Lentiviral Vector and Retroviral Vector Exposure Response Plan

Purpose

Lentiviral and retroviral vectors retain some properties of the wildtype infectious viruses from which they were derived (HIV in the case of lentiviral vectors), including the ability to integrate into the genome of susceptible hosts. Therefore, exposure response to these vectors resembles the response for exposure to HIV and must be treated seriously and quickly. This exposure response plan provides:

Page 2: instructions to the exposed person for first aid, reporting, and seeking medical care (page 2)
Page 2: a method for clear communication between the exposed person and medical provider of the properties of lentiviral or retroviral vector involved in the exposure (page 2)
Page 3: a summary of recommendations to the medical provider for conducting a risk assessment of the exposure, ordering tests, and providing post-exposure prophylaxis and follow-up care (page 3)
Page 4: background information to assist with documenting the properties of the viral vector involved, performing a risk assessment, and making treatment decisions (page 4)
Page 5: the reference used to create this plan for more information for lab personnel and the medical provider (page 5)

Review this exposure response plan before beginning work with lentiviral or retroviral vectors to be prepared to respond to an exposure quickly and to identify any high-risk conditions you may be able to eliminate in your viral vector constructs and protocols to prevent or reduce the risk of exposure.

Principal Investigator and Project Information

*Fill out the following table **before** beginning work with lentiviral or retroviral vectors or when information changes. Keep one exposure response plan per IBC registration or per lentiviral/retroviral vector construct.*

Principal Investigator (PI) name:	
PI email:	
PI office phone number:	
PI emergency phone number:	
Department Head (DH) name:	
DH office phone number:	
DH emergency phone number:	

Procedure for Exposed Person

*Complete the following steps **as soon as possible** after exposure to begin treatment and satisfy UT reporting requirements. Seek assistance completing the following steps if available/needed. Treatment must be started ASAP (no later than 72 hours post-exposure) to effectively prevent infection with lentivirus or other retroviruses used as vectors. The effectiveness of treatment diminishes with time.*

First Aid

1. Remove exposed PPE and garments and dispose in biohazardous waste.
2. Wash the exposure site:
    i. Dermal or percutaneous (e.g., spill on intact or broken skin, cut, or needlestick): wash with soap and water for 15 minutes.
    ii. Mucous membranes (e.g., splash to eyes or mouth): rinse with water only for 15 minutes.

Viral Vector Information

3. Fill out the following form with information about the viral vector **to give to the medical provider** and aid you in reporting.

Agent:	☐Lentiviral vector ☐Other retroviral vector, specify:
If lentiviral vector, what generation?	
Route of exposure:	
Transgene expressed:	
Promoter:	
Tropism/pseudotyping:	
Self-inactivating LTRs?	☐Yes ☐No ☐Other, specify:

Seeking Medical Care and Reporting

4. Report to supervisor. If you cannot reach your supervisor, report to your department head. If no one is available, proceed to step 5.
5. Employees (e.g., lab technician, paid graduate student, etc.), call Corvel at 1-866-245-8588. Convey to the Corvel triage nurse that this is an emergent situation similar to an HIV exposure. Non-employees (e.g., volunteer, visiting scholar, or undergraduate student receiving credit hours, etc.), skip this step.
6. Initiate medical follow-up **ASAP** and bring this plan. Employees, report to the medical provider Corvel specifies.
7. After the initial medical visit, schedule a follow-up with your doctor and/or whoever the medical provider specifies as they will determine how long you will need to take medication.
8. Fill out the On-the-Job Injury form (for employees) or the General Liability form (for non-employees) on the UT Risk Management website **within 24 hours** of the exposure. https://riskmanagement.tennessee.edu/incident-reporting/
9. Meet with UT-Biosafety. Filling out the form from step 8 will alert UT-Biosafety to the exposure. You may also contact us at utbiosafety@utk.edu.

The goal of reporting is to gather as much information as possible to determine how future exposures can be prevented and is not intended to be punitive.

Recommendations for Medical Providers

The following is a summary of the recommendations given in the 2024 paper by Fujumoto et al. (see page 5) for the convenience of the medical provider. Please refer to the reference provided for additional information. UTK EHS – Biosafety does not provide medical advice.

1. Verify that first aid has been performed (see page 2). If not, ensure that it is performed in the hospital.

2. Perform a risk assessment based upon the viral vector information on page 2 and the following risk assessment chart to determine if post-exposure prophylaxis is advised.

High-risk exposures	**Low-risk exposures**
• Low generation lentiviral vector systems with fewer plasmids (1st* & 2nd generation/1 or 2 plasmids) • Percutaneous or mucous membrane exposure • High-consequence transgene encoded (silencing of tumor suppressor genes, oncogene expression e.g., Ras) • Wildtype LTRs • Strong promotors (e.g., CMV, SV40) • Pseudotyping to increase host range (e.g., VSV-g)	• Higher generation lentiviral vector systems with more plasmids (3rd & 4th generation/3 or 4 plasmids) • Dermal exposure or bite from infected animal • Low-consequence transgene encoded (e.g., fluorescent protein) • Self-inactivating LTRs • Weak or no promotors • No psuedotyping/wildtype envelope

3. Perform baseline blood tests at the time treatment is initiated or as soon after first treatment as possible. Baseline tests should include:
   i. Blood counts
   ii. Metabolic panels
   iii. Testing for HIV
   iv. Testing for Hepatitis B

   Baseline testing for HIV should be performed at initiation of treatment as lentiviral vector exposure can cause some HIV PCR tests to become positive and existing HIV infections can potentially result in the lentiviral or retroviral vector becoming replication competent. UTK does not perform the above testing and does not have this information on file.

4. Post-exposure prophylaxis should be started **as soon as possible** and is no longer effective later than 72 hours post-exposure.

   Post-exposure prophylaxis should include both:
   i. Dolutegravir 50 mg integrase inhibitor taken once a day for 7 days (or 28 days for replication competent lentiviral or retroviral vectors)
   ii. Tenofovir disoproxil fumarate 300 mg nucleotide reverse transcriptase inhibitor taken once a day for 7 days (or 28 days for replication competent lentiviral or retroviral vectors)

   *This is an off-label use but is routinely used for HIV/viral vector post exposure prophylaxis and has been demonstrated to be effective and generally well tolerated. NNRTIs, protease inhibitors, entry inhibitors, and fusion inhibitors are **not** effective for lentiviral or retroviral vectors.*

5. Order a follow up medical visit for one week post-exposure to determine if the post-exposure prophylaxis should be continued beyond 7 days and to repeat blood testing from step 3.

Background Information

Lentivirus vs Retrovirus: Lentiviruses are a type of retrovirus. Lentiviruses can infect both non-dividing and actively dividing cells whereas retroviruses can only infect actively dividing cells.

Tropism: The preference of a virus for a particular host/tissue type.

Pseudotyping: Adding the envelope proteins of another virus onto a viral vector. This can result in changes in tropism. E.g., vesicular stomatitis virus glycoprotein (VSV-g) which allows the viral vector to infect a broad range of hosts and cell types including human mucous membranes and airway cells. This impacts the risk assessment of aerosol exposures.

Transgene: The "payload" gene that has been artificially introduced into the viral vector for the purpose of expression in a host. The transgene impacts the risk assessment of an exposure. High-risk transgenes include drug resistance genes, oncogenes (e.g., Ras), proto-oncogenes (e.g., genes used to induce pluripotent stem cells), toxins, metabolic genes, genes that shut off important cellular functions, etc.

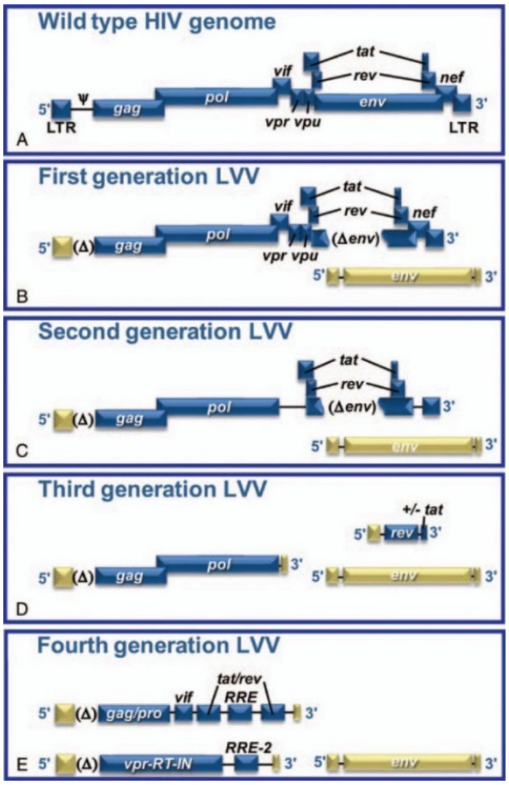
Exposure level: Risk assessments should consider titer, volume, and exposure routes. The average viral load of an untreated HIV patient is 1 x 10^5 viral copies/mL of serum. Most lab viral constructs are at least this concentrated.

Insertional mutagenesis: Viral vectors are designed to insert into the genomes of the host cell. The random location of insertion could cause activation of oncogenes or inactivation of tumor suppressing genes.

Long Terminal Repeat (LTR): LTRs and the genes between them (e.g., the transgene and promotor) are integrated into the host genome. Deleting the 3'LTR renders the viral vector self-inactivating (also called a SIN LTR) after integration.

Replication incompetence: Viral vectors are designed to integrate into host DNA without replicating and creating new viral particles.

Replication rescue/Recombination: Rescue of replication ability can occur randomly in rare cases. There is concern that HIV infection could supply the viral vector with the genes to become replication competent.



Lentiviral vector packaging system generations

*The development of LVV packaging systems from HIV. **A** Wild-type HIV genome with all of its genes and regulatory elements provides the backbone for LVVs. **B** *1st generation LVVs removed the envelope protein and the psi packaging signal and incorporated a heterologous promoter to reduce recombination potential. **C** 2nd generation LVV removed accessory genes (vif, vpr, vpu, and nef) to reduce the virulence of any potential replication-competent retrovirus. **D** 3rd generation LVV eliminated the transactivator gene, tat, and split the vector into three plasmids to reduce further recombination potential, retaining only the three genes necessary for transgene expression (gag, pol, rev). **E** 4th generation LVV split gag and pol onto separate plasmids to reduce even further recombination potential. This generation added back some HIV genes to enhance transduction efficiency and transgene expression.*

Schlimgen et al.,(2016). Risks Associated with Lentiviral Vector Exposures and Prevention Strategies. JOEM. doi: 10.1097/JOM.0000000000000879.

**1st generation lentiviral vector work is not allowed by the IBC at UTK.*

Reference

Fujimoto, Gary R. MD; Wooley, Dawn P. PhD, SM[NRCM], RBP, CBSP; Byers, Karen B. MS, RBP, CBSP; Yang, Otto O. MD; Behrman, Amy J. MD, FACOEM, FACP; Winters, Thomas H. MD, FACOEM, FACPM; Hudson, T. Warner MD, FACOEM, FAAFP. Update on Managing the Risks of Exposure to Lentiviral and Retroviral Vectors. Journal of Occupational and Environmental Medicine 66(10): p 818-825, October 2024. DOI: 10.1097/JOM.0000000000003166