Editorial

Future VIROLOGY

Emerging role for pharmacogenomics in HIV research in Africa

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"the emerging role for pharmacogenomics in HIV research in Africa, could remain a pipedream, unless there is training and funding, together with technology and human capacity building, for such work"

Tweetable abstract: Pharmacogenomics (Pgx); the study of how genes affect drug response may optimize treatment by improving effectiveness and safety of medications. To apply current guidelines for African HIV-infected patients Pgx research is key.

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Pharmacogenomics is the study of genes that affect response to drugs. It combines pharmacological and genomics principles, to predict effectiveness and safety of therapeutic agents. This is, in part, because drug response and toxicity are influenced by pharmacokinetic factors that result in interindividual variability in drug-metabolizing enzymes and membrane transporters [1]. Variants of relevance include members of the cytochrome P450 (*CYP450*) family. Genetic variation of *CYP450* genes alone is estimated to influence a quarter of all drug therapies [2]. Pharmacogenomic research is thus imperative for development and function of drugs, including antiretrovirals, anticancer medicines, antibiotics and lipid-lowering therapies, among others.

Pharmacogenomics research in Africa is especially valuable in the context of high genetic variability [1,3], high HIV burden and growing noncommunicable disease incidence. A recent publication on whole genome sequencing in hundreds of people from across Africa revealed an unexpectedly large number of new single-nucleotide variants [4]. Yet, less than a quarter of participants in current genomics (and by extension pharmacogenomics) research are non-Europeans, leaving out a large majority of human genetic variants [5]. The need for more inclusive genetic research further attests to the emerging role for pharmacogenomic studies across Africa.

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Antiretrovirals have improved the quality of life for HIV-infected individuals, by suppressing viral replication, globally [6]. However, variability in their pharmacokinetics (PK) and pharmacodynamics (PD) and the potential impact on virologic outcomes and adverse events, remains a major challenge. Moreover, genetic characteristics that influence PK and PD of drugs are poorly understood in African populations, thereby limiting treatment optimization [7]. Identified gene variants are useful for screening HIV-infected patients prior to treatment [1,2]. Likewise, study of additional pharmacogenomic parameters, such as clinical response to treatment or the ability to predict treatment failure, need to be carried out.

When managing HIV infection with antiretrovirals, the aim is to suppress viral replication [8]. More than a third of HIV-infected patients on treatment fail to achieve durable virologic suppression, while more than half of those who achieve virologic suppression develop toxicities related to elevated levels of antiretroviral medicines [9]. These differences are attributed to patient factors that impact drug metabolism and/or exposure to drugs: such as genetic variants and easy-to-study characteristics including BMI, comedication with other medicines or with traditional medicines and failure to take drugs daily (non-adherence) [8]. A few studies have been carried out on the easy-to-study characteristics, but there is a dearth of information on the role of genetic variants in African HIV-infected populations.

Medical treatment is sometimes based on anecdotal evidence, which in some cases may be unreliable. Resulting poor clinical outcomes and adverse effects lead to patient dissatisfaction, high costs and poor treatment adherence, especially for chronic diseases [10]. Moreover, drugs with narrow therapeutic indices, such as carbamazepine, efavirenz and warfarin, have demonstrated that clinical outcomes can be strongly influenced by genetic variability [11]. Additionally, pharmacogenomic testing has been shown to reduce the risk of drug toxicity, by as much as a third, during the first 6 months of warfarin therapy. A number of African studies, were premised on observations from the USA and Europe, that showed association between warfarin drug response and variation in two genes, *CYP2C9* and *VKORC1*. Associations between warfarin levels and *VKORC1 and CYP2C9* genetic variants were corroborated in Egyptians, Ghanaians and South Africans, but not in Sudanese and Kenyan individuals [12]. Such results speak to the heterogeneity of Africans among themselves and with other populations. Hence, the urgent need for broader pharmacogenomic studies across different African populations.

Moreover, when the human leucocyte antigen (*HLA-B*15:02)* genotype was characterized in Asian seizure patients, to exclude slow metabolizers of carbamazepine, there were fewer cases of adverse events [11]. Another gene variant of *HLA* (*HLA-B*57:01)* strongly correlates with increased risk of potentially life-threatening hypersensitivity reactions to abacavir [13]. Abacavir, is an antiretroviral drug, used in both pediatric and adult patients. Though work on *HLA* has demonstrated importance of pharmacogenomics, work needs to be carried out including more diverse populations.

Pharmacogenomics improves treatment efficacy and reduces cost of treatment [6]. However, African pharmacogenomics research lags behind. There is a need to identify variants of pharmacogenomic relevance, within African populations [6]. This is crucial as the current evidence shows that not all identified genetic variants are applicable to the majority of African populations [1,5]. Hence, pharmacogenomic research is needed to provide robust clinical evidence, aid in drug development and for identifying genetic variants specific to highly diverse African populations.

The US FDA provides guidance, based on pharmacogenomics, for nearly 100 drugs that include antiviral agents, analgesics, anesthetics, antiarrhythmics, antihypertensives, lipid modifying agents, anti-inflammatory agents, antibacterial agents, antineoplastics, anticoagulants and acid suppressants [2,6,11,14]. Such guidance will not benefit African patients, without supporting evidence from pharmacogenomics studies, on local populations. Hence the requirement for local pharmacogenomics research in Africa.

Pharmacogenomics in HIV research in Africa could also provide information for 'precision public health' approaches. Such novel approaches to precision medicine have potential to help policy makers to base healthcare decisions on genetic makeup of populations and communities. For instance, countries could tweak essential medicines lists to avoid medicines predicted to cause problems in their populations. This is vital because inter- and intra-population PK and PD differences suggest that a single prescribed dosage may not be appropriate for the treatment of disease, across different populations [15]. An example, of a missed opportunity was a study describing the distribution of *CYP2B6*6* gene polymorphisms and the need for efavirenz dose reduction for patients from Zimbabwe, in 2007 [16]. This was mostly ignored but eventually corroborated in 2014, by results from the ENCORE1 study, which precipitated in efavirenz dose reductions, globally. The lack of data and information regarding gene polymorphisms of African relevance affords many such missed opportunities.

There are reports of concentration-dependent toxicities in patients with elevated peak plasma levels. Similarly, low plasma concentrations have been reported in individuals receiving adequate dosage. Genetic variations in drug metabolizing enzymes may contribute to such observations [9,17]. The extent of these genetic variations remains largely unidentified in African populations. This ought to spark renewed enthusiasm for pharmacogenomic studies [17]. Additionally, a number of international cohort studies have been carried out to determine safety and efficacy of antiretroviral drugs, in HIV cohorts and controls. Few have explored the role of genetic diversity on drug metabolism and treatment outcomes, in African populations. Yet, Africa is the epicenter of HIV and African populations exhibit greater genetic diversity than other world populations [1,9,17]. It is indeed, opportune time for pharmacogenomic studies to determine genes that can be used to screen patients in real-life HIV patient cohorts in Africa.

In spite of general consensus, by various African researchers, about the need to carry out more robust pharmacogenomics studies, there remains constraints of funding, technology and human capacity [18,19]. In this regard, the emerging role for pharmacogenomics in HIV research in Africa, could remain a pipedream, unless there is training and funding, together with technology and human capacity building, for such work. Local funding in Africa is short, while global funding acquisition is heavily curtailed by lack of competitive advantage in some of the criteria for awarding grants, such as: experience of investigator, resources and environment. In spite of these shortcomings, many African laboratory-based pharmacogenomics researchers, must collaborate and possibly be involved in clinical trials. Such collaborations would provide data and evidence for application of pharmacogenomics in improving HIV treatment outcomes in Africa.

An example of a collaboration that primarily focuses on pharmacogenomics is the African Pharmacogenomics Consortium (APC), that was formally launched on the 6 September 2018. The effort, though recent, aims to address challenges of conducting and applying pharmacogenomics in Africa and identifying opportunities for advancement of individualized drug use on the continent [20]. More such collaborations are required to push the treatment optimization agenda forward. Collaborations ought to strengthen scientific and technical merit when applying for much needed research grants.

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