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AIDS 2020, **34**:1987–1992

See related paper on page 1979

Perspectives of Saskatchewan researchers and community members on HIV-1 strains circulating in Saskatchewan

Brumme *et al.* [1] published an article about HIV-1 adaptation to certain host HLA alleles for HIV-1 strains circulating in Saskatchewan, Canada. For various social and structural reasons, in Saskatchewan, Indigenous people account for 65–80% of HIV-1 infections, despite making up only 16% of the provincial population [2]. The article focuses on the HLA-B*51 allele, which is normally protective, but not in certain populations where the HIV-1 has acquired adaptive mutations. Such mutations result in faster progression of HIV-1 infection and limits further genetic diversification of the virus. This phenomenon has already been reported to occur in people of Japanese ethnicity that predominantly carry the HLA-B*51 allele [3–5], but had not been previously studied in Saskatchewan, although anectodal evidence suggests that Saskatchewan HIV-1 cases have faster progression. The authors demonstrated that the DNA sequences of HIV-1 samples from Saskatchewan contained the adaptive mutations. However, the authors did not genotype Saskatchewan donors for their own study, but assumed the predominant host HLA allele based on another Saskatchewan study [6] and presumed the cultural identity of these 'de-identified' donors as being Indigenous people based on the over-representation of Indigenous people in the Saskatchewan epidemic [2].

Despite the authors' good intentions, this study created an ethical storm in Saskatchewan communities. Multiple news outlets reported the authors' quote that, 'It's almost as if the virus is nastier (in Saskatchewan)' [7], which further stigmatized HIV-1 in a province already dealing with the ongoing effects of colonialism and racism [8–10] and chronic under-resourcing to respond to the level of HIV-1 infection. Equally important is that this study ascribes culture to the donors, and thereby interferes with the right of Indigenous peoples to control their own data [8–12]. Due to these ethical impacts, we believe that Brumme *et al.* [1] provides an educational opportunity to explore how to better consider research ethics as an *ongoing* and *changing* process.

A university research ethics board (REB) may require that researchers engage in discussion with people whose perspectives can help identify the ethical implications of the research and suggest ways to minimize any associated risks. For Indigenous peoples in Canada, this engagement is to come *before* any secondary data use or attempt to create a linkage with an Indigenous community through interpretation of findings. However, discussion with communities is not intended to serve as proxy consent. This is outlined in several documents, with Chapter 9 of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2) being cited most often. There are also Indigenous ethical standards, including the First Nations Information Governance Centre's Ownership, Control, Access and Possession guidelines, ILO C169 – Indigenous and Tribal Peoples Convention (defines free, prior, and informed consent for Indigenous peoples), and the United Nations Declaration on the Rights of Indigenous Peoples, the latter of which the Canadian government committed to fully implementing as part of its adoption of the Truth and Reconciliation Commission's Calls to Action [11,13–20]. Collectively, these necessitate that Indigenous peoples (often an Indigenous advisory group) determine how and for what purposes their data (in this case HIV-1 sequences) will be used, analyzed, interpreted, reported, and stored. The Indigenous advisory group should involve Indigenous people with lived HIV experience, researchers with Indigenous-specific expertise, and community organizations working with Indigenous people living with or at risk for HIV or other sexually transmissible and blood–borne infections. More specifically to HIV, The Greater Involvement of People Living with HIV/AIDS outlines the importance of including people living with HIV in the research team [21]. These documents are in place because donors have a legitimate interest in the uses to which their biological samples is put that goes well beyond concerns about possible reidentification. There are community or collective interests in not being stigmatized and marginalized. In the study by Brumme *et al.* [1] there is a misunderstanding of this relation of donors to the researchers (or biobank) to which their data or biological samples are given or stored.

The study by Brumme *et al.* [1] appears to have only practiced the minimum procedural ethics and this is evidenced by several statements that do not recognize Indigenous peoples' rights or self-determined research ethics, nor does it meaningfully acknowledge the ongoing colonial biases in their discipline of study [15]. For example, the authors state that there was a genetic bottleneck that occurred in North American Indigenous people 'coincident with colonization' [1]. This does not reflect the conclusions of the referenced studies, or historical understandings of any 'genetic bottleneck' as

resulting from the deaths of Indigenous people as a direct result of colonial practices [15,22,23]. If the British Columbia, Canada-based REBs that approved this study were not aware of the statistics for HIV in a separate province, Saskatchewan, and that they would intersect with ethical considerations for Indigenous health research, they should have informed themselves or declined to provide a review pertaining to research outside their jurisdiction. Furthermore, there was no consideration that, by using Indigenous peoples' genetic data from an unrelated study [6], this study is akin to studies conducted by R. H. Ward on blood samples gathered in the early 1980s from the Nuu-chah-nulth People, ostensibly for arthritis but used for anthropological and other purposes [24,25].

Not even explored by Brumme *et al.* [1] is that the anectodal clinical observations of faster progression of HIV in Saskatchewan may be due to later diagnosis and not HLA adaptation. It is known that there are several structural barriers that prevent early testing and continued access to care in Saskatchewan, some of which relate to living in remote areas, racism, and difficulty for Indigenous peoples to engage in hegemonic Western healthcare systems [2,15]. Further, the authors based their data on Saskatchewan statistics, stating that 80% of the HIV+ population identifies as Indigenous [1]. However, the HIV-1 sequences were taken from samples in the study drawn from 2000 to 2016 and Saskatchewan Health Region records show that from 1985 to 2007 only 50% of the HIV+ samples were from Indigenous people [2]. Only in 2008 did the numbers show that 76% of HIV+ samples were from Indigenous people [2]. Lastly, the HLA allele in question was shown by one of the authors in an earlier work to not be detrimental to HIV-1 fitness and as a result, there is no selective pressure to lose the adaptive mutation once obtained [26]. In these situations where Indigenous peoples' health research has been done 'to' rather than 'with' Indigenous people, the results are usually correlative, not causative and do little to uplift Indigenous self determination or ability to set research priorities. An investigation of the Principal Investigator for the Saskatchewan study regarding the obligation to engage with community as set out in TCPS2, Chapter 9, was conducted by the Office of the Vice-President, Research at one of the institutions that approved the research. Although there was admission that the research had caused inadvertent and unintentional harms when it was shared through popular media, the conclusion was that nothing had been done incorrectly. Nevertheless, the institution declared a commitment to develop training materials to prevent such occurrences in the future and stated that there is much to be learned from this case.

In summary, the study by Brumme *et al.* [1] constitutes a major Indigenous concern by violating both national and international aspirational documents, which Canada has committed to fully implement. Research in this domain needs to consider that there is not only individual ownership of biodata or samples taken, but a collective ownership that needs to be considered and respected regardless of the time the study started or type of data or samples obtained. Only with Indigenous community involvement in the research design or a formalized community approval process could the samples be put to use in a good way. We hope in the future more researchers learn to consider the ethical issues that cross both Western and Indigenous ethical boundaries.

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Conflicts of interest

There are no conflicts of interest.

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Pharmacokinetics of tenofovir disoproxyl fumarate/emtricitabine in a client on pre-exposure prophylaxis after a total gastrectomy

Bariatric surgery can influence the pharmacokinetics of HIV medication, as the pH in the gastrointestinal tract increases and, depending on the type of bariatric surgery (part of), the duodenum and jejunum are bypassed. A few case reports and a small study have been published on pharmacokinetics of emtricitabine (FTC) and/or tenofovir in obese HIV patients that underwent bariatric surgery, some showing a transient decrease in tenofovir concentrations [1–3]. However, no data are present yet in case of PrEP (pre-exposure prophylaxis) and bariatric surgery.

We present the case of a man aged 32 years old, MSM, who wanted to start PrEP. Due to hereditary diffuse gastric cancer, he has had a total gastrectomy, with Roux and Y anastomosis in 2011. Therefore, we monitored FTC and tenofovir plasma concentrations, and, after obtaining the pharmacokinetics results, investigated a doubled dose regimen.

To determine C_{trough}, T_{max} and area under the curve $(AUC)_{0-24h}$, two full pharmacokinetics curves of FTC and tenofovir were drawn at approximately 0, 1, 2, 3, 4 and 8 h after administration of tenofovir disoproxil fumarate (TDF)/FTC. The predose concentrations were also used as $T = 24$ h results. The first curve was drawn after more than 1 month of use of TDF/FTC once daily (245/200 mg) as PrEP. The second curve was recorded after 5 days use of a double dose TDF/FTC once daily (490/400 mg). No PrEP was used in between. Before each start of PrEP, the client tested negative for HIV. At the start of PrEP at the standard dose, he was 1.84 m, 60.4 kg and had an estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration) of 144 ml/min/1.73 m^2. At the start of the double dose he was 62.4 kg with an eGFR of 128 ml/min/1.73 m^2. Aspartate aminotrasferase and alanine transaminase were normal. Nucleoside reverse transcriptase inhibitor plasma levels were measured by a validated liquid chromatography-mass spectrometry