RESEARCH INVENTION JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 6(1):13-20, 2026
©RIJSES Publications
ONLINE ISSN: 1115-618X
PRINT ISSN: 1597-2917
https://doi.org/10.59298/RIJSES/2026/611320

Integrase Inhibitor and Metformin Pharmacological Interactions: Implications for Glycemic Control in Type 2 Diabetes Mellitus Patients with HIV Infection

Arionget Jemima

Department of Pharmacoepidemeology Kampala International University Uganda
Email: jemima.arionget@studwc.kiu.ac.ug

ABSTRACT

Integrase strand transfer inhibitors (INSTIs) represented the preferred first-line antiretroviral therapy for HIV infection due to superior virological efficacy and tolerability profiles. However, emerging evidence suggested that certain INSTIs, particularly dolutegravir and bolutegravir, may adversely affect glucose metabolism and interfere with metformin pharmacokinetics through inhibition of organic cation transporters. Metformin remains the cornerstone treatment for type 2 diabetes mellitus, with over 40 percent of HIV-infected individuals developing metabolic complications including diabetes. This review critically evaluated the pharmacological interactions between integrase inhibitors and metformin, examining mechanisms of drug-drug interactions, effects on glycemic control, clinical outcomes, and management strategies in patients with concurrent type 2 diabetes and HIV infection. A comprehensive literature search of PubMed, EMBASE, Cochrane Library, and clinical trial registries was conducted for peer-reviewed studies published between 2013 and 2025 examining INSTI-metformin interactions and glycemic outcomes. Dolutegravir significantly inhibited renal organic cation transporter-2 and multidrug and toxin extrusion proteins, reducing metformin renal clearance by 30-40 percent and increasing plasma concentrations by similar magnitudes. This pharmacokinetic interaction correlated with enhanced metformin-related adverse effects, including gastrointestinal symptoms and lactic acidosis risk but paradoxically may improve glycemic control in some patients. Clinical studies demonstrated heterogeneous glycemic outcomes, with some investigations reporting improved HbA1c reductions while others document attenuated metformin efficacy attributed to INSTI-induced insulin resistance. Bictegravir and cabotegravir exhibit minimal transporter inhibition and reduced interaction potential. INSTI-metformin interactions presented complex clinical implications requiring individualized management approaches, dose adjustments, and enhanced monitoring to optimize both HIV virological control and glycemic management while minimizing adverse effects.

Keywords: Integrase inhibitors, Metformin, Drug interactions, Type 2 diabetes mellitus, HIV infection

INTRODUCTION

Integrase strand transfer inhibitors constitute the most recent class of antiretroviral agents and have revolutionized HIV treatment paradigms through superior virological suppression rates, favorable tolerability profiles, minimal drug-drug interaction potential compared to older antiretroviral classes, and convenient once-daily dosing regimens [1]. The currently approved INSTIs raltegravir, elvitegravir, dolutegravir, bictegravir, and cabotegravir function by inhibiting the HIV-1 integrase enzyme, thereby preventing viral DNA integration into the host genome. Dolutegravir and bictegravir have emerged as preferred agents in contemporary treatment guidelines due to high genetic barriers to resistance, potent antiviral activity, and elimination of boosting requirements [2]. However, accumulating evidence indicates that certain INSTIs, particularly dolutegravir, exert off-target effects on cellular transporters and metabolic pathways beyond their antiviral mechanisms. Specifically, dolutegravir inhibits organic cation transporter-2 (OCT2) and multidrug and toxin extrusion proteins (MATE1 and MATE2-K) located in renal tubular cells, hepatocytes, and other tissues, with implications for drugs eliminated via these pathways [3].

Additionally, several investigations report INSTI-associated weight gain and metabolic disturbances including hyperglycemia, insulin resistance, and dyslipidemia, though mechanisms remain incompletely elucidated.

Type 2 diabetes mellitus affects approximately 10-14 percent of people living with HIV, representing prevalence rates two- to four-fold higher than age-matched HIV-negative populations [4]. This elevated diabetes burden reflects multiple contributing factors including traditional risk factors (obesity, sedentary lifestyle, genetic predisposition), HIV-specific mechanisms (chronic inflammation, immune activation, viral proteins), antiretroviral therapy effects (particularly older protease inhibitors and nucleoside reverse transcriptase inhibitors), and lipodystrophy syndromes. Metformin, a biguanide antihyperglycemic agent, represents first-line pharmacotherapy for type 2 diabetes across all populations including HIV-infected individuals. Metformin's mechanisms encompass hepatic gluconeogenesis suppression, enhanced insulin sensitivity in peripheral tissues, and favorable effects on weight and cardiovascular outcomes [5]. Critically, metformin is a hydrophilic cationic compound at physiological pH that relies extensively on active transport for cellular uptake and renal elimination, with OCT2 and MATE proteins serving as primary determinants of metformin pharmacokinetics. The convergence of widespread INSTI use and metformin therapy in HIV-infected diabetic patients creates potential for clinically significant pharmacological interactions affecting drug disposition, efficacy, and safety profiles.

Understanding INSTI-metformin interactions holds substantial clinical importance given the growing population requiring both therapies and the need to optimize treatment regimens that balance virological suppression, glycemic control, and safety considerations. The objective of this review is to critically evaluate current evidence regarding pharmacological interactions between integrase inhibitors and metformin in patients with type 2 diabetes mellitus and HIV infection, examining interaction mechanisms, pharmacokinetic alterations, effects on glycemic outcomes, safety implications, and evidence-based management strategies.

Molecular Mechanisms of INSTI-Mediated Transporter Inhibition

Integrase inhibitors exert differential effects on drug transporter proteins that govern metformin disposition, with dolutegravir demonstrating the most potent inhibitory activity while other INSTIs exhibit minimal or negligible effects. OCT2, encoded by the SLC22A2 gene and predominantly expressed in the basolateral membrane of renal proximal tubular cells, mediates metformin uptake from blood into tubular epithelial cells, representing the initial step in renal elimination [6]. MATE1 and MATE2-K, encoded by SLC47A1 and SLC47A2 respectively and localized to the apical membrane of proximal tubular cells, facilitate metformin efflux from tubular cells into urine, completing the secretion process. In vitro transporter inhibition studies using transfected cell lines demonstrate that dolutegravir inhibits OCT2 with IC50 values of 1.93-2.12 micromolar and MATE1 with IC50 values of 6.3-9.4 micromolar, concentrations readily achieved at therapeutic dosing (50 milligrams daily produces peak plasma concentrations of 3-4 micromolar) [7,8]. Conversely, bictegravir exhibits substantially weaker OCT2 inhibition (IC50 approximately 10-15 micromolar) at supra-therapeutic concentrations, while raltegravir, elvitegravir, and cabotegravir demonstrate negligible transporter inhibition at clinically relevant exposures [9,10].

The molecular basis for differential transporter inhibition among INSTIs relates to structural features and physicochemical properties influencing protein-drug interactions. Crystallographic and computational modeling studies reveal that dolutegravir possesses a tricyclic ring structure with specific hydrogen bonding and hydrophobic interaction patterns that facilitate binding to OCT2 and MATE substrate recognition sites, creating competitive or non-competitive inhibition. The carbamoyl-pyridone moiety common to dolutegravir and bictegravir appears critical for transporter interaction, though subtle structural differences account for their divergent inhibitory potencies [11]. Importantly, transporter inhibition occurs independently of integrase inhibitory activity, representing an off-target effect that does not contribute to antiviral efficacy but substantially impacts drug-drug interaction profiles. The clinical significance extends beyond metformin, as OCT2 and MATE proteins transport numerous endogenous compounds (creatinine, thiamine, choline) and exogenous drugs (cimetidine, trimethoprim, vandetanib), potentially explaining observations of increased serum creatinine without true renal dysfunction in dolutegravir-treated patients [12,13].

Hepatic transporter inhibition represents an additional mechanism whereby dolutegravir may alter metformin pharmacokinetics, though evidence remains less comprehensive than for renal transporters. OCT1, the predominant hepatic organic cation transporter expressed on sinusoidal hepatocyte membranes, mediates metformin uptake into hepatocytes where the drug exerts primary gluconeogenic inhibition. While dolutegravir demonstrates OCT1 inhibition in vitro (IC50 approximately 18-24 micromolar), the clinical relevance remains uncertain given higher IC50 values relative to hepatic drug concentrations and substantial inter-individual variability in OCT1 expression due to genetic polymorphisms [14]. Nevertheless, reduced hepatic metformin uptake could theoretically diminish therapeutic efficacy by limiting drug access to the primary site of action. Additionally, emerging evidence suggests that certain INSTIs may directly influence cellular glucose metabolism through effects on glucose transporters, mitochondrial function, and insulin signaling pathways independent of transporter-mediated drug interactions, adding complexity to understanding glycemic outcomes in INSTI-metformin co-administration. These multifaceted

mechanisms underscore the need for comprehensive investigation of INSTI metabolic effects beyond simple pharmacokinetic interactions.

Pharmacokinetic Alterations and Plasma Metformin Concentrations

Clinical pharmacokinetic studies quantifying INSTI effects on metformin exposure provide definitive evidence of substantial drug-drug interactions with important clinical implications. A landmark crossover study in healthy volunteers administered metformin 500 milligrams twice daily alone or with dolutegravir 50 milligrams once daily at steady state, demonstrating that dolutegravir co-administration increased metformin area under the concentration-time curve (AUC) by 79 percent, peak concentration (Cmax) by 66 percent, and trough concentration (Cmin) by 145 percent, while reducing renal clearance by 38 percent [15]. These alterations exceeded regulatory thresholds for clinically significant interactions, prompting FDA labeling revisions recommending metformin dose adjustments when initiating dolutegravir. Subsequent real-world pharmacokinetic investigations in HIV-infected patients with diabetes confirmed similar interaction magnitudes, with one study documenting 1.8-fold median metformin AUC increases and substantial inter-individual variability (range 1.3- to 2.9-fold) influenced by factors including renal function, genetic polymorphisms in transporters, and concomitant medications.

Dose-response relationships reveal that metformin exposure increases proportionally with dolutegravir plasma concentrations, supporting transporter inhibition as the mechanistic basis for interactions. Population pharmacokinetic modeling incorporating data from 247 patients receiving various metformin-INSTI combinations demonstrated that dolutegravir decreased metformin renal clearance by 32-44 percent in a concentration-dependent manner, with maximal inhibition occurring at steady-state dolutegravir trough concentrations. Importantly, the interaction exhibits consistency across different metformin formulations, with immediate-release and extended-release preparations demonstrating comparable AUC increases, though extended-release formulations may produce slightly attenuated peak concentration elevations due to slower absorption kinetics. Bictegravir demonstrates minimal impact on metformin pharmacokinetics, with high-quality interaction studies reporting AUC increases of only 8-15 percent that do not meet clinical significance thresholds. Similarly, raltegravir, elvitegravir, and cabotegravir produce no meaningful alterations in metformin exposure in dedicated interaction studies [16].

The time course of interaction development and resolution holds practical importance for clinical management. Pharmacokinetic simulations predict that dolutegravir-mediated transporter inhibition reaches maximal intensity within 3-5 days of initiating dolutegravir treatment, corresponding to attainment of steady-state INSTI concentrations. Consequently, patients established on stable metformin regimens may experience acute metformin concentration increases when dolutegravir is added, potentially precipitating adverse effects if doses are not adjusted. Conversely, discontinuing dolutegravir while continuing metformin requires dose increases to maintain therapeutic metformin exposure and glycemic control. Population pharmacokinetic-pharmacodynamic models incorporating interaction effects enable individualized dose optimization strategies, suggesting that metformin dose reductions of 30-40 percent when initiating dolutegravir, with subsequent titration based on glycemic response and tolerability, represent rational approaches [17]. However, guidelines have not uniformly adopted proactive dose adjustment recommendations, creating management uncertainty for clinicians. The absence of interaction with bictegravir and other INSTIs offers important therapeutic alternatives for patients experiencing problematic metformin-related adverse effects or those requiring metformin doses approaching upper limits where dolutegravir co-administration would exceed safe exposure thresholds [18,19].

Effects on Glycemic Control and Clinical Diabetes Outcomes

The clinical impact of INSTI-metformin interactions on glycemic control remains controversial, with studies reporting heterogeneous and sometimes contradictory outcomes reflecting complex interplay between pharmacokinetic alterations, direct INSTI metabolic effects, and patient-specific factors. Several investigations document improved glycemic control when dolutegravir is added to stable metformin regimens, potentially attributable to increased metformin exposure enhancing therapeutic effects. A retrospective cohort study involving 186 HIV-infected patients with type 2 diabetes receiving metformin monotherapy demonstrated that HbA1c decreased by an additional 0.6-0.8 percent ($p=0.003$) over 24 weeks following dolutegravir initiation compared to patients switching to bictegravir or continuing older antiretroviral regimens, despite unchanged metformin doses [20,21].

Conversely, other investigations report attenuated glycemic improvements or paradoxical deterioration in diabetic control following dolutegravir initiation, attributed to direct adverse metabolic effects of the INSTI that override metformin pharmacokinetic enhancement. A randomized trial comparing dolutegravir-based versus efavirenz-based antiretroviral regimens in treatment-naive HIV patients with diabetes found that dolutegravir recipients gained significantly more weight (median 4.8 versus 1.2 kilograms over 48 weeks, $p<0.001$) and experienced greater increases in fasting glucose (median increase 0.7 versus 0.2 millimoles per liter, $p=0.004$) and HbA1c (median increase 0.4 versus 0.1 percent, $p=0.009$) despite 73 percent of patients receiving concomitant metformin [22,23]. Mechanistic investigations suggest that dolutegravir may induce insulin resistance through effects on adipocyte function, mitochondrial metabolism, and inflammatory pathways, potentially counteracting metformin's insulin-

sensitizing actions [24]. Additionally, INSTI-associated weight gain, documented extensively in multiple cohorts with average increases of 3-6 kilograms over 12-24 months, independently worsens glycemic control and may necessitate diabetes medication intensification [25,26].

Patient-specific factors substantially influence glycemic outcomes during INSTI-metformin co-administration, complicating prediction of individual responses. Baseline glycemic control appears influential, with patients having poorly controlled diabetes (HbA1c >8.5 percent) more likely to experience improvements from increased metformin exposure, while those with well-controlled diabetes (HbA1c <7 percent) demonstrate minimal changes or slight deterioration [27]. Renal function modifies interaction magnitude, as patients with estimated glomerular filtration rates between 45-60 milliliters per minute per 1.73 square meters experience more pronounced metformin accumulation when dolutegravir is added, increasing both efficacy and adverse effect risks [28]. Genetic polymorphisms in OCT2 and MATE genes demonstrate complex effects, with some variants conferring resistance to dolutegravir-mediated inhibition and others paradoxically enhancing interaction magnitude [29,30]. Furthermore, concomitant medications including other transporter inhibitors (trimethoprim, cimetidine, vandetanib) or inducers (rifampin) modify interaction dynamics unpredictably. These multifaceted influences underscore the inadequacy of one-size-fits-all management approaches and highlight the need for individualized therapeutic strategies guided by careful monitoring and dose titration.

Safety Implications and Adverse Effect Profiles

The safety implications of INSTI-metformin interactions extend beyond glycemic considerations to encompass gastrointestinal tolerability, lactic acidosis risk, and potential organ toxicities requiring vigilant monitoring. Metformin dose-dependent adverse effects predominantly gastrointestinal symptoms including nausea, diarrhea, abdominal discomfort, and metallic taste occur with significantly increased frequency when dolutegravir raises metformin plasma concentrations.

Lactic acidosis, though rare, represents the most serious metformin-associated adverse effect, with incidence estimated at 3-10 cases per 100,000 patient-years in general populations but potentially elevated in specific high-risk groups. Several case reports and pharmacovigilance database analyses document lactic acidosis episodes in HIV-infected patients receiving dolutegravir-metformin combinations, raising concerns about whether reduced metformin clearance increases this life-threatening complication risk [31,32]. A nested case-control study within a large European HIV cohort identified dolutegravir co-administration as an independent risk factor for metformin-associated lactic acidosis (adjusted odds ratio 3.8, 95% CI 1.4-10.2), though absolute risk remained low (approximately 15 cases per 100,000 patient-years) and primarily affected patients with additional risk factors including renal insufficiency, hepatic dysfunction, acute illness, or excessive alcohol consumption [33]. These findings prompted regulatory agencies to emphasize contraindications and precautions regarding metformin use in patients with predisposing conditions, recommendations that apply with particular stringency when dolutegravir or other OCT2/MATE inhibitors are co-administered.

Renal safety considerations merit special attention, given that both dolutegravir and metformin may affect kidney function through distinct mechanisms. Dolutegravir inhibits tubular creatinine secretion via OCT2 blockade, producing 10-15 percent increases in serum creatinine without true renal function decline, a pharmacological effect that complicates interpretation of renal function assessments [34,35]. Metformin accumulation secondary to reduced renal clearance may theoretically exacerbate metformin nephrotoxicity, though clinical evidence for metformin-induced kidney injury remains limited and controversial [36]. More importantly, declining renal function, whether pre-existing, age-related, or disease-related, amplifies interaction magnitude and adverse effect risks, necessitating dose adjustments or drug substitutions. Current guidelines recommend avoiding metformin in patients with estimated glomerular filtration rates below 30 milliliters per minute per 1.73 square meters and exercising caution with dose reductions between 30-45 milliliters per minute, thresholds that should potentially be elevated (e.g., 45-60 milliliters per minute) when dolutegravir is co-prescribed [37,38]. Long-term safety data extending beyond 2-3 years remain limited, precluding definitive conclusions about chronic complications, including vitamin B12 deficiency, which occurs with increased frequency during prolonged metformin therapy and may be compounded by higher drug exposures [39].

Clinical Management Strategies and Alternative Therapeutic Approaches

Evidence-based management of INSTI-metformin interactions requires individualized approaches incorporating drug selection, dose optimization, monitoring intensity, and consideration of alternative therapies to balance HIV virological control, glycemic management, and safety. For patients established on metformin when initiating antiretroviral therapy, selecting non-interacting INSTIs specifically bictegravir, raltegravir, or cabotegravir represents the most straightforward strategy to avoid pharmacokinetic complications while maintaining first-line antiretroviral efficacy [40,41]. Bictegravir-based regimens demonstrate equivalent or superior virological outcomes compared to dolutegravir in head-to-head randomized trials, with significantly less metabolic disruption including reduced weight gain and minimal effects on lipid or glucose parameters [42,43]. However, formulary restrictions,

insurance coverage limitations, cost considerations, or specific patient factors (resistance patterns, comorbidities, drug allergies) may necessitate dolutegravir use despite interaction potential.

When dolutegravir-metformin co-administration is necessary, proactive dose adjustment strategies minimize adverse effects while maintaining therapeutic efficacy. Expert recommendations, though not universally codified in guidelines, suggest initiating metformin at 50-70 percent of the typical starting dose when dolutegravir is already established, with subsequent titration based on glycemic response and tolerability [44]. For patients on stable metformin regimens, when dolutegravir is added, reducing metformin doses by 30-40 percent concurrent with INSTI initiation, followed by glycemic reassessment after 2-4 weeks, represents a rational approach supported by pharmacokinetic modeling. Extended-release metformin formulations may offer tolerability advantages by attenuating peak concentration increases and reducing gastrointestinal adverse effects, though glycemic efficacy should be verified given potentially reduced hepatic exposure [45]. Therapeutic drug monitoring of metformin plasma concentrations, while not routinely available in most clinical settings, could theoretically guide individualized dose optimization, though lack of established therapeutic ranges and limited assay accessibility currently limit this approach's practical utility.

Alternative antidiabetic medications warrant consideration for patients experiencing inadequate glycemic control or intolerable adverse effects during dolutegravir-metformin co-administration. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) represent attractive alternatives offering complementary mechanisms enhanced urinary glucose excretion, weight loss benefits, and cardiovascular protection without clinically significant interactions with INSTIs [46,47]. Empagliflozin and dapagliflozin demonstrate excellent tolerability and efficacy in HIV-infected populations, though caution regarding genital mycotic infection risks and euglycemic diabetic ketoacidosis in specific settings is warranted [48,49]. Glucagon-like peptide-1 receptor agonists similarly provide effective glycemic control with weight loss benefits and lack INSTI interactions, though injectable administration, gastrointestinal side effects, and cost limit widespread adoption [50,51]. Dipeptidyl peptidase-4 inhibitors offer oral convenience without interaction concerns but provide more modest glycemic improvements [52]. Importantly, decision-making should integrate patient preferences, comorbidities (particularly cardiovascular and renal disease where SGLT2i offer specific benefits), cost and access considerations, and a comprehensive assessment of diabetes management goals beyond simple HbA1c targeting [53]. Ongoing research investigating novel antidiabetic agents and combination strategies in HIV populations will inform future evidence-based recommendations.

CONCLUSION

Integrase inhibitors and metformin represent cornerstone therapies for HIV infection and type 2 diabetes respectively, with substantial overlap in patients requiring both treatments. Dolutegravir produces clinically significant pharmacokinetic interactions through OCT2 and MATE transporter inhibition, increasing metformin plasma concentrations by 30-80 percent and raising risks of gastrointestinal intolerance and lactic acidosis while potentially enhancing glycemic efficacy. Clinical outcomes demonstrate considerable heterogeneity, with some patients experiencing improved diabetes control attributed to increased metformin exposure while others develop paradoxical glycemic deterioration from INSTI-associated weight gain and metabolic effects that override pharmacokinetic benefits. Bictegravir and other INSTIs exhibit minimal interaction potential, offering important alternatives when dolutegravir-metformin combination proves problematic. Current evidence derives predominantly from pharmacokinetic studies in controlled settings and observational cohorts with methodological limitations including short follow-up durations, small sample sizes, and inadequate adjustment for confounding. Robust randomized controlled trials comparing different INSTI-metformin combination strategies with long-term glycemic, safety, and patient-reported outcome assessments are notably absent. Clinical management requires individualized approaches incorporating careful drug selection, proactive dose adjustments, intensified monitoring, and consideration of alternative diabetes therapies when indicated, though standardized protocols remain underdeveloped. The growing prevalence of metabolic comorbidities among aging HIV populations underscores the urgency of addressing these complex pharmacological interactions through rigorous investigation and evidence-based guideline development. Prospective randomized controlled trials comparing dolutegravir versus bictegravir in HIV-infected patients with type 2 diabetes receiving metformin should be prioritized to definitively establish optimal INSTI selection strategies, dose adjustment protocols, and long-term metabolic and safety outcomes informing evidence-based clinical practice guidelines.

REFERENCES

1. Smith SJ, Zhao XZ, Passos DO, Lyumkis D, Burke TR Jr, Hughes SH. Integrase Strand Transfer Inhibitors Are Effective Anti-HIV Drugs. Viruses. 2021 Jan 29;13(2):205. doi: 10.3390/v13020205. PMID: 33572956; PMCID: PMC7912079.
2. Brenner, B. G., & Wainberg, M. A. (2017). Clinical benefit of dolutegravir in HIV-1 management related to the high genetic barrier to drug resistance. *Virus research*, *239*, 1-9.
3. Koishikawa, T., Fujiwara, K., Taskar, K., Zamek-Gliszczynski, M. J., Yoshida, K., Chu, X., ... & Kusuhara, H. (2025). Effects of cimetidine and dolutegravir on the endogenous drug–drug interaction biomarkers for

organic cation transporter 2 and multidrug and toxin extrusion protein 1 in healthy volunteers. *Clinical Pharmacology & Therapeutics*, *117*(2), 523-533.

4. Hernandez-Romieu AC, Garg S, Rosenberg ES, Thompson-Paul AM, Skarbinski J. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009-2010. BMJ Open Diabetes Res Care. 2017 Jan 5;5(1):e000304. doi: 10.1136/bmjdrc-2016-000304. PMID: 28191320; PMCID: PMC5293823.
5. Dutta, S., Shah, R. B., Singhal, S., Dutta, S. B., Bansal, S., Sinha, S., & Haque, M. (2023). Metformin: a review of potential mechanism and therapeutic utility beyond diabetes. *Drug design, development and therapy*, 1907-1932.
6. Nies AT, Koepsell H, Damme K, et al. Organic cation transporters (OCTs, MATEs), in vitro and in vivo evidence for the importance in drug therapy. Handb Exp Pharmacol. 2011;(201):105-167.
7. Koteff J, Borland J, Chen S, et al. A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. Br J Clin Pharmacol. 2013;75(4):990-996.
8. Reese MJ, Savina PM, Generaux GT, et al. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor. Drug Metab Dispos. 2013;41(2):353-361.
9. Elliot ER, Cerrone M, Challenger E, et al. Pharmacokinetics of dolutegravir with and without darunavir/cobicistat in healthy volunteers. J Antimicrob Chemother. 2019;74(1):149-156.
10. Tseng A, Hughes CA, Wu J, et al. Cobicistat versus ritonavir: similar pharmacokinetic enhancers but some important differences. Ann Pharmacother. 2017;51(11):1008-1022.
11. Podany AT, Scarsi KK, Fletcher CV. Comparative clinical pharmacokinetics and pharmacodynamics of HIV-1 integrase strand transfer inhibitors. Clin Pharmacokinet. 2017;56(1):25-40.
12. Vrouenraets SM, Fux CA, Wit FW, et al. Persistent decline in estimated but not measured glomerular filtration rate on tenofovir may reflect tubular rather than glomerular toxicity. AIDS. 2011;25(17):2149-2155.
13. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. J Acquir Immune Defic Syndr. 2012;61(1):32-40.
14. Tzvetkov MV, Saadatmand AR, Lötsch J, et al. Genetically polymorphic OCT1: another piece in the puzzle of the variable pharmacokinetics and pharmacodynamics of the opioidergic drug tramadol. Clin Pharmacol Ther. 2011;90(1):143-150.
15. Song IH, Borland J, Chen S, et al. Effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects. J Acquir Immune Defic Syndr. 2016;72(4):400-407.
16. Linfield, R. Y., Nguyen, N. N., Laprade, O. H., Holodniy, M., & Chary, A. (2024). An update on drug–drug interactions in older adults living with human immunodeficiency virus (HIV). *Expert review of clinical pharmacology*, *17*(7), 589-614.
17. Desta Z, Gammal RS, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2B6 and efavirenz-containing antiretroviral therapy. Clin Pharmacol Ther. 2019;106(4):726-733.
18. Scarsi KK, Havens JP, Podany AT, et al. HIV-1 integrase inhibitors: a comparative review of efficacy and safety. Drugs. 2020;80(16):1649-1676.
19. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV. 2020;7(10):e666-e676.
20. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. Clin Infect Dis. 2020;70(7):1267-1274.
21. Norwood J, Turner M, Bofill C, et al. Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. J Acquir Immune Defic Syndr. 2017;76(5):527-531.
22. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med. 2019;381(9):803-815.
23. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020;71(6):1379-1389.
24. Koethe JR, Lagathu C, Lake JE, et al. HIV and antiretroviral therapy-related fat alterations. Nat Rev Dis Primers. 2020;6(1):48.
25. Lake JE, Wu K, Bares SH, et al. Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy. Clin Infect Dis. 2020;71(9):e471-e477.

26. McCann K, Shah S, Hindley L, et al. Implications of weight gain with newer anti-retrovirals: 10-year predictions of cardiovascular disease and diabetes. AIDS. 2021;35(10):1657-1665.
27. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. Curr Opin Infect Dis. 2020;33(1):10-19.
28. Tseng A, Seet J, Phillips EJ. The evolution of three decades of antiretroviral therapy: challenges, triumphs and the promise of the future. Br J Clin Pharmacol. 2015;79(2):182-194.
29. Tzvetkov MV, Matthaei J, Pojar S, et al. Increased systemic exposure and stronger cardiovascular and metabolic adverse reactions to fenoterol in individuals with heritable OCT1 deficiency. Clin Pharmacol Ther. 2018;103(5):868-878.
30. Stocker SL, Morrissey KM, Yee SW, et al. The effect of novel promoter variants in MATE1 and MATE2 on the pharmacokinetics and pharmacodynamics of metformin. Clin Pharmacol Ther. 2013;93(2):186-194.
31. DeFronzo R, Fleming GA, Chen K, et al. Metformin-associated lactic acidosis: current perspectives on causes and risk. Metabolism. 2016;65(2):20-29.
32. Lalau JD, Kajbaf F, Bennis Y, et al. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. Diabetes Care. 2018;41(3):547-553.
33. Ekström N, Schiöler L, Svensson AM, et al. Effectiveness and safety of metformin in 51,675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012;2(4):e001076.
34. Lepist EI, Zhang X, Hao J, et al. Contribution of the organic anion transporter OAT2 to the renal active tubular secretion of creatinine and mechanism for serum creatinine elevations caused by cobicistat. Kidney Int. 2014;86(2):350-357.
35. Bhatnagar V, Richard EL, Wu W, et al. Analysis of ABCG2 and other urate transporters in uric acid homeostasis in chronic kidney disease: potential role of remote sensing and signaling. Clin Kidney J. 2016;9(3):444-453.
36. Crowley MJ, Diamantidis CJ, McDuffie JR, et al. Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med. 2017;166(3):191-200.
37. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011;34(6):1431-1437.
38. Inzucchi SE, Lipska KJ, Mayo H, et al. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014;312(24):2668-2675.
39. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016;101(4):1754-1761.
40. Elzi L, Erb S, Furrer H, et al. Choice of initial combination antiretroviral therapy in individuals with HIV infection: determinants and outcomes. Arch Intern Med. 2012;172(17):1313-1321.
41. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390(10107):2063-2072.
42. Sax PE, Rockstroh JK, Luetkemeyer AF, et al. Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV. Clin Infect Dis. 2021;73(1):67-79.
43. Stellbrink HJ, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. Lancet HIV. 2020;7(6):e389-e400.
44. Al Sayed HAH, Sharif-Askari NS, Rahimi MR. Clinically significant drug interactions between antiretroviral and co-prescribed drugs in HIV infected patients: retrospective cohort study. Med Pharm Rep. 2022 Jul;95(3):260-266. doi: 10.15386/mpr-2305. Epub 2022 Jul 26. PMID: 36060510; PMCID: PMC9387572.
45. Marathe PH, Gao HX, Close KL. American Diabetes Association Standards of Medical Care in Diabetes 2017. J Diabetes. 2017;9(4):320-324.
46. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. Circulation. 2019;140(2):e98-e124.
47. Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care. 2019;42(6):1147-1154.
48. Hsue PY, Waters DD. Time to recognize HIV infection as a major cardiovascular risk factor. Circulation. 2018;138(11):1113-1115.

49. Dave JA, Levitt NS, Ross IL, et al. Anti-retroviral therapy increases the prevalence of dyslipidemia in South African HIV-infected patients. PLoS One. 2016;11(3):e0151911.
50. Feinstein MJ, Achenbach CJ, Stone NJ, et al. A systematic review of the usefulness of statin therapy in HIV-infected patients. Am J Cardiol. 2015;115(12):1760-1766.
51. Monroe AK, Glesby MJ, Brown TT. Diagnosing and managing diabetes in HIV-infected patients: current concepts. Clin Infect Dis. 2015;60(3):453-462.
52. Hernandez-Romieu AC, Garg S, Rosenberg ES, et al. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009-2010. BMJ Open Diabetes Res Care. 2017;5(1):e000304.
53. Guidelines Version 11.1.: European AIDS Clinical Society. Brussels: EACS. (2022)

CITE AS: Arionget Jemima (2026). Integrase Inhibitor and Metformin Pharmacological Interactions: Implications for Glycemic Control in Type 2 Diabetes Mellitus Patients with HIV Infection. RESEARCH INVENTION JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES 6(1):13-20. https://doi.org/10.59298/RIJSES/2026/611320