**Risk of Lentivirus Exposures in the Research Lab**

**Does It Exist and If So, What To Do About It?**

By David V. Diamond, MD, CSS, FACOEM

**Question:** Do you offer post exposure prophylaxis which has very low risk to a researcher who has parenteral exposure to a replication deficient, HIV-derived virus, that has unknown but theoretical health risk? **Answer:** Maybe!

**Introduction**

Modern synthetic biology is in a quest to figure out how the genome works. One increasingly popular method is to engineer snippets of genetic material into viruses that have the capacity to then integrate into the DNA of human host cells, in culture, and then measure what happens. Genes can thus be manipulated in their expression to answer research questions and potentially allow gene therapies to be developed. Neat! Except, manipulating genetic material is tricky business. Artificial mutations may cause the cells to become cancerous and/or express uncontrolled novel proteins. In addition, “replicative deficient” viruses, derived from such pathogens as HIV, could possibly avoid methods used to degrade them, or combine with wild types to skirt control and become infectious - and that could be trouble!

In 2015, a group of concerned research and occupational health professionals met to consider what the magnitude of these risks might be and what to do about it. From that meeting, and much follow-up on virtual discussion, a summary was written and published as a guideline in JOEM (Risks Associated with Lentiviral Vector Exposures and Prevention Strategies, December 2016). I was part of that group, and in this article, I will summarize the key points made. I would also like to solicit your feedback on this matter since, in the end, the published suggestions were only “guestimates” regarding how best to manage these exposures given the limitations of our knowledge and the uncertainties of both the risks and benefits of these approaches.

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**Ron and Jay’s Truck**

**Stop, or Go?**

Part II

By Ron Blum, MD, FACOEM, FAAFP; President of NECOEM

and Jay Poliner, MD, MPH, FACOEM

This is the second in a series of case presentations for Certified Commercial Driver Medical Examiners (MEs) forwarded to us by NECOEM members. Have an interesting case to share, or wonder how the experts would have handled a complicated case? Do you have a different opinion on how to handle these cases? Please send your feedback to Susan Upham, MD, MPH, FACOEM, NECOEM Reporter Editor, at supham@roadrunner.com.

**Case 1: History of substance abuse, ME shopping, and FMCSA action**

A driver in his mid-20s has a history of a motor vehicle accident requiring cervical fusion. Although his cervical injury healed without interfering with his ability to safely operate a commercial vehicle, he became addicted to opiates used for pain management. He also admitted to alcohol abuse. His medical history was otherwise negative, including no prescription use or diagnosis of psychiatric disorders. He completed a drug treatment program several months ago, attended AA meetings several times per week, and claimed sobriety to all substances in the past 3 months. His exam, including a detailed neurological exam, was normal. He refused to provide additional information, and when asked to complete a Substance Abuse Professional (SAP) evaluation, told the examiner he would go elsewhere for an exam.

This examiner’s decision: *Does not meet standards.*

**R&J:** We concur with the Medical Examiner’s request for a SAP evaluation to confirm the driver’s sobriety. If

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**Occupational Health Risks**

**Question:** What are the occupational health risks of exposure to lentiviral vectors (LVV)? There are two types of theoretical risks: 1) oncogenic and 2) infectious. The oncogenic risk refers to the fact that cells that are infected with LVV would become cancerous through the activation of oncogenes or inactivation of tumor suppressor genes. Additionally, LVV can cause oncotic changes through insertions, gene disruption, overexpression of normal cellular genes, or transduction of an oncogenic transgene. Such oncogenic changes will be carried by the infected cell and its progeny.

Examples from 5 limited gene therapy trials are cited in the JOEM article. These found that the risk for cancer induction is real. In clinical studies, high doses of replicative competent retroviral vectors were integrated into host DNA as planned. However, subsequently a number of the patients went on to develop hematologic malignancies or clonal expansions due to mutagenesis from these insertions.

The second concern with LVV exposure is the infectious risk due to recombination of a replication deficient LVV with a related replication competent virus. In the laboratory, the genes of advancing generations of LVV are significantly modified via multiple steps to prevent this from occurring, [see Figure 1], but there still remains a potential risk due to the presence of wild types in the lab environment or in vivo.

### Figure 1: Generations of LVV modification to reduce replication capacity.

A Wild-type HIV genome with all of its genes and regulatory elements provides the backbone for LVVs. B: First-generation LVVs removed the envelope protein and the psi packaging signal and incorporated a heterologous promoter to reduce recombination potential. C: Second generation of LVV removed accessory genes (vif, vpr, vpu, and nef) to reduce the virulence of any potential replication-competent retrovirus. D: Third-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: Fourth-generation LVV split the 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.

A recent case report from Italy highlights this concern. An unexplained occurrence of an HIV infection was reported to have occurred in a lab employee who was working with a replicative deficient LVV strain but apparently was infected by another infectious lab strain that inadvertently entered his research area (Soria et al. Clin Inf Diseases. 2017).

In assessing such exposures, three factors impact the degree of risk. The first factor is the route of exposure. Since LVV are derived from blood-borne pathogens, clinically relevant exposures in the lab would be through parenteral inoculations, contact with mucosal surfaces, or direct contact with non-intact skin. Airborne transmission and droplet transmission beyond a short distance would not be considered sources of infection. The second factor involves the impact of particular genetic characteristics of the viral vectors. Presented below is Table 2 from the JOEM article, which outlines those characteristics which would assist the clinician in determining the exposed individual’s risk for the aforementioned adverse outcomes. Of higher concern are vectors with oncogenic constructs, fewer plasmids, more native (“wild type”)
genes, a strong promoter capacity, lower percent of delet-ed/substituted genome, and an expanded host range. The third factor relates to the level of exposure, with higher risk related to exposures of large volume and/or concentra-
tion.

Risk Reduction
Risk reduction or elimination could be achieved by implement-ing various procedural standards related to work with LVV. These include reduction of the concentration and volume of LVV, elimination of the use of sharps, use of bio-containment, use of personal protective equipment (gloves, eye protection, mask), and performance of post-
exposure washing and flushing.

Our Group’s Question: “In addition to these measures, would post-exposure prophylaxis [PEP] with antiviral medication be of benefit, and, if so, when, what and for how long.” In considering this question, the example of PEP effectiveness for occupational exposure to HIV was cited. Of course, there is a difference in the magnitude and duration of risk between replication incompetent LVV exposures and infectious HIV. The principle activities that could be targeted by PEP would be LVV DNA transcription and integration, and not the ongoing replication of the virus. Therefore, medication theoretically needs to be given as soon as possible, but not for as long as PEP for HIV exposure.

Based on the biology of LVV, as illustrated in Figure 2, the medications that would be expected to most likely block the disruption of host DNA would be a reverse trans-
scriptase inhibitor and an integrase inhibitor. Anti-HIV drugs that are specific for entry and fusion would not likely work on LVV since the viruses are usually pseudotyped* with heterologous envelope proteins, and protease inhibitors would not be effective since LVV do not contain genes for replication and expression. *(Wikipedia: “Pseudotyping is the process of producing viruses or viral vectors in combination with foreign viral envelope pro-
tiens. The result is a pseudotyped virus particle. With this method, the foreign viral envelope proteins can be used to alter host tropism or an increased/decreases stability of the virus particles.”)

Post Exposure Prophylaxis
Let’s review some basic themes related to of our under-
standing of the risks of LVV exposure.
1) There are potential risks of insertional mutagenesis and oncogenesis – but there are no definite reports and the risk is likely very low.
2) It would be difficult to document such harms as it may take years and occur rarely.
3) There is a logic to treatment based in part on HIV PEP guidelines but there is no proof such PEP would be effective.
4) Current PEP for HIV is relatively low risk with a tolera-
ble side effect profile - so much so that pre-exposure prophylaxis [PreEP] is widely prescribed to those at risk.

Our proposed treatment for LVV exposures is outlined below.

Initiation of treatment 0-72 hours after exposure
Duration of treatment 7 days
Types of treatment
Integrate inhibitor e.g. raltegravir
With or without
Nucleoside reverse transcriptase
inhibitor (NRTI) e.g. tenofovir

Initiation of treatment is recommended to be within 0-72 hours, but sooner is better and initiation within 2 hours or less would theoretically be optimal. A 7-day course of treatment is advised, though re-
search scientists think the window where potential transcription and integration needs blocking is likely a bit shorter. Either an integrase inhibitor alone, or with the addition of a reverse transcriptase inhibi-
tor is suggested. Assessment of pre-existing HIV and Hepatitis B and C should be done at baseline, along with renal function, to avoid inducing resistance; blood testing should not delay initiation of treatment however.

Implications for the Occupational Health Professional
Given the need for quick response and treatment in select cases, a LVV post-exposure response plan [ERP] should be developed for each LVV research lab and protocol. The plan can be developed by the researchers themselves, in consultation with the biosafety pro-
fessionals, the Institutional Biosafety Committee and the occupational medicine clinicians. All lab workers should have knowledge of the risks of LVV exposures and the risks and potential benefits of PEP. Written copies of the ERP should be ready at hand to bring to the medical treatment facility providing emergency evaluation.

Bottom Line
LVV exposures in research labs do occur, and there is a theoretical concern that such events may pose a long term oncogenic health haz-
ard. In assessing this risk, as with blood borne pathogens, factors such as route of exposure, dose of exposure, nature of the LVV and it’s genetic components need to be considered. If deemed appropri-
ate, PEP should be offered. A short-term course of integrase inhibi-
tor and NRTI antiviral medication theoretically could reduce the health risk of the exposure with minimal harm. In order for PEP to be optimally effective, it must be given shortly after exposure. This

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Denver is nicknamed the Mile-High City because its official elevation is exactly one mile (5280') above sea level, making it the highest major city in the United States.
Drs. Adamo, Berube, Blum

Enjoying Denver Botanical Gardens, D. Plantamura and Dr. C. Hix

Outgoing ACOEM Executive Director Barry Eisenberg receives honorary Fellow award by President Jim Tacci.

Tired after a long day of courses in the Mile High City. Drs. Taiwo, Slade and Borak.

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**Board Member Profile:**

**Diane Chen, MD, MPH**

Diane Chen, MD, MPH, is a board certified occupational and environmental medicine physician and a board certified anesthesiologist. She received her M.D. degree from Harvard Medical School, H.S.T. division (joint program with Massachusetts Institute of Technology), and her Master of Public Health as well as her occupational and environmental medicine residency training from Harvard T.H. Chan School of Public Health. She received her anesthesiology and critical care residency from Massachusetts General Hospital, and trained at Cornell Medical Center and Memorial Sloan-Kettering Cancer Center for cardiac and thoracic anesthesia. She was a recipient of Harvard University Sheldon Fellowship (Kennedy, Knox and Sheldon Fellowships) and investigated phthalate exposure in Taiwanese children. She is interested in exposure prevention in the biotech industry and was involved with MassBio. She is also interested in data driven analysis of financial performance in employee disability and corporate preventive medicine programs. Diane recently joined AllOne Health Resources as associate corporate medical director. She also serves as medical director at Boston Medical Center occupational medicine, and associate medical director at Partners Healthcare. In her spare time, Diane is involved with her family and enjoys exercising, cooking and gardening.

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**In Memoriam**

**Dr. Richard S. Fraser**

Dr. Richard S. Fraser, 64, of Westwood, MA passed away on March 05, 2017. Dr. Fraser was a talented man who was also devoted to his family. In addition to being a prominent area physician, he was a court-qualified forensic handwriting examiner. He was an actor in community theatre, played multiple instruments, wrote a book on the Yiddish language, and was active in his local Jewish temple.

Fred Kohanna, MD, MBA, FACOEM remembers connecting with him at NECOEM ACs which he regularly attended. “I knew Rick Fraser in the 1980’s when he worked for me at the Faulkner Hospital as an Emergency Medicine physician. He did eventually migrate into Occupational Health and opened up a private office where he provided a variety of occupational health services.”
the driver “goes elsewhere” and is found to be qualified (due to providing an incomplete or inaccurate medical history), he should then be “red-flagged” by FMCSA because of the two conflicting Medical Examiner determinations. Both MEs may be asked by FMCSA to submit the driver’s MCSA-5875 “Medical Examination Report Form.” In a recent discussion, Christine Hydock, Chief, Medical Programs, FMCSA, reminded MEs that they must submit the MCSA-5875 within 48 hours of a request. In addition, it is the MEs responsibility to keep copies of MCSA-5875 forms for three (3) years after completion of an exam.

**Case 2: Severe anxiety disorder and benzodiazepine use**

A middle-aged driver with severe anxiety disorder is on a maximum dose of a selective serotonin reuptake inhibitor, as well as buspirone and lorazepam. When the ME did not certify him, the driver’s mental health provider called the examiner to say that being out of work would be detrimental to the driver’s health.

This examiner’s decision: *Does not meet standards.*

**R&J:** Based on guidance in the report "Opinions of Expert Panel - Psychiatric Disorders and Commercial Motor Vehicle Driver Safety, August 2009"* this driver is not qualified to operate a commercial vehicle in interstate commerce. The report contains the statement: "The MEP (Medical Expert Panel) believes that all individuals currently taking benzodiazepines or similar drugs which act on benzodiazepine receptors should be immediately prohibited from driving a CMV." (Pages 5-7 of the report address benzodiazepines.) We recommend that the driver and his psychiatrist discuss a plan to meet the recommendations of the expert panel as well as the assessment recommendations of the FMCSA for psychiatric conditions, as outlined in the Medical Examiner’s Handbook section on psychological issues (currently under revision). This would include discontinuation of benzodiazepines and other medications that would impair a driver’s ability to safely operate a commercial vehicle.

*Available at https://www.fmcsa.dot.gov/sites/fmcsa.dot.gov/files/docs/Medical-Expert-Panel-Psychiatric-MEP-Panel-Opin.pdf*

**Case 3: Determination pending vs. periodic monitoring and a post-MI driver**

A driver with a history of acute myocardial infarction two years ago presents for recertification. He states that he has not had any symptoms of cardiovascular disease, is tolerating medications prescribed by his internist, but has not had an exercise tolerance test (ETT) since his MI. His current medical certification expires in 30 days. He is normotensive with a negative physical examination, with no other health issues that would disqualify.

This examiner’s decision: *Determination pending.*

Instructions for completion of the evaluation: return with 1) clearance from a cardiologist who understands the functions and demands of commercial driving and 2) the results of an ETT.

**R&J:** The NRCME Medical Examiner Handbook (March 2014) provides guidance on drivers with a history of MI, stating that “post-MI drivers may safely return to any occupational task provided there is no exercise-induced myocardial ischemia or left ventricular dysfunction.” So, the requested study (i.e., ETT) to document that the driver meets standards is appropriate.

A recent FMCSA webinar discussion highlighted the difference between extending this driver’s current medical certificate for an additional 30 days with a “60-day card” vs. “determination pending.” If a 60-day card was used to qualify the driver, a “complete examination” would be required before or after the expiration date of the 60-day card. If the driver was qualified as “determination pending,” he would continue to drive for the duration of his current medical certificate, which is 30 days. If he returned with the requested information prior to the end of the 30-day period, the medical examination report could be amended by the ME and the driver would be eligible to receive a 1-year medical certificate without another “complete examination.” However, if the “determination pending” driver returns with the requested information after the end of the 30-day period when his current certificate had expired, then a complete examination is required.

“Opinions expressed are those of the authors and do not necessarily reflect those of NECOEM or the FMCSA.”

(Drs. Jay Poliner and Ron Blum)

means that lab and biosafety personnel need to discuss and prepare before a clinical event occurs.

This brings us back to the initial question: “Do you offer post exposure prophylaxis which has very low risk to a researcher who has parenteral exposure to a replication deficient, HIV derived virus, that has unknown but theoretical health risk?” The answer: “It depends”.

In considering this answer, we have a common problem in the practice of occupational medicine, giving mixed messages. On the one hand, we like to reassure the exposed worker that there is a very low likelihood of health risk as a result of the incident, “so do not worry”. Then, in the next sentence, we say “but just in case, take this medicine for prevention”, implying that the risk is not so trivial. It is a delicate balance of reassurance and prudence, made more difficult in the environment of panic after an accident and absent any research evidence of risk or benefit. Solution: Have the discussion and try to make a decision before any event, but realize that the decision may need to be revisited depending on the details of each specific exposure.

OK, there you have it. Now let me know what you think. Does this make sense, what do you think, what would you do? Contact me at: diam@med.mit.edu

References
R Schlimgen PhD et al. JOEM. December 2016.
Wikipedia: Pseudotyping.
Introducing New ACOEM Fellow
Kevin Johnson, DO, MPH, FACOEM

Dr. Johnson is a commissioned officer in the Navy, an Undersea Medical Officer (UMO) and a trained acupuncturist. He was influenced to train in OEM from many, mostly military, OEM physicians he met. He applied for "out-service" residency training and, upon approval, was subsequently accepted to Harvard's OEM Residency.

During residency, Kevin was named Chief Resident and researched the effects of sleep and transportation workers. This was later published in the JOEM and resulted in his receiving an ACOEM resident research award. Kevin earned his MPH in 2012 and completed residency in 2013. While in the Boston area, Kevin ran for the Greater Boston Track Club and competed in multiple races including the 2013 Boston Marathon, finishing just before 2 bombs went off near the finish line.

Following graduation, he served as the Department Head for occupational medicine in Bremerton, WA for 3 years and during that time was promoted to Lt. Commander. While there, Kevin and his family became active in hiking/backpacking and Alpine skiing and he continued his passion for running, completing the Seattle Marathon in 3 hours and 40 seconds, a personal best.

Kevin is currently on 3 year orders to Portsmouth, NH, serving as the Senior Medical Officer and department head for occupational medicine, preventive medicine, audiology, optometry, radiation health and industrial hygiene at the Naval Branch Health Clinic. He was also recently named a Fellow of ACOEM. Kevin and his family currently live in York, ME and continue to be active in Alpine skiing, hiking, and backpacking, and have recently started Nordic skiing.

Congratulations Dr. Johnson on your achievement!

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2017 Annual Conference Preview

What is your employer policy?
Marijuana: legal and clinical ramifications

What Can Sentinel Events Tell Us?

Clinical Updates for the workplace:
Hand, ankle injuries, pain management with acupuncture,
New interventions: traumatic brain and musculoskeletal injuries,
Sleep and transportation, ID, lab OH, and much more

Public Health and CLIMATE CHANGE

NEW for 2017: Wednesday, November 29, evening program
Reprocessing Traumatic Memories of Work Injuries(EMR Course):
Practical Clinical Strategies for Trauma Recovery and RTW
6:30 to 9:30 PM light dinner included (additional registration)

Trauma symptoms related to work injuries are very common. These symptoms often are a hidden cause of delayed recovery as, unfortunately, patients rarely disclose their psychological symptoms related to trauma. Eidetic memory reprocessing (EMR) is a brief, limbic-based, structured exposure that is highly effective for addressing trauma symptoms and facilitating trauma recovery and return to work. EMR is straightforward to learn and can be performed in the office by a trained health care provider. This course will explore the physiological basis of post-traumatic symptoms and the foundational concepts, criteria, and procedure for performing EMR therapy. At the end of the course, you will be able to identify trauma symptoms that can be treated by this technique and effectively apply EMR to aid injured workers in trauma recovery in the clinic setting.
The New England College of Occupational and Environmental Medicine is a not-for-profit regional component society of the American College of Occupational and Environmental Medicine whose mission is to provide leadership to promote the optimal health and safety of workers, workplaces, and environments by: educating health professionals, employers, employees, payers, and the public; encouraging research and the development of new knowledge; championing the highest possible quality of OEM practice; guiding workplace and public policy; and advancing the field of occupational and environmental medicine.

“WHAT IS IT?”

The above two images show workers at work during factories circa early 1900s. They worked with a chemical that caused, among its notable effects, well known cardiac changes. The skin color changes that it produced gave these workers a popular nickname. What Is It?

Please send responses to Dr. Abhijay Karandikar at dr_abhik@yahoo.com Readers who send in correct responses will be identified in the next issue. The correct answer will be published in the next issue of the NECOEM Reporter.

This section is a series of trivia, facts, figures, etc. related to the field of occupational medicine. If you have any such interesting or fun-filled material, please e-mail it to the associate editor at dr_abhik@yahoo.com. All material should be related to the specialty of occupational and environmental medicine and have an educational, inspirational, historic or other relevant value.

ERRATUM: The response in last issue “What Is It” section erroneously listed Vinyl chloride monomer as chloroethane. It should be chloroethene.