0.01, respectively)[29]. No other expected or unsolicited AE, including runny nose and nasal congestion, differed between the two groups.

In a placebo-controlled RCT of LAIV3 use in adults with HIV (n=57 total; 28 received LAIV3) and without HIV (n=54 total; 27 received LAIV3), the rate of runny nose/nasal congestion was statistically significantly higher in LAIV3 recipients than placebo overall, but did not differ between the HIV-infected and non-HIV infected recipients of LAIV3 (61% vs. 78%)[30]. There were no significant differences in rates of other AE between LAIV and placebo recipients, or by HIV status.

Adverse events by vaccine type
In an RCT of children with HIV who received LAIV3 (n=122) or IIV3 (n=121), AE within 28 days of vaccination were similar for the two groups except for injection site reactions after IIV3 (23%) and more frequent nasopharyngeal symptoms after LAIV3 than IIV3 (52% vs. 31%, p=0.002)[28]. Pulmonary signs and symptoms, including asthma, wheezing, cough, chest pain and pneumonia, were not significantly different after LAIV3 than IIV3 (32% vs. 26%). Severity of reactions was also similar for the two groups.

Menegay et al. (2017) conducted a retrospective cohort study on ILI occurring within 30 days after vaccination with IIV or LAIV in HIV-infected US Air Force members. Of all active Air Force members diagnosed with HIV infection who received influenza vaccines over a ten year period, only one of 121 LAIV vaccinations (0.8%) was followed by an ILI diagnosis (defined as visits with an ICD-09 code for fever, an included acute respiratory code, or unspecified viral illness) within the 30-day post-vaccination period, compared to 16 ILI diagnoses associated with IIV. The number of IIV vaccinations was not stated[34].

No serious or severe AE attributable to LAIV were reported in any study.

Canadian Adverse Events Following Immunization Surveillance System
Since 2010 when LAIV was first licensed for use in Canada, there have been no reports of AE following vaccination with LAIV in HIV-infected individuals of any age.

III.4.2 Effects on HIV Infection
In two studies of children with HIV (n=146 total), LAIV3 had no significant effect on HIV RNA viral load or CD4 count[27][28]. One placebo-controlled study of adults with HIV who received LAIV3 (n=28) also showed no significant effect on HIV RNA viral load or CD4 count compared to placebo recipients (n=29)[30].

III.4.3 Vaccine Virus Shedding
Four studies reported on the effect of HIV status on LAIV vaccine virus shedding; three in HIV-infected children and young adults[27-29] and one in HIV-infected adults[30].

Vaccine virus shedding by HIV infection status
In two studies that looked for LAIV vaccine virus shedding in a total of 65 children and young adults with HIV and 80 without, there were no significant differences by HIV status in the proportions of subjects who shed vaccine virus, the quantity of virus shed[27][29], the types of virus shed, or the timing or duration of shedding[29]. In a study of adults, shedding of LAIV vaccine virus

was infrequent; one of 28 HIV-infected adults shed vaccine virus while none of the 27 non-HIV infected adults shed vaccine virus[30]. While another study did not report how many HIV-infected children shed vaccine virus, the authors stated that the frequency of shedding of vaccine virus was similar to that previously reported in both HIV-infected and non-HIV infected children, as well as in HIV-infected adults[28].

Immunologic predictors of vaccine virus shedding
Two studies investigated associations between various baseline immunologic parameters and vaccine virus shedding[28][29].

In a study of 113 HIV-infected children who received LAIV3[28], shedders of A(H1N1) had significantly lower HI and MN titres at baseline than children without shedding ($p < 0.001$ for both)[31]. A similar but non-significant trend was also seen for HI and MN titres with shedding of B[31] and for HI titres with A(H3N2)[28]. There were increased concentrations of salivary IgG and IgA at baseline in non-shedders compared to shedders of any influenza vaccine strain ($p = 0.05$ and 0.02, respectively). Neither HI nor MN baseline titres of ≥1:40 were completely protective against shedding[31].

A study of LAIV4 in children and young adults found no significant association between pre-vaccination serum HI or mucosal IgA antibody levels and vaccine virus shedding in 45 HIV-infected recipients[29]. In non-HIV infected recipients, high pre-vaccination serum HI titres were found to be significantly associated with low shedding of B/Victoria and B/Yamagata ($p < 0.001$), and high baseline nasal IgA concentrations were significantly associated with low B/Yamagata shedding ($p = 0.01$)[29].

IV. DISCUSSION

The present systematic review identified eight articles[27-34] that reported on five studies investigating the immunogenicity, the safety or both, of the administration of LAIV in HIV-infected individuals. Of the five studies identified, four were of good quality and one was fair. Common methodological concerns included small sample size[27][30] and differences between study groups at baseline[28][29][31-33].

Immunogenicity was studied in a total of 191 children and adults aged <25 years plus 28 adults over 18 years of age[27-33]. For serological responses, there were no major differences in HI antibody responses following receipt of LAIV between individuals with and without HIV[27][29][30]. In the study of Curtis et al. (2015), HI response to influenza B/Yamagata was better in the group with HIV than in the HIV negative control group. The HIV positive group was significantly older than the HIV negative group, which should have biased the results towards a lower response in this group[29][33].

Significant increase in MN titres was observed against mismatched, but not the vaccine A(H1N1) strain in a study of HIV-infected children and young adults[29][33].

The proportions of HIV-infected individuals with HI titers of ≥40 to LAIV and IIV were similar for influenza A(H1N1) and A(H3N2) but higher with IIV for influenza B and antibody titers were statistically significantly higher with IIV for influenza A(H3N2) and B vaccine strains[28] and for mismatched strains[31].

The proportion of HIV-infected individuals with MN titres ≥1:40 was similar post-vaccination for LAIV and IIV, but the magnitude of response was higher for IIV than LAIV[31]. As noted earlier, immunologic correlates of protection against influenza are relatively well established for HI antibodies for adults, but not for MN antibodies for adults and not for any serological response for children.

LAIV induces humoral and mucosal antibody responses as well as T cell responses, mimicking to some extent infection with wild strain influenza virus. Correlates of protection have not been established for LAIV, and HI titre may underestimate protection[35]. Mucosal IgA response or cell-mediated immunity have been suggested as contributing to protection after LAIV but have not been validated as correlates of protection (Weinberg 2016).

Only two studies looked at mucosal antibody responses. The available data suggest that there is no important difference in nasal IgA antibody response to LAIV by HIV status[29][33], or in salivary IgG antibody response to LAIV and IIV in HIV-infected individuals[28][31].

There is a paucity of evidence for cell-mediated responses. One study investigated memory B cell responses and T cell responses in children and young adults. IgG memory B cell responses did not significantly differ by HIV status for influenza A(H1N1) or A(H3N2); however, a lower absolute response to B/Yamagata post-vaccination was observed in the HIV-infected group[29][33]. The magnitude of the rise in T cell response did not differ by HIV status[29][33]. An earlier study in children with HIV found that, contrary to previous results in healthy children, T cell responses to both LAIV and IIV decreased below baseline post-vaccination, more so with IIV than with LAIV[28][32]. Similar results have not been reported elsewhere. Note that the immunologic correlates of cell-mediated responses for protection against influenza have not been well established.

AE following LAIV were studied in a total of 191 children and young adults (<25 years of age) and in 28 adults (with another 61 adults investigated only for vaccine-associated ILI)[27-30][34]. In both children and adults with HIV, rates of AE, including fever events and ILI, following receipt of LAIV were comparable to rates observed in individuals without HIV receiving LAIV except for more muscle aches and decreased energy in those with HIV[27][29][30]. Rates of AE in individuals with HIV receiving LAIV or IIV were also similar[28][34], with the exception of more frequent but expected nasopharyngeal symptoms (runny nose and nasal congestion) after LAIV[28].

Reports of ILI post-LAIV were rare. There were no serious adverse events (SAE) attributable to LAIV reported in HIV-infected subjects in any of the studies. However, the total number of subjects assessed is insufficient to detect uncommon or rare AE[36]. No AE were reported through CAEFISS. Given the small number of HIV-infected children in Canada, LAIV use would likely not have been sufficient to detect rare AE. It should also be noted that prior to the release of this Statement, NACI considered the use of LAIV in individuals infected with HIV to be contraindicated. LAIV also had no significant impact on HIV RNA viral load or CD4 count[27][28][30]. Vaccine virus shedding was studied in 191 children and young adults and 28 adults with HIV and did not differ by HIV infection status[27-30].

No studies were identified on the efficacy or effectiveness of LAIV in children or adults with HIV infection. However, studies with sufficient sample size required to address this evidence gap may not be feasible, particularly in children, given the limited numbers of children with HIV in high income countries where LAIV is used.

V.   RECOMMENDATIONS

The following section outlines the recommendations that NACI has made regarding the use of LAIV in HIV-infected individuals. Additional information on the strength of NACI recommendations and the grading of evidence is available in Table 4.

V.1 Recommendations for Individual Level Decision-Making

1. NACI recommends that LAIV may be considered as an option for children 2–17 years of age with stable HIV infection on highly active antiretroviral therapy (HAART) and with adequate immune function* (Discretionary NACI recommendation).
  ➢ NACI concludes that there is fair evidence (based on immunogenicity data) to recommend the use of LAIV vaccine as an option for children 2–17 years of age with stable HIV infection on HAART and adequate immune function (Grade B Evidence).
  ➢ NACI concludes that there is insufficient evidence to detect uncommon AE related to the use of LAIV in HIV infected children. LAIV appears to have a similar safety profile to IIV (Grade I Evidence).

*LAIV should only be considered in children with HIV who meet the following criteria:
  • Receiving HAART for ≥4 months;
  • CD4 count ≥500/µL if 2–5 years of age, or ≥200/µL if 6–17 years of age (measured within 100 days before administration of LAIV); and
  • HIV plasma RNA <10,000 copies/mL (measured within 100 days before administration of LAIV).

These criteria were based upon those used in the studies of LAIV in children with HIV[27-29], relevant guidance from reputable international organizations[19-21], NACI's guidance regarding the use of live attenuated MMR and varicella vaccines in individuals with HIV infection[37], and the revised United States Centers for Disease Control and Prevention (CDC) immune classification criteria for pediatric HIV infection[38]. Where thresholds from these sources differed, the most stringent criteria were selected.

Intramuscular (IM) influenza vaccination still is considered the standard for children living with HIV by NACI and CPARG, particularly for those without HIV viral load suppression (i.e. plasma HIV RNA >40 copies/mL). However, if IM vaccination is not accepted by the patient or substitute decision maker, LAIV would be reasonable for children meeting the criteria outlined above.

Summary of evidence and rationale

NACI concludes that LAIV is immunogenic in children on HAART with stable HIV infection and adequate immune function. This recommendation is "discretionary"; therefore, the decision to use LAIV in children with stable HIV should be made on a case-by-case basis. The evidence is considered Grade B as there is no direct evidence on the efficacy or effectiveness of LAIV in HIV-infected individuals and the sample size for the evidence base is small.
  o There is evidence that LAIV is immunogenic in children 2–17 years of age with stable HIV infection on HAART and with adequate immune function
  o LAIV appears to have a similar safety profile to IIV; however, the evidence base is too small to effectively detect uncommon, rare, and very rare AE related to the use of LAIV in HIV-infected children.

o   Children with HIV receive all the routine childhood vaccines and additional parenteral vaccines warranted by their actual or potential immunocompromised state[37]. Therefore, offering intranasal LAIV instead of IIV avoids one IM injection annually, and may improve acceptance of the seasonal influenza vaccine[39, 40].

NACI concluded that the quantity of evidence available on the immunogenicity and safety of LAIV in adults with HIV is insufficient to justify a recommendation for the use of LAIV in this group. (Grade I Evidence). This recommendation is based on expert opinion. In addition, NACI considered that most studies have found LAIV to have similar or slightly lower efficacy than IIV in adults[8] and consequently recommends IIV for adults with chronic conditions. Therefore, IIV remains the recommended formulation of influenza vaccine for adults with HIV and LAIV remains contraindicated in this population.

V.2 Management Options

With the publication of this NACI Statement, there are two influenza vaccines that may be used in children with HIV infection. The decision on which vaccine option is preferable depends on availability and key considerations for each vaccine. The relative merits of both vaccines are summarized in Table 3.

Table 3. Management options for influenza vaccination in children on HAART with stable HIV infection and adequate immune function

Options	Factors for consideration	Decision Points
1. IIV	***Immunogenicity*** IIV may be immunogenic in immunocompromised individuals depending on the degree of immune compromise. ***Safety*** IIV has been shown to be safe for HIV-infected individuals, and inactivated vaccines in general are safe for immunocompromised individuals. ***Acceptability*** IIV is given as an IM injection, which still is considered the standard for influenza vaccination in this group by NACI and CPARG.	***Immunogenicity*** Both vaccines are immunogenic but stimulate different types of immune responses. ***Safety*** Both vaccines appear to have similar safety profiles with regard to frequency and severity of AE, although injection site reactions were seen only with IIV and nasal symptoms were more common with LAIV. Although no safety concerns have been identified, the presence of uncommon AE related to LAIV in individuals with HIV is not known. ***Acceptability*** Some children and their parents may prefer intranasal vaccination; however, individual preferences vary. Therefore, a discussion with the patient or substitute decision maker on their preference for route of administration should take place prior to vaccination.
2. LAIV	***Immunogenicity*** LAIV is immunogenic in HIV-infected children with mild or moderate immunosuppression. ***Safety*** The sample sizes from studies assessing safety are not sufficient to detect uncommon AE. ***Acceptability*** LAIV is given intranasally, into both nostrils. Influenza vaccine given intranasally may be preferred to IM injection by some children and their parents.	

TABLES

Table 4. NACI Recommendations: Strength of Recommendation and Grade of Evidence

STRENGTH OF NACI RECOMMENDATION	GRADE OF EVIDENCE
Based on factors not isolated to strength of evidence (e.g. public health need)	*Based on assessment of the body of evidence*
Strong "*should/should not be* offered" ➢ Known/Anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not") ➢ Implication: A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A - *good evidence* to recommend B – *fair evidence* to recommend C – *conflicting evidence*, however other factors may influence decision-making D – *fair evidence* to recommend against E – *good evidence* to recommend against I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making
Discretionary "*may be* considered" ➢ Known/Anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists ➢ Implication: A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable	A - *good evidence* to recommend B – *fair evidence* to recommend C – *conflicting evidence*, however other factors may influence decision-making D – *fair evidence* to recommend against E – *good evidence* to recommend against I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making

Table 5. Ranking Individual Studies: Levels of Evidence Based on Research Design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 6. Ranking Individual Studies: Quality (internal validity) Rating of Evidence

Quality Rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

*General design specific criteria are outlined in Harris et al. (2001)[24].

Table 7. Summary of Evidence on the Immunogenicity of LAIV in HIV-Infected Individuals

	STUDY DETAILS				SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings**	**Level of Evidence**	**Quality**
King JC, Treanor J, Fast PE, Wolff M, Yan L, Iacuzio D, Readmond B, O'Brien D, Mallon K, Highsmith WE, Lambert JS, Belshe RB. *Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)–infected and non–HIV-infected adults*. J Infect Dis 2000;181:725-8[30]	LAIV3	RCT US Multicentre Influenza season unknown Funded by the NIH and Aviron (Mountain View, CA)	Adults 18–58 years of age HIV+: 51% female mean age, 40 years 28 vaccinated with LAIV3 29 received placebo HIV-: 65% female mean age, 34 years 27 vaccinated with LAIV3 27 received placebo HIV+ adults were considered eligible if they met the following criteria: CDC class A1-2, plasma HIV RNA PCR <10,000 copies/mL, >200 CD4 cells/µL within 3 months prior to vaccination and on stable antiretroviral regimen if CD4 ≤500 cells/µL.	Pre-vaccine: % with HI titre <1:8: | Strain	HIV+	HIV-
---	---	---
A(H1N1)	4%	11%
A(H3N2)	4%	4%
B	31%	11% | Seroconversion rate 28–35 days post-vaccination: | Strain	HIV+ LAIV3	HIV+ placebo	HIV- LAIV3	HIV- placebo
---	---	---	---	---
A(H1N1)	4%	8%	4%	0%
A(H3N2)	8%	8%	0%	0%
B	0%	4%	4%	0% | There were no important differences in HI GMT titres before and 28–35 post-vaccination in any participant group.	I	Good Small sample size.
King JC, Fast PE, Zangwill KM, Weinberg GA, Wolff M, Yan L, Newman F, Belshe RB,	LAIV3	RCT US Multicentre	Children 1–7 years of age HIV+:	HI seroconversion rate 28–35 post-vaccination with 2nd dose of LAIV: | Strain	Seroconversion rate (95% CI) HIV+	Seroconversion rate (95% CI) HIV-
---	---	---
A(H1N1)	69% (39, 91)	71% (49, 87)		I	Good Small sample size.

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of Evidence*	*Quality*
Kovacs A, Deville JG, Jelonek M. *Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children.* Pediatric Infect Dis J 2001; 20(12):1124-113[27]		1999–2000 influenza season Funded by the NIH and Aviron (Mountain View, CA)	24 children were vaccinated following schedule 1 or 2 46% female mean age, 4.7 years age range 1.0–7.9 years HIV-: 25 children were vaccinated following schedule 1 or 2 40% female mean age, 4.3 years age range 1.0–7.8 years Schedule 1: Day 0: LAIV3 (1st dose) Day 28–35: placebo Day 56–70: LAIV3 (2nd dose) Schedule 2: Day 0: placebo Day 28–35: LAIV3 (1st dose) Day 56–70: LAIV3 (2nd dose) HIV+ children were considered eligible if they met the following criteria: CDC class N1-2 or A1-2, HIV plasma RNA <10,000copies/mL, CD4 measured <100 days of enrolment.	<table><tr><td>A(H3N2)</td><td>38% (14, 68)</td><td>17% (5, 37)</td></tr><tr><td>B</td><td>62% (35, 90)</td><td>42% (22, 63)</td></tr><tr><td>Any strain</td><td>77% (46,95)</td><td>83% (63, 95)</td></tr></table> Seroconversion rate 28–35 post-vaccination with 2nd dose of LAIV in children seronegative† at baseline: <table><tr><td>Strain</td><td colspan="2">Seroconversion rate (95% CI)</td></tr><tr><td></td><td>HIV+</td><td>HIV-</td></tr><tr><td>A(H1N1)</td><td>86% (42, 100)</td><td>94% (71, 100)</td></tr><tr><td>A(H3N2)</td><td>Not assessed</td><td>100% (5, 100)</td></tr><tr><td>B</td><td>100% (37, 100)</td><td>89% (52, 100)</td></tr><tr><td>Any strain</td><td>88% (47, 100)</td><td>100% (84, 100)</td></tr></table> † Seronegative defined as baseline HI titre ≤4.		

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of Evidence*	*Quality*
Levin MJ, Song LY, Fenton T, Nachman S, Patterson J, Walker R, Kemble G, Allende M, Hultquist M, Yi T, Nowak B. *Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children.* Vaccine. 2008; 26: 4210–4217[28] Supplemented with additional details from Weinberg et al. (2010a) for MN [31] and Weinberg et al. (2010b) for CMI outcomes[32].	LAIV3	RCT US multicentre 2004–2005 influenza season Funded by the NIH	HIV-infected children 5–18 years of age LAIV3: 122 HIV+ children vaccinated with LAIV3; 47% female; mean age, 11.4 years IIV3: 121 HIV+ children vaccinated with IIV3 (Fluzone®, Aventis Pasteur, Inc.); 47% female; mean age, 11.9 year Children were considered eligible if they met the following criteria: on stable HAART regimen for ≥16 weeks and HIV-1 plasma RNA <60,000 copies/mL within 60 days prior to screening. Must have received IIV in at least one of the previous 2 years Stratified into three groups by immunological status	Pre-vaccine % with HI titre ≥40: | Strain	LAIV	IIV	p-value
---	---	---	---
A(H1N1)	42%	46%	Not significant
A(H3N2)	78%	88%	<0.05
B	23%	37%	<0.05	 HI GMT LAIV3/IIV3 ratios at 4 weeks and 24 weeks post-vaccination (LAIV3/IIV3): 	Strain	4 weeks Ratio (95% CI)	24 weeks Ratio (95% CI)
---	---	---
A(H1N1)	0.74 (0.53, 1.03)	0.81 (0.57, 1.15)
A(H3N2)	0.39 (0.29, 0.51)	0.62 (0.46, 0.82)
B	0.49 (0.39, 0.62)	0.54 (0.43, 0.67) | HI seroprotection rates post-vaccination: | Strain	4 weeks LAIV3	4 weeks IIV3	24 weeks LAIV3	24 weeks IIV3
---	---	---	---	---
A(H1N1)	63%	67%	45%	55%
A(H3N2)	92%	96%	95%	97%
B	33%	69%	32%	63% | Difference in seroprotection rates post-vaccination (%IIV3-%LAIV3): | Strain	4 weeks (95% CI)	24 weeks (95% CI)
---	---	---
A(H1N1)	4% (-9, 16)	10% (-3, 23)
A(H3N2)	4% (-2, 12)	3% (-3, 9)
B	35% (23, 47)	31% (18, 43) | HI seroconversion rates post-vaccination: | Strain	4 weeks LAIV3	4 weeks IIV3	24 weeks LAIV3	24 weeks IIV3
---	---	---	---	---
A(H1N1)	32%	33%	22%	16%
A(H3N2)	14%	44%	29%	34%		I	Good HI test used cold-adapted antigen, which may underestimate HI response to A(H1N1) with IIV[28]. Baseline higher proportion with titer of ≥40 for AHN2 and B in IIV vs LAIV group[28]. Salivary antibody may not reflect antibody production in the respiratory tract[31].

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of Evidence*	*Quality*
				(see content below)		

Summary of Key Findings:

B	11%	34%	11%	22%

Difference in seroconversion rates post-vaccination (%IIV3-%LAIV3):

Strain	4 weeks (95% CI)	24 weeks (95% CI)
A(H1N1)	1% (-12, 13)	-5% (-16, 5)
A(H3N2)	30% (18, 41)	5% (-8, 17)
B	23% (13, 34)	11% (1, 20)

The antibody responses to LAIV3 and IIV3 were similar regardless of the HIV immunological group.

HI GMT at 4 weeks post-vaccination were inversely related to baseline HIV RNA levels for LAIV3 for one strain [A(H3N2), p=0.02] and for IIV3 for all strains [A(H1N1), p=0.03; A(H3N2), p=0.05; B, p=0.004].

IIV3 HIV+ recipients had significantly higher GMT compared with LAIV3 recipients against mismatched A(H3N2) and B viruses at 4 and 24 weeks post-vaccination.

HI titres against mismatched influenza strains:

Strain	Week	LAIV3 n	LAIV3 GMT (95% CI)	IIV3 n	IIV3 GMT (95% CI)	p value
A/Sydney (H3N2)	0	116	65.2 (52.6, 80.8)	119	78.3 (63.4, 96.8)	0.23
	4	114	88.2 (72.7,106.9)	112	191.1 (157.3,232.0)	<0.0001
	24	110	100.2 (82.0, 122.4)	116	169.5 (139.5,206.0)	0.0003
B/Yamanashi	0	116	13.4 (10.3, 17.6)	119	14.4 (11.1, 18.8)	0.71
	4	114	17.3 (13.4, 22.2)	112	44.1 (34.2, 56.8)	<0.0001
	24	110	16.7 (12.7, 21.9)	116	36.6 (28.1, 47.7)	<0.0001

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of Evidence*	*Quality*
				At 4 weeks post-vaccination, HI titres against A/Sydney (H3N2) and B/Yamanashi (not included in the vaccines administered), were increased with both LAIV3 and IIV3. IIV3 recipients had significantly higher HI titres compared with LAIV3 recipients at 4 and 24 weeks post-vaccination. Proportion of HIV-infected individuals with anti-influenza MN titres post-vaccination ≥1:40: _(see table below)_ Baseline MN titers were similar in the two arms. There were no significant differences between LAIV3 and IIV3 at $p<0.05$ level. The magnitude of MN response was significantly related to baseline MN titres and plasma HIV RNA in multivariate regression analysis. Both vaccines increased salivary IgG antibody levels. The increase in salivary IgG GMT was significantly higher in IIV3 than LAIV3 HIV+ recipients at week 4 ($p=0.05$), but not at week 24 ($p>0.05$). Magnitude of IgG response was significantly related to baseline IgG GMT in multivariate regression analysis. Salivary IgA antibodies detected only in a minority of participants. There were no significant increases in IgA GMT at 4 weeks post-vaccination. At 24 weeks post-vaccination IgA GMT were significantly higher compared to baseline in IIV3 recipients ($p<0.01$), but not in LAIV3 recipients ($p>0.05$). T cell response to A(H3N2) and B vaccine virus decreased significantly by 1.4 fold at 4 weeks post-vaccination with		

Strain	4 weeks		24 weeks	
	LAIV3	IIV3	LAIV3	IIV3
A(H1N1)	96%	100%	96%	97%
A(H3N2)	100%	100%	100%	100%
B	81%	88%	80%	84%

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of Evidence*	*Quality*
				LAIV3 (p≤0.03), but was not significantly different from baseline at 24 weeks. T cell response to circulating and vaccine viruses decreased significantly by 1.5–3 fold at 4 weeks post-vaccination with IIV3 (p<0.001). IIV3 resulted in a significantly greater decrease in T cell response for influenza A strains compared to LAIV3 at 4 and 24 weeks post-vaccination (p≤0.02). There was no significant difference in T cell response for influenza B strains. IIV3 also resulted in a decrease in non-specific response to phytohemagglutinin. There were no differences by HIV immunologic status.		
Curtis D, Ning MF, Armon C, Li S, Weinberg A. *Safety, immunogenicity and shedding of LAIV4 in HIV-infected and uninfected children.* Vaccine. 2015; 33: 4790–4797[29] Supplemented with additional details from Weinberg et al. (2016) for CMI outcomes[33].	LAIV4	Prospective cohort study US Single centre 2013–2014 influenza season Funded by MedImmune and Colorado Clinical and Translational Sciences Institute	Children and young adults 2–25 years of age HIV+: 45 subjects were vaccinated with LAIV4 37.8% female median age, 18 years; 22% < 9 years old HIV-: 55 subjects were vaccinated with LAIV4 45.5% female median age, 10 years; 40% <9 years old HIV+ individuals were eligible if they met the following criteria: CD4 >15% or >200 cells/µL on cART or >25% and >500/µL if not on cART	HI seroprotection rates 14–21 days post-vaccination: <table><tr><td>Strain</td><td colspan="2">Total</td><td colspan="2"><9 years</td><td colspan="2">≥9 years</td></tr><tr><td></td><td>HIV+</td><td>HIV-</td><td>HIV+</td><td>HIV-</td><td>HIV+</td><td>HIV-</td></tr><tr><td>A(H1N1)</td><td>79.6%</td><td>68.6%</td><td>70.0%</td><td>61.9%</td><td>82.4%</td><td>73.3%</td></tr><tr><td>A(H3N2)</td><td>61.4%</td><td>68.6%</td><td>60.0%</td><td>61.9%</td><td>61.8%</td><td>73.3%</td></tr><tr><td>B/Vic</td><td>15.9%</td><td>7.8%</td><td>20.0%</td><td>0%</td><td>14.7%</td><td>13.3%</td></tr><tr><td>B/Yam</td><td>15.9%</td><td>13.7%</td><td>10.0%</td><td>4.8%</td><td>17.7%</td><td>20.0%</td></tr></table> There was no significant difference between HIV+ and HIV- individuals in pre- or post-vaccination seroprotection rates. HIV+ individuals had a significantly higher seroprotection rate to B/Yamagata (p=0.03) at 14–21 days post-vaccination than at baseline, but this was not significant when subdivided by <9 and ≥9 years of age. No other group was significantly different from baseline at 14–21 days. At baseline, ≥58% of participants had seroprotective titres against A(H1N1) and A(H3N2), while <10% had seroprotective titres against B. MN titres against the vaccine and circulating A(H1N1) strains were significantly increased in HIV- individuals at 14–21 days post-vaccination whereas only titres against the circulating A(H1N1) strain were significantly increased in HIV+ individuals.	II-2	Good HIV+ group were older; this may have biased towards better responses in the HIV- group. HIV+ group had higher baseline nasal IgA antibody levels to three of the four viruses and would have biased towards a better response in

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of Evidence*	*Quality*
			All received influenza vaccine in previous season(s)	Baseline nasal mucosal IgA antibody levels were significantly higher in the HIV+ group for A(H1N1), A(H3N2), B/Victoria (p≤0.01), but not for B/Yamagata Significant increases from pre- to post-vaccination were noted for all strains by day 2–5 in HIV- individuals and by day 7–10 in HIV+ individuals. A(H1N1) IgA concentration was no longer significant at day 14–21 in HIV+ individuals. There were no significant differences in IgA antibody concentrations by HIV status. Median fold-increase in T cell response 14–21 days post-vaccination: *table below* HIV+ individuals had significantly lower T cell responses to the A(H1N1) vaccine strain and circulating strain than HIV- individuals before vaccination and at 14–21 days post-vaccination (p≤0.04). The difference in T cell response from pre-vaccination to post-vaccination did not differ by HIV status. There were no significant differences in IgG memory B-cell response at 14–21 days to A(H1N1) vaccine or circulating strain by HIV status but response to B/Yamagata in HIV+ individuals was significantly lower than in HIV- individuals [median interquartile range of 9 (0; 21) vs. 14 (6; 28); p=0.04].		the HIV-group.

Median fold-increase in T cell response 14–21 days post-vaccination:

Strain	<9 years		≥9 years	
	HIV+	HIV-	HIV+	HIV-
A(H1N1) (vaccine)	1.1	1.1	1.0	1.0
B/Yam	1.3	1.3	1.7	1.4

Abbreviations: cART: combination antiretroviral therapy; CDC: Centers for Disease Control and Prevention (United States); CI: confidence interval; CMI: cell-mediated immunity; GMT: geometric mean titre; HAART: highly active antiretroviral therapy; HI: hemagglutination inhibition; HIV: human immunodeficiency virus; HIV+: HIV-infected; HIV-: non-HIV infected; IgA: immunoglobulin A; IgG: immunoglobulin G; IIV3: trivalent inactivated influenza vaccine; LAIV: live attenuated influenza vaccine; LAIV3: trivalent live attenuated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine; MN: microneutralization; NIH: National Institutes of Health (United States); RCT: randomized controlled trial; RNA: ribonucleic acid; US: United States.

Table 8. Summary of Evidence Related to Safety of LAIV in HIV-Infected Individuals

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of evidence*	*Quality*
King JC, Treanor J, Fast PE, Wolff M, Yan L, Iacuzio D, Readmond B, O'Brien D, Mallon K, Highsmith WE, Lambert JS, Belshe RB. *Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)–infected and non–HIV-infected adults.* J Infect Dis 2000;181:725-8[(30)]	LAIV3	RCT US Multicentre Influenza season unknown Funded by the NIH and Aviron (Mountain View, CA)	Adults 18–58 years of age HIV+: 51% female mean age, 40 years 28 vaccinated with LAIV3 29 received placebo HIV-: 65% female mean age, 34 years 27 vaccinated with LAIV3 27 received placebo HIV+ adults were considered eligible if they met the following criteria: CDC class A1-2, plasma HIV RNA PCR <10,000 copies/mL, >200 CD4 cells/µL within 3 months prior to vaccination and on stable antiretroviral regimen if CD4 ≤500 cells/µL.	Proportion experiencing AE within 10 days: See table below. * p<0.05 between LAIV and placebo Runny nose/nasal congestion was higher with LAIV3 than placebo, but there was no significant difference based on HIV infection status. No SAE were attributable to LAIV3. Four possibly vaccine-related AE occurred 28–35 days after vaccination (clinical sinusitis and wheezing in HIV+ LAIV recipients; wheezing in an HIV+ placebo recipient; and bronchitis in an HIV- placebo recipient). All resolved without sequelae. Effects on HIV replication: No significant differences in plasma HIV RNA levels between LAIV3 and placebo recipients or between pre-vaccination levels and post-vaccination levels on days 7–10, 28–35, or 3	I	Good Small sample size. The paucity of AE could have been due to failure of LAIV to replicate in this group with high level of seroprotection pre- vaccine

Proportion experiencing AE within 10 days:

Outcome	LAIV3 HIV+	LAIV3 HIV-	Placebo HIV+	Placebo HIV-
Fever	7%	0%	10%	11%
Runny nose/nasal congestion	61%*	78%*	31%*	44%*
Malaise	25%	26%	24%	26%
Sore throat	25%	22%	7%	22%
Cough	39%	11%	28%	26%
Myalgia	36%	15%	21%	22%
Nausea/ Vomiting	14%	4%	17%	11%
Decreased appetite	11%	11%	10%	19%
Abdominal pain	7%	4%	3%	11%
Headache	39%	44%	31%	41%
AE, any	79%	81%	62%	70%

* p<0.05 between LAIV and placebo

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of evidence*	*Quality*
				or 6 months. Three LAIV3 recipients had transient increases of ≥10-fold rise in HIV RNA levels that returned to baseline by the 90-day post-vaccination visit, and one placebo recipient had an increase which persisted to 90 days post-vaccination. No significant differences in CD4 cell counts between LAIV3 and placebo recipients or between pre-vaccination and post-vaccination (days 28–35 or 3 or 6 months) CD4 cell counts. No CD4 cell counts fell below 200 cells/µL within 1 month of vaccination. Vaccine virus shedding: One HIV+ LAIV3 recipient had a positive culture for vaccine virus (influenza B) 5 days after receiving LAIV3. No other LAIV shedding was detected.		
King JC, Fast PE, Zangwill KM, Weinberg GA, Wolff M, Yan L, Newman F, Belshe RB, Kovacs A, Deville JG, Jelonek M. *Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children.*	LAIV3	RCT US Multicentre 1999–2000 influenza season Funded by the NIH and Aviron (Mountain View, CA)	Children 1–7 years of age HIV+: 24 children were vaccinated following schedule 1 or 2 46% female mean age, 4.7 years age range 1.0–7.9 years HIV-: 25 children were vaccinated following schedule 1 or 2 40% female mean age, 4.3 years	Proportion experiencing AE within 10 days of vaccination: (see table below)	I	Good Small sample size.

Proportion experiencing AE within 10 days of vaccination:

Solicited events	1st dose		2nd dose		Placebo	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Fever	4%	12%	7%	4%	8%	4%
Runny nose	39%	60%	20%	33%	21%	56%
Sore throat	13%	4%	7%	0%	4%	4%
Cough	30%	28%	20%	17%	38%	20%
Muscle aches	0%	0%	0%	0%	4%	0%
Nausea/ Vomiting	9%	0%	7%	0%	8%	4%
Headache	9%	12%	7%	0%	13%	4%
Irritability	17%	4%	0%	8%	13%	16%
Chills	0%	4%	7%	0%	8%	4%
Decreased activity	13%	0%	0%	4%	0%	4%
Itchy or watery eyes	9%	0%	0%	0%	0%	0%

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of evidence*	*Quality*
Pediatric Infect Dis J 2001; 20(12):1124-113[27]			age range 1.0–7.8 years Schedule 1: Day 0: LAIV3 (1st dose) Day 28–35: placebo Day 56–70: LAIV3 (2nd dose) Schedule 2: Day 0: placebo Day 28–35: LAIV3 (1st dose) Day 56–70: LAIV3 (2nd dose) HIV+ children were considered eligible if they met the following criteria: CDC class N1-2 or A1-2 and HIV plasma RNA <10,000 copies/mL. CD4 measured <100 days of enrolment.	See key findings below.		

Ear ache	0%	0%	0%	0%	4%	0%
CDC-ILI	0%	4%	7%	4%	4%	8%
Any of the above	61%	76%	33%	38%	54%	60%

Dose-related AE*:

	1st dose		2nd dose		Placebo	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Any dose-related AE**	22% (5)	8% (2)	13% (2)	0% (0)	17% (4)	4% (1)

*AE occurring within 28-35 days of a study dose and for which the child was seen by a clinician and which were reported as possibly or probably related to the study dose.
**Numbers in parenthesis = number of events.

The following AE were reported 28-35 days following a dose of LAIV or placebo:
1st LAIV dose: HIV+ otitis media (2), upper respiratory infection (URI) (2), sinusitis; HIV- nasal irritation, and nasal congestion.
2nd LAIV dose: HIV+ URI (2); HIV- none.
Placebo: HIV+ wheezing, cough, URI, otitis media; HIV- nasal burning.

There were no significant differences in rates of AE, or AE reported as study dose-related, between HIV+ and HIV- children after LAIV dose 1 or 2 or after placebo. None of the AE identified were judged to be severe.

SAE:
3 SAE occurred after LAIV in 2 HIV+ children, but none judged vaccine-related by the blinded clinical investigator. All resolved without sequelae.

Effects on HIV replication:

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of evidence*	*Quality*
				No significant changes in plasma HIV RNA levels, CD4 cell counts, or CD4% in HIV+ children after receiving either LAIV3 dose. Vaccine virus shedding: No significant prolonged or increased quantity of LAIV virus shedding occurred in HIV+ vs. HIV- children after receiving either LAIV3 dose. Three (13%) HIV+ LAIV3 recipients shed LAIV B virus and 7 (28%) HIV- LAIV3 recipients shed LAIV A, B, or both viruses. No shedding was detected after day 10 after receiving either LAIV3 dose.		
Levin MJ, Song LY, Fenton T, Nachman S, Patterson J, Walker R, Kemble G, Allende M, Hultquist M, Yi T, Nowak B. *Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children.* Vaccine. 2008; 26: 4210–4217[28]	LAIV3	RCT US multicentre 2004–2005 influenza season Funded by the NIH	HIV-infected children 5–18 years of age LAIV3: 122 HIV+ children vaccinated with LAIV3; 47% female; mean age, 11.4 years IIV3: 121 HIV+ children vaccinated with IIV3 (Fluzone®, Aventis Pasteur, Inc.); 47% female; mean age, 11.9 year Children were considered eligible if they met the following criteria: on stable HAART regimen for	Proportion experiencing AE within 28 days: AE within 28 days of vaccination were similar after LAIV3 and IIV3 except for injection site reactions after IIV3 (23% overall) and nasopharyngeal symptoms after LAIV3 (52% vs. 31% after IIV3; p=0.002). AE did not differ by immunological group.	I	Good Unblinded RCT and more frequent clinic visits required for LAIV3 recipients could have contributed to reporting bias with respect to nasopharyngeal symptoms.

Proportion experiencing AE within 28 days:

Outcome	LAIV3	IIV3
Abdominal signs and symptoms	16%	8%
Constitutional signs and symptoms	29%	27%
Ear or eye signs and symptoms	7%	3%
Injection local reaction	0%	23%
Nasopharyngeal	52%	31%
Other	9%	2%
Pulmonary signs and symptoms	32%	26%
Skin abnormality	8%	4%

		STUDY DETAILS			SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of evidence*	*Quality*
			≥16 weeks and HIV-1 plasma RNA <60,000 copies/mL within 60 days prior to screening Stratified into three groups by immunological status Must have received IIV in at least one of the prior 2 years ****	No significant differences between immunological groups for toxicity grade 2 events (occurring in 16–31% of subjects) regardless of vaccine administered. There were 3 subjects with grade 3 events following LAIV3 (malaise, finger pain, and leg boil; one considered vaccine related) and 2 grade 3 events following IIV3 (fever, injection site lump; both considered vaccine related). No grade 4 events were reported. Effects on HIV replication: No significant increases from baseline in plasma HIV RNA levels 28 days or 6 months after LAIV3 or IIV3 in any of the immunological groups. CD4% did not change significantly at 28 days or 6 months after vaccination. Vaccine virus shedding: Influenza vaccine strains isolated from 347 specimens from 122 LAIV3 recipients: A(H1N1): 23 (6.6% of specimens); B: 11 (3.2%); A(H3N2): 3 (<1%). Five specimens contained two vaccine strains. No shedding was detected later than day 15 after LAIV3. HIV+ children who shed A(H1N1) had significantly lower baseline HI (p<0.001) and MN (p<0.001) titres than children without shedding post-vaccination. HIV+ children who shed B had non-significantly lower baseline HI and MN titres. Analysis of A(H3N2) shedding was not performed. Influenza A(H1N1) shedders had significantly lower proportions of subjects with baseline protective HI or MN titres compared with non-shedders (p≤0.01). There was a trend towards lower prevalence of MN titres ≥1:40 among B shedders compared with non-shedders (p=0.06), but no difference in the proportions of subjects with HI titres ≥1:40. Neither baseline HI nor MN titres ≥1:40 were completely protective against vaccine virus shedding.		

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of evidence*	*Quality*
				Baseline salivary IgG and IgA antibody titres were significantly higher in HIV+ children who did not shed any strain compared to children who shed at least one strain (p=0.05 and 0.02, respectively).		
Curtis D, Ning MF, Armon C, Li S, Weinberg A. *Safety, immunogenicity and shedding of LAIV4 in HIV-infected and uninfected children.* Vaccine. 2015; 33: 4790–4797[29]	LAIV4	Prospective cohort study US Single centre 2013–2014 influenza season Funded by MedImmune and Colorado Clinical and Translational Sciences Institute All received influenza vaccine in a previous season	Children and young adults 2–25 years of age. HIV+: 45 children were vaccinated with LAIV4 37.8% female median age, 18 years; 22% <9 years HIV-: 55 children were vaccinated with LAIV4 45.5% female median age, 10 years; 40% <9 years Individuals were considered HIV+ if they met the following criteria: CD4 >15% or >200 cells/µL on cART or >25% and >500/µL if not on cART	Proportion experiencing AE within 6 weeks: | Outcome	HIV+	HIV-
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Fever	0%	1.8%
Runny nose	37.8%	29.1%
Nasal congestion	37.8%	29.1%
Sore throat	13.3%	9.1%
Headache	17.8%	14.5%
Muscle aches	17.8%*	3.6%*
Decrease in energy	24.4%*	5.4%*
Decreased appetite	13.3%	3.6%
Any other symptoms	20.0%	9.1%
Unscheduled medical visits	4.4%	18.2%	 * p<0.05 SAE: There were no vaccine-related SAE. Vaccine virus shedding: No difference between HIV+ and HIV- in type or number of LAIV viruses shed, timing or duration of shedding, or amount of LAIV virus shed. Shedding of any LAIV virus on day 7–10 was detected in 13 (31%) HIV+ and 11 (21%) HIV- subjects (p=0.4). Overall, 30 (67%) HIV+ and 28 (55%) HIV- subjects shed any LAIV virus up to 14–21 days post-vaccination (p=0.14).	II-2	Good HIV+ group significantly older than HIV- group.

STUDY DETAILS					SUMMARY	
Study	*Vaccine*	*Study Design*	*Participants*	*Summary of Key Findings*	*Level of evidence*	*Quality*
				In HIV+, there were no significant associations between pre-vaccination HI or nasal IgA antibody levels and vaccine viral shedding. In HIV-, high pre-vaccination HI titres were associated with low shedding of B/Victoria and B/Yamagata (ρ≤-0.52, p<0.001) and high baseline nasal IgA concentrations were associated with low B/Yamagata shedding (ρ=-0.33, p=0.01).		
Menegay JL , Xu X, Sunil TS, Okulicz JF. *Live versus attenuated influenza vaccine uptake and post-vaccination influenza-like illness outcomes in HIV-infected US Air Force members.* J Clin Virol. 2017; 95:72-75[34]	LAIV (formulation not stated) IIV (formulation not stated)	Retrospective cohort study No funding declared 2005–2015	All active duty US Air Force members diagnosed with HIV (n=437) 2% female 61 received LAIV at least once after HIV diagnosis (121 doses) 376 received only IIV after HIV diagnosis. (number of doses not stated)	Post-vaccination ILI: There was one report of post-vaccination ILI after 121 doses of LAIV (0.8%). There were 17 cases of ILI within 30 days of vaccination with 16 cases occurring after IIV compared to 1 case after LAIV. IIV was associated with ILI diagnosis (p=0.032).	II-2	Fair Discrepancies between data in text and tables; do not affect conclusion of 1 case of ILI after 121 doses of LAIV

Abbreviations: AE: adverse event; cART: combination antiretroviral therapy; CDC: Centers for Disease Control and Prevention (United States); HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; HIV+: HIV-infected; HIV-: non-HIV infected; IIV3: trivalent inactivated influenza vaccine; ILI: influenza-like illness; LAIV: live attenuated influenza vaccine; LAIV3: trivalent live attenuated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine; NIH: National Institutes of Health (United States); RCT: randomized controlled trial; RNA: ribonucleic acid; SAE: serious adverse event; URI: upper respiratory infection; US: United States.

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
CAEFISS	Canadian Adverse Events Following Immunization Surveillance
cART	Combination antiretroviral therapy
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence interval
CMI	Cell-mediated immunity
CPARG	Canadian Pediatric & Perinatal HIV/AIDS Research Group
GMT	Geometric mean titre
HAART	Highly active antiretroviral therapy
HI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
HIV+	HIV-infected
HIV-	Non-HIV infected
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
ILI	Influenza-like illness
IM	Intramuscular
IWG	Influenza Working Group
LAIV	Live attenuated influenza vaccine
LAIV3	Trivalent live attenuated influenza vaccine
LAIV4	Quadrivalent live attenuated influenza vaccine
MMR	Measles-mumps-rubella
MN	Microneutralization
NACI	National Advisory Committee on Immunization
NIH	National Institutes of Health (United States)
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SAE	Serious adverse event
US	United States
URI	Upper respiratory infection

ACKNOWLEDGMENTS

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Appendix A: PRISMA Flow Diagram

Efficacy, effectiveness, immunogenicity, and safety of LAIV in HIV infected individuals. April 13, 2018

Identification

Records identified through database searching
(**n = 359**)

Records identified through other sources
(**n = 2**)

Records after duplicates removed
(**n = 220**)

Screening

Records screened
(**n = 220**)

Records excluded
(**n = 203**)

Eligibility

Full-text articles assessed for eligibility
(**n = 17**)

Full-text articles excluded:
(**n = 9**)
Reviews: 3
Did not assess HIV-infected individuals: 1
Did not assess seasonal influenza vaccine: 2
No full text: 3

Included

Articles included in the synthesis
(**n = 8**)
RCT: 5 articles (3 studies)
Prospective cohort: 2 articles
(1 study)
Retrospective cohort: 1