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EDITORIAL COMMENTARY

Strategies for Implementation Research to Investigate the Negative Pharmacokinetic Interaction Between Efavirenz and Dolutegravir

Gene D. Morse

University at Buffalo, Buffalo, New York, USA

(See the Brief Report Article by Haas and Acosta on pages 1820–2.)

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The report from Haas and Acosta in this issue of *Clinical Infectious Diseases* presents a pharmacokinetic and pharmacogenomic analysis utilizing plasma concentration and genotype data obtained during their study of healthy, white volunteers receiving efavirenz followed by dolutegravir. This study also examined the relationship of the *CYP2B6* genotype polymorphism to the pharmacokinetic interaction between efavirenz and dolutegravir. The authors indicate that the safest strategy for using dolutegravir in a second-line regimen would be to switch directly from efavirenz-containing regimens only in individuals with an undetectable viral load. The implementation of this recommendation is likely to be variable among low- and middle-income countries (LMICs) and would likely be facilitated by additional clinical research.

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Correspondence: G. D. Morse, University at Buffalo, Buffalo, Center for Integrated Global Biomedical Sciences, 701 Ellicott Street, Buffalo, NY 14203 (emorse@buffalo.edu).

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EFAVIRENZ PHARMACOGENOMICS/PHARMACOKINETICS AND LOWER DOLUTEGRAVIR EXPOSURE

This complex interaction occurs when prior efavirenz dosing in certain individuals is discontinued but sustained efavirenz plasma concentrations result because these individuals have a "slow metabolizer phenotype." Frequent *CYP2B6* polymorphisms, especially *CYP2B6* 516G→T (rs3745274, *6 allele) and 983T→C (rs28399499, *9 allele), identify slow metabolizers associated with increased plasma efavirenz exposure, with slow metabolizer genotypes are present in Asians (30%), Africans (25%), and Europeans (5%). Thus, a key point is to consider that this interaction may occur in 25%–30% of individuals receiving dolutegravir in a second-line regimen in LMICs. As a result of the prolonged decline in efavirenz plasma concentrations, hepatic enzyme induction persists, leading to lower dolutegravir plasma concentrations. Based on these data, introducing dolutegravir at the recommended dose may result in "underdosing" in selected individuals. As this regimen switch may occur in some who may be failing their initial regimen, a question to consider is "How can this negative pharmacokinetic interaction be identified and potential drug resistance minimized when a switch to dolutegravir is planned in individuals in LMICs?"

LMICS AND CAPACITY TO CONDUCT TO CLINICAL RESEARCH TO MINIMIZE NEGATIVE OUTCOMES FROM THE EFAVIRENZ-DOLUTEGRAVIR INTERACTION

There has been substantial effort put into establishing LMIC laboratory capacity to support human immunodeficiency virus (HIV) pharmacokinetics and pharmacogenomics research. These efforts have been highlighted in reviews and individual examples of clinical pharmacology [1–12] and pharmacogenomics [8, 13–19] research programs that have been previously reported. The result of these capacity-building efforts, along with current funding to further expand research laboratory infrastructure, has led to LMIC opportunities that are now able to conduct implementation/translational research and investigate clinical challenges such as how to approach the efavirenz-dolutegravir negative pharmacokinetic interaction in clinical care settings. The additional laboratory capacity has been accompanied by mentored training of scientists and technical staff, further increasing the ability to conduct important clinical research.

Table 1. Representative Implementation Research Approach in Africa to Investigate the Efavirenz-Dolutegravir Pharmacokinetic Interaction in Second-line Treatment Regimens

Gap for Second-line Dolutegravir Implementation Research	Organization	Contribution
Dolutegravir rollout sponsor	PEPFAR	Multiple country organization for implementing dolutegravir access
Clinical care site	Hospital-based clinic, Ministry of Health Clinic	Recruitment of participants into protocol
Clinical research unit	NIAID/DAIDS Clinical Trials Units	Study design, regulatory compliance, staff mentoring
Research and training	Fogarty International Center	Funding for HIV research and training programs, support for pilot research projects for scholars
Pharmacogenomics	H3Africa	Laboratory technology for genotyping, sample collection, and transport guidelines
Pharmacovigilance	Pharmacovigilance System in Sub-Saharan Africa	Umbrella organization for organizing the implementation research project
Pharmacokinetics	Clinical Pharmacology Laboratories (eg, South Africa, Zimbabwe, Uganda)	Bioanalysis research with required mass spectrometry instrumentation, validated drug assays
Data collection and harmonization	IeDEA Cohort Consortium	Data collection to facilitate multiple clinical research sites, data analysis

Abbreviations: HIV, human immunodeficiency virus; IeDEA, International Epidemiology Databases to Evaluate AIDS; NIAID/DAIDS, National Institute of Allergy and Infectious Diseases, Division of AIDS; PEPFAR, US President's Emergency Plan For AIDS Relief.

A REPRESENTATIVE IMPLEMENTATION RESEARCH APPROACH IN AFRICA

The next step in adapting these efavirenz and dolutegravir pharmacogenomic/pharmacokinetic data to LMICs would be to (1) identify clinical sites where dolutegravir is being rolled out for first- and second-line HIV-1 therapy, (2) identify clinical research teams that have the capacity to conduct research protocols, (3) identify laboratories with pharmacogenomic assay capability (eg, polymerase chain reaction, next-generation sequencing) and drug assay capability to measure efavirenz and dolutegravir concentrations, and (4) establish a pharmacovigilance network to provide a measure of quality assurance for similar studies across LMICs [20, 21]. All of these items are readily available in LMICs; however, some additional communication among programs would be needed to organize this type of implementation/translational research. Table 1 includes a representative approach with groups that would be able to organize, fund, and evaluate dolutegravir use in second-line regimens and identify key programmatic components that are still needed and can be developed through clinical research and education training programs. There are multiple regions, organizations, and clinical research sites that could also conduct this type of implementation research.

Some of these programs provide funding support for pilot research and could be organized in a manner that leverages the "in kind" resources offered by many of these initiatives.

CONCLUSIONS

The report of a negative pharmacokinetic interaction between efavirenz and dolutegravir could have important clinical implications for second-line treatment of HIV infection in LMICs. However, additional studies are needed to examine the impact of this interaction on the success of dolutegravir-containing second-line regimens. Recent capacity building and program implementation efforts provide the infrastructure to continue this area of clinical research that is needed to determine the incidence of the slow metabolizer phenotype and the percentage of individuals who experience reduced dolutegravir plasma concentrations, as well as the impact of these findings on drug resistance and second-line treatment failure. Establishing a cross-agency, multicenter study would be well-positioned to examine these questions and provide additional guidance for regimen selection, dolutegravir dosing, and clinical monitoring.

Notes

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