National survey assessing knowledge and management of the drug interaction between dolutegravir and metformin by Canadian HIV practitioners

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Abstract

Background: A well-described pharmacokinetic drug interaction between dolutegravir and metformin results in increased exposure to metformin. However, no conclusive management recommendations exist. This study was conducted to examine current Canadian practice.

Objectives: The study objectives were to describe Canadian practitioners’ knowledge and management of the interaction, including assessment of interprofessional or regional variations, and to identify factors that influence the decision to administer metformin and dolutegravir concomitantly.

Methods: The study was an online survey of Canadian physicians, nurse practitioners, and pharmacists caring for HIV-infected patients. The survey consisted of multiple choice, short answer, and case-based questions administered via SimpleSurvey. An iterative process was used to pilot the survey electronically in French and English prior to two waves of survey dissemination.

Results: The survey was distributed to 179 practitioners (response rate 36 %, completion rate 83%). The majority (93%) knew the interaction increased metformin exposure; of these, 65% correctly identified the magnitude. In clinical scenarios, 67-90% of respondents administered the medications concomitantly, with some electing to decrease the metformin dose. Closer monitoring of renal function, diabetes, and metformin tolerability, including lactic acidosis, was suggested by respondents co-administering dolutegravir and metformin. Diabetes-related factors, dolutegravir dose, and renal dysfunction commonly affected co-therapy decisions. There was minimal variation by profession, though practice in Alberta may differ slightly.

Conclusion: A majority of clinicians did not consider co-administration of dolutegravir and metformin to be contraindicated. However, factors such as maximum metformin dose, renal dysfunction, and diabetes-related conditions were most likely to affect decisions to continue co-therapy.

Keywords: dolutegravir, metformin, drug interaction, Canada, survey
Introduction

International guidelines recommend the use of dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), in combination with nucleoside reverse transcriptase inhibitor (NRTI) backbone for initial antiretroviral therapy (ART) of Human Immunodeficiency Virus (HIV) in adults(1–5). Advantages of DTG include its efficacy, tolerability, ease of administration (once daily without regard to food), and few drug interactions(1,4,6). In addition, DTG has a higher genetic barrier to resistance than other currently marketed INSTIs, with no currently identified transmitted resistance(4). Consequently, DTG remains a viable treatment option in treatment-experienced, INSTI-resistant patients when dosed twice daily, whereas the usual once daily dosing can be used in both treatment-naïve and treatment-experienced, INSTI-naïve patients in the absence of concomitant therapy with UGT1A/CYP3A inducers(7). Because of these favourable characteristics, use of DTG is expected to increase: one forecast for low- and middle-income countries (LMIC) shows up to 57% of adults living with HIV using DTG as part of a first-line regimen by 2025(8). According to this model, 14.8 million patients will be using DTG in LMICs alone by the year 2025(8).

In 2009, the prevalence of diabetes in Canada was 6.8% and this number is expected to continue to increase(9). Because metformin is effective at lowering blood glucose, well-tolerated, poses a low risk of hypoglycemia and weight gain and has a potential cardiovascular benefit in overweight patients, it is recommended as first-line pharmacotherapy for type 2 diabetes(9). Therefore, it is reasonable to expect that metformin may be used in conjunction with ART, including DTG. Metformin pharmacokinetics must be considered when it is administered with DTG. After uptake into renal tubular cells via organic cation transporter (OCT) 2, metformin is excreted unchanged in the urine via active tubular secretion(10,11). However, DTG is a known inhibitor of OCT2(7,10,12,13).

In an open-label, parallel-group, three period crossover study in healthy adults, Song et al. examined metformin’s area under the curve (AUC) and maximum concentration (C_{max}) in patients receiving metformin 500 mg q12h with concomitant DTG dosed at either 50 mg q24h (cohort 1) or 50 mg
q12h (cohort 2)(10). Three time periods were studied: metformin alone (5 days), metformin and DTG (7 days), and metformin alone (10 days). A dose-dependent effect of DTG on metformin pharmacokinetics was found: metformin AUC was increased 79% and $C_{\text{max}}$ was increased 66% with DTG 50 mg q24h, whereas AUC was increased 145% and $C_{\text{max}}$ was increased 111% with DTG 50 mg q12h. After DTG was discontinued, metformin returned to similar concentrations as before initiation of DTG therapy. Co-administration of the drugs was well-tolerated despite the increase in metformin exposure; nonetheless, the authors suggest adjusting the dose of metformin is warranted given increased metformin exposure. A recent retrospective study reported the effects of at least six months of concomitant DTG and metformin on glycemic control in 15 patients(14). No difference in glycemic control was noted before and after DTG therapy was initiated, and no cases of lactic acidosis occurred. Additionally, no association between DTG trough concentration and percentage change in glycemic control was noted.

Guidance on the management of concomitant treatment with metformin and DTG varies by resource. The authors of the pharmacokinetic study suggest that for patients stabilized on DTG therapy who are subsequently commencing metformin, the standard dosage titration of metformin can be initiated(10). However, in patients taking metformin who are starting or stopping DTG, they suggest monitoring of glycemic control and consideration of metformin dose adjustments(10). The product monograph and HIV guidelines support this recommendation(4,7). While some practice guidelines suggest adjusting the metformin dose with concomitant therapy, others provide more specific recommendations(3,6). For example, the United States (US) Department of Health and Human Services guidelines suggest limiting the metformin dose to a maximum of 1,000 mg daily and monitoring closely for metformin adverse effects(4). The University of Liverpool HIV Drug Interaction tool, a recognized drug interaction resource, also suggests a 1,000 mg daily maximum dose, with an additional recommendation to monitor renal function during co-administration due to the potential for increased risk of lactic acidosis resulting from increased metformin concentrations in patients with moderate renal impairment(15).
Concern regarding the DTG-metformin interaction may stem from a potential increased risk of lactic acidosis, given that metformin is well-tolerated and has little risk of hypoglycemia(9). Metformin seems to have less effect on serum lactate than other biguanides, but lactic acid accumulation could occur as a result of metformin inhibition of gluconeogenesis(16–18). While the true incidence of metformin-associated lactic acidosis (MALA) is unknown, studies have reported between 1.5-530 cases per 100,000 person-years(16–18). Though MALA is likely a very rare event, chronic renal insufficiency, liver function abnormalities, heart failure, peripheral vascular disease, and age > 65 years have been identified as factors that may increase the risk(16,18). Additionally, the low incidence of MALA reported in the literature may be due in part to attributing comorbidities or risk factors as the cause of lactic acidosis, rather than metformin(19).

There may be an association between biguanide dose and serum concentration and serum lactate(18). A French pharmacovigilance database study found a correlation between metformin plasma concentration, plasma lactate, and pH; however, the majority of these patients had altered renal function(17). Other studies have suggested varying correlation between serum metformin and lactate concentrations(19,20). However, metformin concentrations are often not measured in MALA studies, making it difficult to elucidate the correlation between metformin concentration and lactic acidosis(19). Despite the uncertain correlation between metformin concentration and plasma lactate and the fact that metformin concentration may not correspond well with clinical presentation, high metformin levels have been associated with more severe lactic acidosis(21). When metformin levels are > 5 mcg/mL, metformin may be implicated as the cause of lactic acidosis(22). Lower threshold levels, such as 4 mcg/mL, have also been used to relate lactic acidosis to metformin exposure(20).

These studies did not take into consideration the potential role of genetic variation in metformin clearance. A single nucleotide polymorphism (SNP) in the OCT2 gene was associated with increased metformin renal clearance (CL_R) in those heterozygous for the variant allele (OCT2-808G/T) in one study of unrelated European and African Americans, while studies of this genotype in Asian populations have
shown decreased metformin CL\textsubscript{R}(23–25). Though the effect of the SNP on metformin clearance remains unclear, it is another factor that may impact metformin serum concentrations.

The highest geometric mean metformin C\textsubscript{max} reported in the pharmacokinetic study of co-administration of metformin and DTG was 1.85 mcg/mL with metformin dosing of 500 mg q12h and DTG 50 mg q12h, which is well below suggested threshold for implicating metformin as the cause of lactic acidosis(10). With various doses of metformin, the average steady-state concentration (C\textsubscript{av}) is reportedly up to 2.5 mcg/mL, which is consistent with the range of 1-2 mcg/mL reported in the product monograph(22,26).

A decreased incidence of MALA has been suggested when prescribing criteria for metformin are adhered to, including consideration of decreased metformin clearance(21). When metformin dose is too high, even healthy individuals with no predisposing event can experience MALA(21). Though the metformin C\textsubscript{max} achieved in the pharmacokinetic study by Song et al. were below the threshold concentration of 4-5 mcg/mL (at which lactic acidosis would be attributable to metformin), the study examined healthy patients, metformin dose was likely lower than in typical clinical practice (at 500 mg q12h), and the relationship between metformin concentration and serum lactate is uncertain. The debatable relationship between plasma metformin and lactate concentrations notwithstanding, it is possible metformin C\textsubscript{max} could theoretically reach a concentration of 4-5 mcg/mL when DTG is administered concomitantly, considering the percentage increase in metformin C\textsubscript{max} and metformin concentrations reported in the literature. In addition, genetic variation in OCT2 transport could further impact metformin clearance. Given the demonstrated decrease in metformin clearance when co-administered with DTG, the inconsistent clinical recommendations for managing the interaction, genetic variation in OCT2, and the potential for adverse effects and fatality should MALA occur, it is important to examine current Canadian practice.

Methods

Overview
The study was an electronic survey administered via SimpleSurvey, a web-based platform. It was distributed to physicians (HIV specialist physicians and HIV primary care physicians), pharmacists (hospital and community), and nurse practitioners involved in the care of HIV patients across Canada. The sample frame was identified by purposeful selection and was meant to identify practitioners whose practice has a focus on providing care to HIV patients, as this is how the majority of patients obtain their care. Completion of the survey was voluntary and participants could cease completion of the survey at any time. Consent was given in the first page of the survey, with implied consent if respondents accepted to continue to survey. As an incentive, participants had the option to enter a random draw for one of three gift certificates (valued at $100 each), which took place after the survey had closed. Participation in this draw was voluntary and responses were not linked to responses from the survey. The study was approved by the Ottawa Health Science Network – Research Ethics Board (OHSN-REB #20170141-01H).

**Survey Development & Piloting**

Investigators developed the survey with assistance from a survey expert at The Ottawa Hospital Research Institute. Participant demographic information and practice experience (multiple choice questions), general knowledge of the interaction and its clinical significance (multiple choice, case-based, open-ended questions) and factors that could potentially impact management (as rated on a scale) were incorporated into the survey (Appendix 1). The decision to examine sequence of therapy and renal function in case format was made by consensus between the principal investigators. Respondents were also asked to rate patient-specific factors based on how likely each was to affect the decision to continue co-therapy with DTG and metformin. The survey was designed to take approximately 15 minutes to complete. Adaptive questioning was used to reduce complexity of completing the survey. Predetermined questions were set to be mandatory to complete, with optional questions indicated in Appendix 1. Participants were required to answer all mandatory questions on each survey page before they could proceed to the next page of the survey. Participants were not able to review or change their answers after each page of the survey had been submitted. The electronic survey was piloted, in French and English,
via the think-aloud technique of cognitive testing, whereby a total of seven pharmacists described their thought process and understanding of survey questions aloud while completing the survey, in the presence of the primary investigators(27). Data from these surveys were not compiled, as the pharmacists were not part of the intended survey sample population, but had sufficient medical knowledge to understand the survey questions to allow for piloting. This piloting process was iterative, whereby changes were made as needed to clarify the survey prior to further piloting, to allow for assessment of improvement based on feedback and observations provided.

**Survey Dissemination**

To allow for detection of technological issues, the survey was disseminated in two waves. The first wave was distributed to two academic centres. Technological issues identified during the first week of the initial wave of survey distribution were corrected prior to the second wave of distribution to the rest of the survey population. Please refer to Figure 1 for flow diagram of the recruitment and dissemination process and Appendix 2 for survey distribution email. As shown in Figure 1, the survey utilized the Canadian HIV and Viral Hepatitis Pharmacists (CHAP) network to disseminate the survey to other health care professionals involved in caring for HIV-infected patients. Active since 1997, CHAP consists of pharmacist leaders from each province Canada(28). The organization also maintains a list of pharmacists with academic and community practices. The survey employed a snowball technique, allowing respondents in each of the two waves to further distribute the survey to other eligible practitioners. A reminder email was sent when one week remained to complete the survey (Appendix 3). Those who had further disseminated the survey were requested to also forward the reminder email. The survey remained open for a period of approximately five weeks. The investigators requested that each participant complete the survey only once. The target response rate was 60%, with target completion rate (number completing last survey question/number of consenting participants) of 80%.

**Data Analysis**
In the event that there was a potential for data de-identification resulting from low regional response rates (less than 5 responses in a given region), data was merged prior to presentation to avoid this risk.

The data analysis was largely descriptive in nature. Statistical testing was limited to surveys in which responses were recorded in the knowledge section of the survey. However, demographic information for all respondents was presented to allow for description of the population the survey reached. All statistical analyses were performed at $\alpha=0.05$ level of significance using SPSS v.20. Chi-Square test was used to test for differences between cofactors (region and profession) and factors related to the knowledge section (transporter mediating interaction), case 1 (proportion who chose DTG and both continued metformin 1000 mg BID or changed dose), case 2 (proportion who initiated metformin and titrated as per product monograph), and case 3 (discontinued metformin, decreased metformin dose, and no change in metformin dose). In order to assess for consistencies between the three different case scenarios, the Wilcoxon signed ranks test was used to compare respondents who co-administered metformin and DTG across case scenarios.

**Results**

The survey was distributed to 179 practitioners (Figure 2). Response rate was 36% (64 consenting participants/179 survey recipients) and completion rate was 83% (53 participants completed last survey question/64 consenting participants). Please refer to Table 1 for characteristics of survey respondents. Responding practitioners were concentrated in Quebec, Ontario, and Alberta, with most working from large clinics (> 70% had a personal case load between 25-250 patients in the preceding three months). Three quarters of respondents were hospital HIV specialist pharmacists or HIV specialist physicians. All non-pharmacists had a dedicated clinical pharmacist working at their practice. On a scale of zero to 10, with 10 being most confident, practitioners’ median confidence in treating HIV was 9 ($Q_1$, $Q_3$: 8, 10) and diabetes was 6 ($Q_1$, $Q_3$: 5, 7.25).
In terms of respondents’ baseline knowledge of the interaction, 93% of participants recognized that the interaction results in increased metformin exposure, while 2% responded that DTG exposure was increased and 5% did not know the result of the interaction. Of those who correctly identified that the interaction increases metformin exposure, 65% correctly answered the multiple choice question concerning the magnitude of the increase. Many respondents (61%) correctly answered that the interaction was mediated by OCT2 (Figure 3). However, only 51% of participants correctly responded that the interaction was dependent on DTG dose, with 20% incorrectly responding that the interaction was not dose-dependent and 29% who did not know. Approximately one-third (36%) of respondents incorrectly responded that adverse effects related to the interaction had been published in the literature, 38% did not know, and 25% correctly answered that no adverse effects have been published to date. The most commonly identified potential toxicities associated with exposure to high metformin concentrations included gastrointestinal intolerance (diarrhea, flatulence, nausea, vomiting, abdominal pain/cramping), lactic or metabolic acidosis, and hypoglycaemia. Other responses included hepatotoxicity, nephrotoxicity, and no potential toxicities.

The first patient case involved a patient newly diagnosed with HIV infection with stable diabetes well-controlled with metformin 1000 mg po BID (Appendix 1). As shown in Table 2, 77% initiated DTG and continued metformin, though more than half of survey respondents reported that they would decrease the metformin dose with concomitant DTG administration. Comments provided in terms of choice of HIV therapy in this scenario included suggestions to follow blood glucose control and that a dosage adjustment may not be necessary; others commented that they would decrease the metformin dose but follow blood glucose and adjust as appropriate. Other respondents were reassured by the patient’s normal renal function. However, one respondent commented that the patient may want a single tablet regimen and that abacavir, a component of the DTG single tablet regimen, may increase the cardiovascular risk in this diabetic patient; therefore, this respondent would prefer to avoid the interaction by giving another INSTI-based single tablet regimen. Several comments also recognized that both drugs are first-line therapies for
the disease they treat. One justification for not adjusting the metformin dose was the lack of adverse clinical effects with the combination to date and the fact that the maximum dose of metformin (2550 mg) still leaves some buffer room in a patient taking 2000 mg daily. Of note, there were a few responses that patients treated with DTG-based therapy have had poor blood glucose control. In terms of supplemental follow up given the drug interaction, 45% said they would monitor blood glucose, glycosylated haemoglobin (HbA1c), or symptoms of hypoglycaemia; 20% responded follow up would not be significantly different; 10% reported that they would follow up more frequently or earlier; and 8% of respondents would counsel patients regarding potential adverse reactions with increased metformin exposure.

A second patient case examined management of new diabetes in a patient whose HIV was stably treated with a once daily DTG-based regimen (Appendix 1). As shown in Table 3, the majority (57%) of respondents’ first choice for antidiabetic therapy was metformin. Of those who responded “other”, management options included initiation of metformin at a lower dose/titration to a maximum of 500 mg po BID, referral to primary care physician/endocrinologist for management of diabetes, or replacement of DTG. Participants were also asked how they would proceed in terms of HIV therapy; most respondents continued current DTG therapy (Table 4). Of those who provided comments, many suggested limiting the dose of metformin to 1000 mg daily. However, one comment suggested that if the dose required was higher than this, that practitioner would consider changing DTG to another HIV therapy, while others suggested you could titrate according to patient response and stability and with close monitoring, avoidance of the combination is not required. Another comment recognized the numerous options for diabetic treatment and suggested that as the patient is tolerating HIV therapy with DTG well, they would not modify this to have the chance to give metformin. Again, it was noted that the NRTI backbone could be optimized to decrease cardiovascular complications.

The final patient case examined the effect of declining renal function in a patient stabilized on both DTG-based HIV therapy and metformin 1000 mg po BID (Appendix 1). As illustrated in Table 5,
the largest proportion of respondents would decrease the metformin dose. Of those suggesting a dose decrease, 74% suggested 500 mg po BID, 17% suggested 750-850 mg po BID, 4% answered 250 mg po BID, and 4% did not know. Supplemental monitoring (aside from usual monitoring) most commonly performed by those who indicated that they would co-administer DTG and metformin in this situation is shown in Figure 4. Respondents who indicated no additional monitoring was required were not directed to this survey question. As illustrated in Figure 5, most respondents would continue current HIV therapy with DTG. Comments provided included some practitioners choosing to wait until further information regarding deterioration of renal function was available to change therapies, noting that some of the increase in serum creatinine may be related to DTG, and comments regarding the NRTI backbone (cardiovascular risk with abacavir and dose adjustment requirements with lamivudine in renal dysfunction). Comments were made that the patient’s HIV disease was well-controlled and no recognized toxicity had been noted, therefore some respondents would continue the combination. However, one respondent noted that in their experience with the combination of metformin and DTG, patients have been requiring changes in therapy. It was noted that it would be prudent to avoid metformin, as MALA occurs in patients with renal failure and another risk factor, which could be the increase in exposure to metformin caused by DTG. It was noted that the patient in the scenario was in a “gray zone” for metformin based on renal function and would follow renal function more closely.

Statistical comparisons of knowledge and management of the interaction are displayed in Table 6. As a consequence of number of survey respondents, to avoid potential for identifying individual respondents, regional comparisons were limited to Ontario versus Quebec versus Alberta. Pharmacists seemed to have a better knowledge of the mechanism of the interaction than physicians, though there was no statistically significant difference. Respondents from one province managed the interaction between metformin and DTG differently when HIV was newly diagnosed. Fewer practitioners in this province chose to co-administer metformin and DTG, but those who did were less likely to reduce metformin dose. By looking at the percentages, it is likely that Alberta was the province that managed this differently,
though this study was not powered to show statistical significance because of the multiple comparisons that would have required. Otherwise, there was little regional or interprofessional variation in the management of the interaction. No significant differences were found between those who co-administered DTG and metformin in case 1 versus case 2 or case 1 versus case 3 (p=0.583, p=0.192 respectively, Pearson Chi-Square). In the repeated analysis, of respondents who changed their decision to co-administer metformin and DTG between the cases, more people went from co-administering metformin and DTG in case 1 (new HIV) to not co-administering the medications in case 2 (new diabetes) (16 co-administered metformin and DTG in case 1 but not in case 2 versus 6 who did not co-administer in case 1 but did in case 2, p=0.033). Between case 1 and case 3 (declining renal function), there were no statistically significant differences in those who changed their decision to co-administer the medications (p=0.09). However, there was a trend towards more respondents changing their decision and co-administering DTG and metformin in case 3 (12 individuals co-administered in case 3 but not in case 1 vs. 5 individuals who co-administered DTG and metformin in case 1 but not in case 3). As this association shows the opposite direction of responses of the analysis between case 1 versus case 2, case 2 may be the scenario that leads to a change in behaviour.

The survey also presented respondents with multiple factors that may influence the decision to continue co-therapy with DTG and metformin. Higher metformin and DTG dose, renal dysfunction, presence of other antidiabetic agents, and low-normal blood glucose were the factors endorsed in the survey as most likely to impact the decision to co-administer DTG and metformin (Figure 6). Comments were made that if patients had viral co-infection or ethanol use and compromised hepatic function, that would impact the decision to administer the combination of DTG and metformin, and that some of the factors may impact the dosing of metformin but not the decision to administer it altogether.

Discussion
Given a lack of evidence of adverse clinical outcomes and varying clinical management recommendations surrounding the drug interaction between metformin and DTG, we surveyed Canadian health care practitioners’ knowledge and management.

While almost all practitioners were aware that exposure to metformin is increased when DTG is administered concomitantly, only approximately two thirds of these were able to identify the magnitude of this increase. In addition, relatively few practitioners recognized that no adverse effects related to the interaction have been documented in the literature to date. Taken together, this may explain the high proportion of practitioners who adhere to the more concrete management recommendation to limit metformin dose to 500 mg po BID when co-administering the drug with DTG. However, perhaps as a reflection of the lack of published adverse effects or lack of knowledge of the magnitude of the interaction, a few practitioners suggested co-administering metformin at a higher dose (750-850 mg po BID) even in the setting of declining renal function.

In the two survey case scenarios in which the patient was already on stable HIV treatment with DTG, the large majority of practitioners did not change the HIV therapy, despite the fact that practitioners stated they had a higher overall level of confidence in managing HIV therapy. This may reflect caution in changing a well-tolerated, efficacious ART regimen for a drug interaction that has not yet led to reports of clinical adverse outcomes. Furthermore, in patients taking metformin already with new HIV diagnosis (case 1), the majority of survey respondents still elected to initiate ART with DTG, which may be a reflection of overall preference for this agent due to good tolerability, efficacy, and ease of administration.

Though the cases were designed with as few confounding variables as possible so that respondents would focus on the interaction between DTG and metformin, some findings are important to note despite our survey design. Firstly, some respondents commented that they may not select DTG not only to avoid the interaction, but to allow for a single tablet regimen that does not include abacavir, in order to minimize cardiovascular risk in a diabetic patient (e.g. elvitegravir/cobicistat, tenofovir, emtricitabine). Also, in case 3 some respondents identified that DTG is known to increase serum
creatinine, though without a true detrimental effect on renal function. Thus, though this case was meant to identify management of the interaction in a patient with chronic kidney disease-related decline in renal function, there is a potential that some survey participants may not have interpreted it in this manner. An additional finding in the survey comments was the fact that at least some respondents have had poor experiences with co-administering DTG and metformin and blood glucose control. It is not clear whether this is due to decreasing the dose of metformin when co-administering the two medications or another factor; however, given the magnitude of increase in metformin exposure (AUC) and $C_{\text{max}}$, decreasing the dose would be expected to result in similar metformin concentrations and thus similar glycemic control.

In this current survey, we did not find significant variations in practice decisions by region or profession. These analyses were limited due to imbalances in the respondents, which were predominantly pharmacists from three populous provinces.

In terms of respondents who changed their co-administration behaviour from one case to another, case 2 (new diabetes) appeared to have been the case that resulted in a change. This may be explained by the myriad of type 2 diabetes treatment options available and the fact that the patient was adherent to and tolerating effective HIV treatment, thus more respondents may have elected to choose alternate diabetes treatment.

Among factors that could potentially impact decision to co-administer metformin and DTG, higher DTG and metformin doses were most frequently identified as important. These would increase the magnitude of the interaction and increase metformin exposure, respectively. Thus, these are logical choices to affect such a decision. Renal dysfunction was another one of the top factors affecting continuation of co-therapy, which may be explained by metformin dosing recommendations based on renal function, the drug interaction, and risk of MALA with renal dysfunction(16,18,22).

Monitoring parameters in those co-administering DTG and metformin were consistent with those anticipated given metformin’s adverse effect profile and the treatment of diabetes: closer monitoring of glycaemia, more frequent/earlier follow up, and counselling patients regarding adverse effects such as GI
intolerance or lactic acidosis. Although metformin does not usually result in hypoglycaemia when administered as the sole antidiabetic therapy, perhaps concern regarding this potential toxicity stems from an unknown effect of increased exposure to the agent. However, metformin’s antihyperglycaemic effect is mediated by enhanced sensitivity to existing insulin in the liver and peripheral tissues and would therefore not be anticipated to result in hypoglycaemia even at higher concentrations(9,22). In fact, there appears to be a decrease in liver glycogen to counter hypoglycaemia as metformin approaches lethal levels in animals(22). Considering this, it is not surprising that a recent study of 15 patients receiving DTG and metformin did not find any differences in mean fasting blood glucose or HbA1c and reported no association between DTG trough concentration and percentage differences in blood glucose(14). It is important to note that no cases of lactic acidosis were identified in this study, but nevertheless the study population was relatively young and had normal renal and hepatic function, eliminating those risk factors for MALA.

This study has a few limitations that should be acknowledged. Firstly, the survey response rate was 36%, despite taking numerous steps in an attempt to increase response rate. For example, we offered monetary incentives to complete the survey and sent a reminder email. One potential cause of low response in our survey design was the use of spam filters. It is possible that our initial and reminder contacts to some participants were filtered into junk email folders or that delivery was blocked by some email accounts (e.g. workplaces). To minimize this risk, the survey link was sent using our institutional email rather than the survey platform. We also avoided survey platforms for which some institutions blocked Internet links, but the potential that some participants’ were not able to access the survey for this reason remains. We contacted potential participants in their mother tongue, when this was known, though further personalization was not possible given the snowball technique. To increase response rate, non-monetary incentives, statements that others had responded, and a graphic in the survey distribution email could also have been used(29). Survey participants could also have been universally pre-notified of the upcoming survey(30). However, ultimately our target response rate may have been overly ambitious in
light of decreased response rates reported with web surveys as well as overall decreasing participation in surveys (30–32). For example, in one review of 31 studies, the average response rate was 36.83%, which is in keeping with our results (30). The high proportion of pharmacists responding to the survey may be related to the fact that the topic of drug interactions is highly relevant to this proportion, which may have attracted more of these professionals given that studies have shown increased response rates for interesting topics (29). Secondly, the survey results best represent the practice of pharmacists and HIV specialist physicians working in large hospitals or clinics in Ontario, Quebec, and Alberta. Meanwhile, other regions and primary care providers are under-represented in the survey results. Although there is a readily available sample frame for pharmacists via the CHAP network, we identified a lack of corresponding national network of specialists, primary care physicians, and nurse practitioners, which may partially explain lack of representation of these practitioners. While we were able to reach many specialist physicians working in academic centres, primary care practitioners working in HIV care were more difficult to identify. Notably, no nurse practitioners responded to the survey: it is not clear whether this is due to a paucity of nurse practitioners employed in HIV care or a failure to reach these health care providers with this survey. A third limitation is the potential for selection bias as a consequence of employing a snowball technique in an attempt to reach these individuals. Another potential source of sampling bias is the identification of pharmacists and primary care providers within associations, as these practitioners may receive more continuing education and may therefore be more likely to have a better baseline knowledge of the interaction. On the other hand, we believe the majority of HIV-infected patients are likely to be receiving their care from these practitioners; thus, this sample may provide a more accurate reflection of current Canadian practice. Additionally, association lists may become out-dated. However, the list of CHAP members is updated annually to ensure accuracy. In the event that CHAP pharmacists were unable to forward the survey, we attempted to contact the HIV specialist physicians directly. A further limitation to the survey is the fact that there was no mechanism to prevent respondents from answering the survey multiple times, especially given that there was an incentive to complete the
survey. However, we requested in the survey instructions that each practitioner completes the survey only once. One potential solution to dealing with multiple responses is to limit completion of the survey based on IP address, but this would have eliminated responses from multiple practitioners working in the same clinic or institution. We assessed duplication of IP addresses in survey results: eight IP addresses were repeated. Of these, three IP addresses had surveys in progress or completed that we judged as potentially having been initiated by the same individual. However, we could not ascertain this with confidence to remove these survey attempts as duplicates. Consequently, response rate may appear falsely elevated based on the fact that the same individual may have initiated some of these survey attempts. On the other hand, completion rate would appear falsely low if this was truly the case, as removing these attempts would remove some surveys that were in progress when the survey closed. In addition, respondents may also have chosen to refer to clinical resources before or during the survey, but again were instructed to avoid doing so and to answer based on current knowledge. Finally, as previously discussed, while the response rate of 36% is acceptable for online surveys, a higher response rate would better represent national practice and increase statistical power. However, the completion rate of 83% indicates little attrition, which may reflect ease of completion of the survey.

In conclusion, despite widespread knowledge of the DTG-metformin interaction, a majority of Canadian health care providers co-administer metformin and DTG in the absence of data on adverse clinical effects. Given the high proportion of survey respondents indicating that they would co-administer these medications, future observational studies are warranted to assess clinical outcomes.
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### Table 1

**Characteristics of Survey Respondents**

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<th>n (%)</th>
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<td><strong>Province of Practice</strong></td>
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<td>• British Columbia</td>
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<td>• Alberta</td>
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</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td></td>
</tr>
<tr>
<td>• Infectious disease specialist</td>
<td>12 (19)</td>
</tr>
<tr>
<td>• HIV Primary Care</td>
<td>8 (13)</td>
</tr>
<tr>
<td>NP – HIV specialist</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pharmacist</td>
<td></td>
</tr>
<tr>
<td>• Hospital HIV specialist</td>
<td>35 (56)</td>
</tr>
<tr>
<td>• Community</td>
<td>5 (8)</td>
</tr>
<tr>
<td><strong>Experience (years)</strong></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>16 (27)</td>
</tr>
<tr>
<td>6-10</td>
<td>15 (25)</td>
</tr>
<tr>
<td>11-15</td>
<td>4 (7)</td>
</tr>
<tr>
<td>16-20</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Caseload</td>
<td>Personal</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>13 (22)</td>
</tr>
<tr>
<td>1-25</td>
<td>8 (14)</td>
</tr>
<tr>
<td>26-100</td>
<td>25 (42)</td>
</tr>
<tr>
<td>101-250</td>
<td>18 (31)</td>
</tr>
<tr>
<td>251-500</td>
<td>5 (8)</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>
Table 2

*Treatment Initiated in a Patient Newly Diagnosed with HIV Taking Metformin 1000 mg po BID*

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir; no change to diabetic co-medications</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Dolutegravir; change metformin dose</td>
<td>31 (61)</td>
</tr>
<tr>
<td>Dolutegravir; change metformin to another oral hypoglycemic agent</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Use another INSTI (raltegravir or elvitegravir)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Avoid INSTI (Initiate protease inhibitor or non-nucleoside reverse transcriptase inhibitor)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Table 3

_Treatment Initiated in a New Diabetic Taking Dolutegravir-based HIV Treatment_

<table>
<thead>
<tr>
<th>Treatment Initiated</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin, titrated as per product monograph</td>
<td>29 (57)</td>
</tr>
<tr>
<td>Alternative oral agent with recommended titration as per product monograph (e.g. sulfonyleurea, meglitinide, dipeptidyl peptidase-4 inhibitor)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Do not know</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (25)</td>
</tr>
</tbody>
</table>
Table 4

*Management of HIV Therapy in a New Diabetic Taking Dolutegravir-based HIV Treatment*

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue current dolutegravir therapy</td>
<td>45 (88)</td>
</tr>
<tr>
<td>Change dolutegravir to other integrase strand transfer inhibitor</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Change class of HIV medication (e.g. protease inhibitor-, non-nucleoside reverse transcriptase inhibitor-based treatment)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Table 5

*Management of Diabetes in a Patient Stabilized on Dolutegravir and Metformin 1000 mg po BID with Declining Renal Function*

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue metformin; start alternative oral agent</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Decrease metformin dose</td>
<td>23 (45)</td>
</tr>
<tr>
<td>No change in diabetes therapy; enhanced monitoring for symptoms of metformin toxicity</td>
<td>18 (35)</td>
</tr>
<tr>
<td>No change in diabetes therapy; no additional monitoring</td>
<td>5 (10)</td>
</tr>
</tbody>
</table>
Table 6

Statistical comparison of survey responses by profession and region

<table>
<thead>
<tr>
<th>OCT2-mediated interaction</th>
<th>Pharmacists (%)</th>
<th>Physicians (%)</th>
<th>p-value</th>
<th>Ontario (%)</th>
<th>Quebec (%)</th>
<th>Alberta (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 - New HIV, on metformin 1000 mg BID</td>
<td>80</td>
<td>54.5</td>
<td>0.094</td>
<td>66.7</td>
<td>82.4</td>
<td>58.4</td>
<td>0.351</td>
</tr>
<tr>
<td>Co-administer DTG &amp; Metformin 1000 mg BID</td>
<td>14.7</td>
<td>17.6</td>
<td>0.785</td>
<td>14.3</td>
<td>11.8</td>
<td>25</td>
<td>0.569</td>
</tr>
<tr>
<td>Case 2 - New Diabetes, on DTG Initiate metformin</td>
<td>64.7</td>
<td>52.9</td>
<td>0.417</td>
<td>71.4</td>
<td>76.5</td>
<td>31.2</td>
<td>0.017</td>
</tr>
<tr>
<td>Co-administer DTG, decrease metformin dose</td>
<td>79.4</td>
<td>70.6</td>
<td>0.484</td>
<td>85.7</td>
<td>88.2</td>
<td>56.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Case 3 - Declining renal function, on DTG &amp; metformin 1000 mg po BID</td>
<td>79.4</td>
<td>76.5</td>
<td>0.318</td>
<td>85.7</td>
<td>76.5</td>
<td>68.8</td>
<td>0.707</td>
</tr>
<tr>
<td>Discontinue metformin</td>
<td>20.6</td>
<td>11.8</td>
<td>0.436</td>
<td>14.3</td>
<td>11.8</td>
<td>31.2</td>
<td>0.313</td>
</tr>
<tr>
<td>Decrease metformin dose</td>
<td>0</td>
<td>11.8</td>
<td>0.107</td>
<td>0</td>
<td>11.8</td>
<td>0</td>
<td>0.158</td>
</tr>
<tr>
<td>Continue metformin</td>
<td>1000 mg po BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DTG dolutegravir, PM product monograph
Figures

*Figure 1.* Process for recruiting and disseminating the survey to pharmacists, physicians, and nurse practitioners. Yellow arrows represent distribution of the survey. Lead investigators distributed the survey to pharmacists within the Canadian HIV and Viral Hepatitis Pharmacists Network (CHAP), who were asked to distribute the survey to their HIV specialist physician colleagues and provide investigators with the name of local primary care groups. Lead investigators contacted the identified primary care groups, who were also able to further disseminate the survey to colleagues. Lead investigators also contacted the HIV physician specialists, if lead pharmacists were unable to do so.
Figure 2. Flow diagram of survey responses and completion
Figure 3. Participants’ responses to mechanism of interaction between dolutegravir and metformin
Figure 4. Most common supplemental monitoring performed by those continuing co-administration of dolutegravir and metformin in a patient with declining renal function, excluding those who stated there was no indication for additional monitoring.

GI gastrointestinal, HbA1c glycosylated haemoglobin, SCr serum creatinine, ACR albumin creatinine ratio
Figure 5. Management of HIV in a Patient Stabilized on Dolutegravir and Metformin 1000 mg po BID with Declining Renal Function
Figure 6. Factors affecting the decision to continue co-therapy with dolutegravir and metformin.

IVDU intravenous drug use, HBV hepatitis B virus, HCV hepatitis C virus, RAM resistance associated mutations
Appendices

1. Survey
2. Survey distribution email
3. Survey reminder email
Appendix 1: Survey

Please select in which language you prefer to complete the survey: English or French

National survey assessing knowledge and management of the drug interaction between dolutegravir and metformin by Canadian pharmacists, physicians, and nurse practitioners involved in the care of HIV patients

Introduction

Integrase strand transfer inhibitors (INSTI) are preferred by many international guidelines as part of initial antiretroviral therapy (ART). Dolutegravir is an effective once daily integrase inhibitor that is characterized by a good tolerance, high genetic barrier to resistance, and few drug-drug interactions. Type 2 diabetes is an increasingly prevalent condition in the Canadian population, with metformin usually recommended as the initial treatment of choice. While it is known that metformin and dolutegravir interact, little has been published surrounding the interaction and its management. This survey aims to assess the knowledge and management of this interaction by Canadian physicians, pharmacists, and nurse practitioners who provide care to HIV-infected patients to identify current clinical practice in Canada and examine regional variations in practice.

The survey will take approximately 15 minutes to complete. At the end of the survey, the participant will have the option to be entered into a draw to win one of three gift cards (valued at $100 each). This is optional and identifying data entered to participate in the draw will not be linked to the participant’s survey responses.

By completing this survey, the participant consents to participate in this study and the eventual presentation and/or publication of the results. The results of the survey will be presented in such a way as to preserve the anonymity of participants. In the event that there is a potential for data de-identification resulting from low regional response rates (less than 5 responses in a given region), data will be merged...
prior to presentation to avoid this risk. Participants may choose to end their participation in the survey at any time by exiting the survey.

**Please complete the survey without consulting clinical resources or colleagues, as the survey is meant to capture current practice and your personal approach. Please complete the survey only once.**

Consent to continue to survey: Yes or No

(next page)

**Part 1: Participant Demographic Information**

1. Which province or territory do you have your practice? (drop down menu)
   - a. BC
   - b. AB
   - c. SK
   - d. MB
   - e. ON
   - f. QC
   - g. NL
   - h. NB
   - i. NS
   - j. PE
   - k. YT
   - l. NT
   - m. NU

2. Please indicate which of the following best describes your occupation:
   - a. Physician – Infectious diseases specialist
   - b. Physician – HIV primary care
   - c. Nurse practitioner – HIV specialist
   - d. Pharmacist – Hospital HIV specialist
   - e. Pharmacist – Community pharmacist
   - f. Other

   (next page)

**If a, b, or c → Do you have a dedicated clinical pharmacist working in your practice?**

**If f → Survey will end but participant will be taken to enter draw for gift certificate.**
3. Indicate the number of years of experience in treating HIV patients
   a. 0-5
   b. 6-10
   c. 11-15
   d. 16-20
   e. > 20

4. HIV Patient Caseload: Indicate the approximate number of HIV-positive patients that you cared for in the last 3 months.
   a. 0
   b. 1-25
   c. 26-100
   d. 101-250
   e. 251-500
   f. >500

5. HIV Patient Caseload: Indicate the approximate total number of patients infected with HIV that are followed in your working place.
   a. 0
   b. 1-25
   c. 26-100
   d. 101-250
   e. 251-500
   f. >500

Part 2: Knowledge of Dolutegravir & Metformin Interaction
6. From a scale of 0 (not confident at all) to 10 (very confident), how confident are you in managing the following conditions (including making drug therapy changes):

   a. HIV: (sliding bar 0-10)
   b. Diabetes: (sliding bar 0-10)

7. Which of the following mediates the interaction between dolutegravir and metformin?

   a. Cytochrome P450 (CYP) 3A4
   b. UDP glucuronosyltransferase (UGT) 1A1
   c. Multidrug and toxin extrusion protein (MATE) 2-K
   d. Organic cation transporter (OCT) 2
   e. P-glycoprotein
   f. Do not know

8. The interaction between dolutegravir and metformin results in which of the following?

   a. An increase in plasma dolutegravir exposure
   b. An decrease in plasma dolutegravir exposure
   c. An increase in plasma metformin exposure
   d. An decrease in plasma metformin exposure
   e. Do not know

   (next page)

If c ➔ What is the magnitude of this interaction

   a. An increase by < 50%
   b. An increase by 50-125%
   c. Greater than a 2-fold increase.

   (next page)

9. The dose of dolutegravir affects the magnitude of the dolutegravir-metformin interaction

   a. True
b. False

c. Do not know

10. Adverse effects related to the metformin-dolutegravir drug interaction have been published in the literature.
    a. True
    b. False
    c. Do not know

11. What is/are the potential toxicity(ies) with exposure to (optional)
    a. high metformin concentrations?
       i. ______________________________
       ii. Do not know
    b. high dolutegravir concentrations? (optional)
       i. ______________________________
       ii. Do not know

Part 3: Management of Dolutegravir & Metformin Interaction

The following three cases are meant to collect information about how practitioners manage the interaction between metformin and dolutegravir. Other details may have been important for treatment selection, but were intentionally omitted in order to focus on the drug interaction management. If you believe that essential information is missing to reflect your clinical practice, please include it in the comment section below.

Case 1
You are seeing MJ, a 52-year-old male, who presents to your clinic today after a new diagnosis of HIV (CD4 count 421, viral load 63,000 copies/mL). MJ has been diagnosed three months ago and is asymptomatic.
Relevant laboratory values include:

- HIV genotype: no resistance associated mutations (RAM).
- Normal renal and hepatic function

Past medical history is significant for type 2 diabetes, which is well-controlled (HbA1c 6.8%) with metformin 1000 mg po BID.

He has heard from a friend about a new antiretroviral, dolutegravir, and wonders if this would be a good option for him.

1. Which of the following best represents the care you would provide to MJ?
   
   a. Dolutegravir is an acceptable alternative. No changes to diabetes co-medications are required.
   
   b. Dolutegravir is an acceptable alternative. Start dolutegravir 50 mg once daily and change metformin dose.
   
   c. Dolutegravir is an acceptable alternative. Start dolutegravir 50 mg once daily and change metformin to another oral hypoglycemic agent.
   
   d. Dolutegravir is not my best option for this patient. I would prefer the use of another integrase inhibitor-based therapy (raltegravir or elvitegravir).
   
   e. I would avoid integrase inhibitors for this patient. I would initiate treatment using a protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI).

Please justify your answer/provide comments: _________________________________________

2. How would follow up for this patient’s diabetes be different from the follow up you would usually provide (e.g. in the absence of the drug interaction)?

__________________________________________

(next page)
Case 2

TC is a 56-year-old female you have been seeing in clinic for the past several years. At today’s clinic visit, TC’s blood work reveals the following:

- HIV viral load is undetectable
- CD4 count is 719.
- Renal & hepatic function - normal

She is compliant with her current regimen of dolutegravir 50 mg once daily with 2 NRTI backbone, and reports no side effects. In the past, she had been on efavirenz + Kivexa then on atazanavir/rtv + Kivexa, which she discontinued due to side effects and for treatment simplification.

TC has no significant past medical history aside from HIV diagnosis, but upon reviewing her file, you notice her HbA1c was 7.9% three months ago (diagnostic of diabetes), and is 7.7% today despite TC’s best efforts to control her blood glucose with diet and exercise.

1. Which of the following is your first choice of drug therapy to treat TC’s diabetes?
   a. Start metformin with recommended titration as per product monograph.
   b. Start alternative oral agent with recommended titration as per product monograph. (e.g. sulfonylurea, meglitinide, DPP-4 inhibitor)
   c. Do not know
   d. Other: ______________________

2. How would you proceed in terms of HIV therapy?
   a. Continue current dolutegravir therapy.
   b. Change dolutegravir to other integrase strand transfer inhibitor (INSTI).
   c. Change class of HIV medication (e.g. protease inhibitor/NNRTI-based treatment)
   d. Other: ______________________

Comments (optional) ________________________________________________________________

(next page)
Case 3

VS is a 60 year old African Canadian woman you have been seeing in clinic for a few years. VS’s current HIV regimen consists of Triumeq (dolutegravir 50 mg/abacavir 600mg/lamivudine 300mg) once daily.

Relevant findings at today’s clinic visit include:

- Viral load undetectable, CD4 count 523
- HIV genotype is pan-sensitive.

VS’s past medical history is significant for hypertension and diabetes (well-controlled, HbA1c 7.1%). For these, she takes hydrochlorothiazide 25 mg po daily and metformin 1000 mg po BID since 2012. Upon reviewing her file, you notice a decline in her renal function:

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Creatinine (µmol/L)</th>
<th>CrCl (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2013</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>September 2014</td>
<td>89</td>
<td>67</td>
</tr>
<tr>
<td>December 2016</td>
<td>102</td>
<td>55</td>
</tr>
</tbody>
</table>

1. How would you proceed in terms of diabetes management?
   a. Discontinue metformin and start alternative oral agent.
   b. Decrease metformin dose.
   c. No change in diabetes therapy; enhanced monitoring for symptoms of metformin toxicity.
   d. No change in diabetes therapy; no additional monitoring.

   (next page)

Sub-question if b: You have selected to decrease metformin dose. What dose would you recommend? ____________________________________________

   (next page)
**Sub-question if b or c:** What supplemental monitoring (aside from usual monitoring) would you perform if a decision was made to administer dolutegravir and metformin concomitantly?

_______________________________________

(next page)

2. How would you proceed in terms of HIV management?
   
a. Continue current dolutegravir therapy.
   
b. Change dolutegravir to other integrase strand transfer inhibitor (e.g. Genvoya, raltegravir)
   
c. Change class of HIV medication (e.g. protease inhibitor/NNRTI-based treatment)

Comments regarding your choice of HIV management (optional):

_______________________________________

(next page)

3. Other comments regarding Case 3 (optional): ________________________________

(next page)

Factors that may influence your decision in continuing co-therapy with metformin and dolutegravir

Please provide a ranking from 0-3 for the degree to which you agree or disagree with the following statement: **The presence of this factor would affect my decision to continue co-therapy with dolutegravir and metformin.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>0 Would NOT affect my decision</th>
<th>1 Would LIKELY NOT affect my decision</th>
<th>2 Would PROBABLY affect my decision</th>
<th>3 Would DEFINITELY affect my decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral co-infection (Hepatitis B, Hepatitis C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Active intravenous drug use (IVDU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of HIV resistance associated mutations (RAMs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose consistently on the lower end of normal range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of antidiabetic agents other than metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dose of metformin (850 mg po TID)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dolutegravir dose (50 mg po q12h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments (optional): __________________________________________

(next page)

**Participation in Draw**: Click English or French link to draw

Thank you for your completion of the survey. You now have the option to enter a random draw for a chance to win one of three gift certificates valued at $100 each. The draw will take place after the survey has closed.

Participating in the draw is optional and any personal information provided will not be linked to your survey responses.

Are you interested in participating in a draw: Yes or No

**Please enter the following information to participate:**
Name ________________________________

Phone ________________________________

Email ________________________________

Thank you for your participation. Submit button
Appendix 2: Survey distribution email

Dear Health Care Professional,

I am conducting a nationwide survey of pharmacists, physicians, and nurse practitioners involved in the care of HIV-infected patients concerning current Canadian practices in the management of the co-prescribing of dolutegravir and metformin.

Because of your role in the care of these patients, you are being asked to complete this survey. The survey will take approximately 15 minutes to complete. At the end of the survey, you will have the option to be entered into a draw to win one of three gift cards (valued at $100 each). Participating in the draw is optional and any personal information provided will not be linked to your survey responses.

By completing the survey, you provide consent to participate in this study and the eventual presentation and/or publication of the results. The results of the survey will be presented in such a way as to preserve the anonymity of participants. In the event that there is a potential for data de-identification resulting from low regional response rates (less than 5 responses in a given region), data will be merged prior to presentation to avoid this risk. Completion of the survey is entirely voluntary and you may withdraw your consent to participate at any time by exiting the survey. Your data will be used only after completion of the survey.

Please complete the survey using only your current knowledge, without accessing clinical resources or collaborating with colleagues. Please complete the survey only once. The survey will remain open for four weeks.

Please access the survey via the following link: _____________
In an effort to maximize participation and thus validity of the survey results, I invite you to distribute the link to the survey to your pharmacist and physician (specialists and primary care) colleagues who are also directly involved in the care of HIV-infected patients. If you choose to do so, please indicate, via email response, the total number of colleagues with whom you have shared the survey, to allow for accurate calculation of survey response rate.

Thank you very much for your time and valuable contribution to this project.

Sincerely,

Pierre Giguère, BScPharm., M.Sc., AAHIVP
Clinical Pharmacy Specialist, The Ottawa Hospital

Ellen Dawson, BScPharm
Pharmacy Resident, The Ottawa Hospital
Appendix 3: Survey reminder email

Dear Health Care Professional,

I am writing to remind you about my survey regarding management of the co-prescribing of metformin and dolutegravir in Canada. **If you distributed the link to your colleagues upon initial receipt of the survey, please forward this reminder email.** If you have already completed the survey, thank you for your participation. If you have not yet had a chance to complete the survey, I would greatly appreciate your response.

The survey takes approximately 15 minutes to complete. At the end of the survey, you will have the option to be entered into a draw to win one of three gift cards (valued at $100 each). Participating in the draw is optional and any personal information provided to do so will not be linked to your survey responses.

By completing the survey, you provide consent to participate in this study and the eventual presentation and/or publication of the results. The results of the survey will be presented in such a way as to preserve the anonymity of participants. Completion of the survey is entirely voluntary and you may withdraw your consent to participate at any time by exiting the survey.

*Please complete the survey using only your current knowledge, without accessing clinical resources or collaborating with colleagues. Please complete the survey only once.*

The survey will remain open for two additional weeks.

Please access the survey via the following link: ____________
Thank you very much for your time and valuable contribution to my project.

Sincerely,

Pierre Giguère, BScPharm., M.Sc., AAHIVP
Clinical Pharmacy Specialist, The Ottawa Hospital

Ellen Dawson, BScPharm
Pharmacy Resident, The Ottawa Hospital