Brief Report

Pharmacogenomics of HIV Therapy: Summary of a Workshop Sponsored by the National Institute of Allergy and Infectious Diseases

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Approximately 1 million people in the United States and over 30 million worldwide are living with human immunodeficiency virus type 1 (HIV-1). While mortality from untreated infection approaches 100%, survival improves markedly with use of contemporary antiretroviral therapies (ART). In the United States, 25 drugs are approved for treating HIV-1, and increasing numbers are available in resource-limited countries. Safe and effective ART is a cornerstone in the global struggle against the acquired immunodeficiency syndrome. Variable responses to ART are due at least in part to human genetic variants that affect drug metabolism, drug disposition, and off-site drug targets. Defining effects of human genetic variants on HIV treatment toxicity, efficacy, and pharmacokinetics has far-reaching implications. In 2010, the National Institute of Allergy and Infectious Diseases sponsored a workshop entitled, Pharmacogenomics – A Path Towards Personalized HIV Care. This article summarizes workshop objectives, presentations, discussions, and recommendations derived from this meeting. Key words: HIV therapy, pharmacogenetics, pharmacogenomics, workshop

A
ccess to antiretroviral therapy (ART) is a cornerstone in the fight against AIDS.1 Interindividual variability in ART pharmacokinetics, efficacy, and toxicity may be affected by genetic variants relevant to drug metabolism, disposition, and off-site targets.2 In June 2010, the National Institute of Allergy and Infectious Diseases (NIAID) sponsored a workshop entitled, Pharmacogenomics – A Path Towards Personalized HIV Care. The impetus was the conviction that knowledge of associations between human genetics and HIV treatment responses can benefit individuals and populations worldwide. This document summarizes the workshop and resultant recommendations.

*See the Acknowledgments for a complete list of participants.
The workshop assembled individuals with complementary expertise to exchange ideas relevant to HIV pharmacogenomics and to develop recommendations for advancing the field. The first day included presentations by invited speakers, with intervening panel discussions. Participants were then assigned to working groups – Accelerating Pharmacogenomic Research, The Path from Bench to Beside, and Pharmacogenomics and Clinical Trials – and were charged with drafting recommendations. Participants reconvened on the second day to review recommendations.

HUMAN GENETIC PREDICTORS IN HIV TREATMENT

Current HIV pharmacogenomic knowledge was reviewed by David Haas. Orally administered antiretrovirals undergo absorption, distribution, metabolism, and elimination (ADME), and many ADME genes have functional variants. Non-ADME genes can also affect treatment responses. Table 1 lists well-established associations between genetics and antiretrovirals. Regarding HLA-B*5701 screening for abacavir hypersensitivity,3–6 guidelines recommend that test positivity be documented as abacavir allergy in the medical record,7 but even such a beneficial test took many years to reach practice. Regarding the relevance of CYP2B6 variants for efavirenz,8–13 population differences in genotype frequency largely explain higher plasma efavirenz exposure among populations of African ancestry. This together with an association between CYP2B6 and central nervous system (CNS) adverse experiences8 led some clinicians to incorrectly infer that efavirenz should be avoided in individuals of African descent. This highlights the potential harm resulting from the uninformed use of genetic information. Multiple genetic variants are also associated with nevirapine toxicities.14–17

Regarding strategies to find new associations, Amalio Telenti considered 3 aspects of pharmacogenomic discovery: (1) intermediate versus clinical phenotypes; (2) genetic and genomic approaches; and (3) discovery, replication, and functional validation. There are many functional variants of potential importance in ADME genes, but for most antiretrovirals little is known about effects of genetic variants on toxicity, efficacy, and pharmacokinetics. To demonstrate that phenotypes with outliers are good endpoints, he described the skewed population distribution of lopinavir pharmacokinetics and the discovery of a possibly causative variant in SLCO1B1.18,19 Multiple loss-of-function variants along an ADME pathway may more profoundly affect pharmacokinetics.20 Genomic discoveries in the general population should be translated into the HIV field, including markers of metabolic complications.21,22

Regarding issues in validation, Marylyn Ritchie discussed statistical issues in genomic association studies. Without very large studies, genome-wide association studies (GWAS) may miss true associations when using thresholds derived from Bonferroni correction (eg, $P < 5 \times 10^{-8}$ for genome-wide significance), but accruing sufficiently large studies is not always feasible. Alternatives include the false discovery rate, permutation testing, and relaxed $P$-value thresholds, emphasizing effect sizes and independent replication. It is unclear

<table>
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<th>Drug</th>
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<tr>
<td>Abacavir</td>
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<tr>
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<td>APOC, others</td>
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whether replication should be at the level of genes, gene pathways, or gene networks. She introduced issues regarding allelic heterogeneity and population differences and noted that most tagging single nucleotide polymorphisms (SNPs) are not functional. Phenotypes may reflect combined effects of multiple rare variants in different individuals or interactions among common and/or rare variants in the same individual. The importance of phenotyping precision may depend on sample size and other aspects of study design.

TRANSLATING GENETIC TESTING INTO CLINICAL CARE

Regarding viral genetics and nongenetic factors, Daniel Kuritzkes reviewed the use of laboratory assays for CD4 cells, HIV-1 RNA, viral drug resistance, and chemokine receptor tropism to inform HIV treatment decisions. Factors associated with HIV disease progression in untreated patients include HLA type, CCR5 genotype, and coinfections. Genomics research has enhanced understanding of viral-host interactions. Host genetic markers could potentially be used to stratify populations based on risk of disease progression, informing decisions about when to start therapy. He considered host and viral factors that affect ART response and noted the potential for genetics to elucidate underlying mechanisms of virus-host interactions during ART.

The US Food and Drug Administration’s (FDA) role in bringing genetic tests to clinical practice was discussed by Shashi Amur. Several FDA centers govern different aspects of antiretroviral drugs and monitoring: Center for Drug Evaluation and Research (CDER) is involved through drug approval and labeling; Center for Biologics Evaluation and Research (CBER) approves tests for HIV monitoring; and Center for Devices and Radiological Health (CDRH) approves human genetic tests. Genetic test information may be included in initial labeling or added later, with strength of evidence affecting strength of label wording. She emphasized an FDA goal of supporting development of genetic predictors of treatment response and toxicity. The already successful incorporation of some genetic tests into clinical care raises optimism that challenges can be overcome.

Lessons from warfarin studies were recounted by Brian Gage, including the initial implication of multiple genes and a Web-based resource for pharmacogenetic dosing. Initial studies identified an association between CYP2C9*2, *3 and warfarin metabolism, which spurred trials of CYP2C9 genotype-based dosing. Initial studies were not highly successful, in part due to reliance on a single gene. Subsequent collaborations demonstrated that to accurately estimate warfarin dose, dosing equations should include at least 2 genes (VKORC1 and CYP2C9) and clinical factors (eg, age, body surface area). This work fostered www.WarfarinDosing.org, a National Institutes of Health (NIH)–supported site that incorporates genetic and nongenetic factors to guide dosing.

Regarding resource-limited settings, Gary Maartens reminded participants that human genetic diversity is greatest in Africa and that Africa also has the greatest HIV burden. Population genetic structure must be considered when assessing genetic tests. For example, while HLA-B*5701 testing is routine in many countries, this variant is rare in native Africans. It was once argued that CD4 cell testing was not feasible in Africa, but it is now available based on its clinical importance and cost-effectiveness. Increased research in Africa will likely identify novel and relevant genetic associations. Furthermore, knowledge of population frequencies of relevant variants may inform policy.

The power of informatics to improve patient care was discussed by Dan Masys. He recounted how, at one major US medical center, implementation of computerized provider order entry (CPOE) markedly reduced medication prescribing errors. Human genomics is the current archetype for health care complexity. Because handling such complex data exceeds the ability of any practitioner, computerized clinical decision support and electronic medical records will be critical. Genomics dramatically increases data complexity, but failure to use such data will lead to suboptimal patient care. Broadly adopting electronic medical records may help solve this problem.

STRATEGIES TO ADVANCE THE FIELD

Regarding clinical trials delivering genetic information, Jacques Fellay noted the importance of large sample sizes, homogenous patient populations, and well-defined phenotypes for genetic association analyses. He recounted the IDEAL
study, a prospective trial of hepatitis C virus (HCV) therapies. Most IDEAL participants consented for genetic research. By GWAS, sustained virologic response rates were 80% and 30% among groups with favorable and unfavorable $\text{IL28B}$ alleles, respectively.\textsuperscript{23} Allele frequencies largely explain racial disparities in HCV treatment response. This GWAS already shapes how HCV treatment and drug development is considered, but it was only possible because consent for genomic research was requested in IDEAL. He emphasized that every clinical trial should include genetic consent and DNA collection for future analyses.

Challenges in prospectively testing genetic markers through clinical trials were described by Elizabeth Phillips. The history of $\text{HLA-B*5701}$ screening for abacavir spanned 6 years from discovery to clinical practice. The prospective, randomized PREDICT-1 study definitively established the value of $\text{HLA-B*5701}$ testing among Caucasians and showed the importance of an intermediate phenotype (abacavir skin patch testing) to define true immunologically mediated abacavir hypersensitivity.\textsuperscript{6} The retrospective, case-control SHAPE study replicated this association in patients of African descent.\textsuperscript{5} Many immune-mediated drug reactions will involve HLA, but the combination of such a strong association for a problem as prevalent as abacavir hypersensitivity is unlikely for most drugs. The abacavir story exemplified the importance of various study designs, intermediate phenotypes, and validation and ongoing quality assurance of laboratory technologies.

Prospective clinical trial designs relevant to pharmacogenomics were discussed by Heather Ribaudo. Clinical trials provide more robust causal evidence than observational studies. With targeted prospective designs, individuals of known genotype may be prospectively studied specifically to collect information on phenotypes likely affected by genetics. With restrictive/enrichment designs, genetic screening enriches the study population for genotypes of interest and then randomizes participants to an intervention. These designs may require relatively few participants to address targeted questions. She described benefits of a large, phase 3 strategy design in which all potential drug recipients are randomized to genetic screening or not (eg, PREDICT-1\textsuperscript{4}). Optimal design depends on the research question. She noted benefits of precise, objective endpoints.

Regarding the cost-effectiveness of genetic testing, Kenneth Freedberg discussed implications of cost-effectiveness analysis applied to clinical trials and strategies of care. Cost-effectiveness is a method of understanding the value of different interventions in HIV, defining the incremental cost-effectiveness ratio in terms of dollars per year of life saved or dollars per quality-adjusted life year saved. He described how higher CD4 counts correlate with lower cost of care. In the United States, $\text{HLA-B*5701}$ testing has been shown to be cost-effective by helping optimize the use of ART. Whether genomic testing will be cost-effective in resource-limited settings will depend on the relative cost of the tests, the prevalence of genomic variances, and cost and availability of different ART regimens.

Regarding diagnostic test development, Christos Petropoulos provided slides describing 2 routes to diagnostic test approval – the Hercep test (Dako North America, Inc., Carpinteria, California, USA) and the Trofile assay (Monogram Biosciences, Inc., South San Francisco, California, USA). Hercep identifies HER2-positive breast cancer, which can be treated with trastuzumab. This standard of care test enables prescribing, with well-aligned positioning of the diagnostic test by drug manufacturer and assay provider. The Trofile assay identifies HIV-1 chemokine receptor tropism and informs prescribing of CCR5 inhibitors. This test is also standard of care but is perceived as a barrier to prescribing. It is best if objectives of pharmaceutical/biotechnology and diagnostic companies can be aligned. Opportunities include reduced health care costs and expanded indications for targeted therapies.

Regarding genetics of complex traits, Teri Manolio described how GWAS has accelerated progress in describing complex traits. She highlighted a Web page summarizing published genome-wide associations (www.genome.gov/gwasstudies/). Lessons from GWAS include surprising signals in unexpected genes, signals in gene “deserts” (regions devoid of protein-coding genes), and individual genes associated with multiple disparate phenotypes. Small genetic odds ratios may reflect contributions of environmental factors. Associations with large effects will be hard to find if causative variants are rare.
RECOMMENDATIONS FROM WORKSHOP PARTICIPANTS

Working groups generated specific recommendations. Major recommendations are listed in Table 2.

Recommendation 1: Every HIV-related clinical trial should offer participants the opportunity to consent for future genetic analyses, with prolonged DNA storage and broad scopes of analyses. At the time of clinical trial performance, all future genomic questions cannot be anticipated. Every HIV-related clinical trial should therefore store DNA for future analysis. Consent should encompass the broadest possible scope of genomic assays and clinical phenotypes. In addition, DNA storage should be without time limit, because important genomic questions may arise decades after trial completion.

Some attendees favored a federal mandate that all clinical trials bank DNA and that consent for genetic analyses be required for participation in any trial. The prevailing sentiment among attendees, however, was that these approaches would be prohibited by legal, confidentiality, and other concerns. An alternative is to require that participants have the opportunity to consent “yes” or “no” for future genetic analyses, without their response affecting trial eligibility. The institutional review board (IRB) for at least one US academic center requires that every protocol offers participants such an opportunity unless the investigator justifies otherwise. Mandating such wording nationally, however, could complicate trials enrollment and affect public sentiment about research. In some situations, “opt-out” consenting may be feasible, in which genetic research is allowed unless the participant proactively declines.

Ethics committees (ECs) and IRBs ultimately decide what is allowed. In the United States, IRB decisions are independent and self-governing. Issues that may cause concern for IRBs include indefinite duration of DNA storage and unlimited scope of analyses. At least some non-US ECs may insist upon narrowly defined scopes of analyses and may be reluctant to allow DNA or genetic data to leave their countries.

Recommendation 2: Create a Web-based catalogue of HIV clinical trials and cohorts suitable for genetic analyses. A barrier to progress in HIV pharmacogenomics is lack of readily available information regarding existing trial and cohort datasets with broad consent and available DNA. Many genomic analyses occur only following chance interactions between genomic investigators and individuals familiar with particular trials or cohorts. Cataloguing such information would facilitate genetic discovery and replication. A Web-based listing of such studies, including selected available phenotypes, need not be expensive and would include both federally funded and non-federal studies. Individuals familiar with each study would contribute a minimal amount of information. Non-US investigators should be involved from the outset. To provide incentive for data uploads, one suggestion was to limit catalogue queries to individuals who have uploaded data. Web sites already exist that compile information about various aspects of clinical trials and/or pharmacogenomics (eg, ClinicalTrials.gov, PharmGKB, HIV-Pharmacogenomics.org). One option would be to grow the catalogue from an existing site.

Recommendation 3: Establish an international HIV pharmacogenomics consortium. Investigators worldwide have interests and expertise directly relevant to HIV pharmacogenomics, but work in relative isolation. This is problematic, as many individual datasets are inadequately powered to identify and/or replicate associations. In

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Table 2. Major recommendations from workshop participants

| 1. | Every HIV-related clinical trial should offer participants the opportunity to consent for future genetic analyses, with prolonged DNA storage and broad scopes of analyses. |
| 2. | Create a Web-based catalogue of HIV clinical trials and cohorts suitable for genetic analyses. |
| 3. | Establish an international HIV pharmacogenomics consortium. |
| 4. | Disseminate information regarding HIV pharmacogenomic research widely and effectively. |
| 5. | Support database, statistical, and computational genomics infrastructures needed for successful HIV pharmacogenomics. |
addition, because genotype-phenotype associations may vary depending on genetic and environmental factors, associations must be studied in different populations and contexts worldwide. The number and diversity of potential pharmacogenomic questions require involvement of many investigators. An international consortium of investigators could work together to identify the most important HIV pharmacogenomic questions, develop phenotype precision and consensus, combine datasets to address questions beyond the scope of individual groups or datasets, and leverage resources to efficiently complete analyses. Such a consortium could also enhance communication among HIV pharmacogenomic investigators.

Recommendation 4: Disseminate information regarding HIV pharmacogenomic research widely and effectively. Pharmacogenomics investigators are understandably enthusiastic about the potential benefits of their work, given the precedent of a genetic screening test that already improves HIV drug safety and reduces cost (ie, HLA-B*5701 for abacavir hypersensitivity). Other groups, however, may not share this enthusiasm, perhaps due to concern that genetic information may personally identify patients, that incorporating genomics into clinical care will increase complexity or cost, or that benefits may not reach populations or countries in which discoveries are made. To engage partners in this endeavor, information regarding benefits and challenges of pharmacogenomic research must be effectively shared with persons living with HIV, providers, researchers, policymakers, and the general public worldwide. The consortium mentioned in Recommendation 3 could play a role in disseminating information.

Recommendation 5: Support database, statistical, and computational genomics infrastructures needed for successful HIV pharmacogenomics. Essential for progress in HIV pharmacogenomics research are robust clinical trial and cohort datasets to merge with genomic data. An underappreciated aspect of this work is the need for personnel with the skills and time for this task. Even with prospective trials and cohorts, considerable data processing may be required to generate clean, well-documented datasets for specific questions. Such work requires individuals who understand subtleties of study design, performance, and data collection. For complex datasets with many possible phenotypes of interest, judgment may be needed to prioritize analyses. There must be sufficient support for all the personnel with complementary expertise needed for these activities. Of note, the preparation of such datasets can be tedious and time-consuming and may not be recognized for academic advancement.

ADDITIONAL POINTS OF DISCUSSION

Workshop participants emphasized a number of other points as follows. (1) To define genotype-phenotype associations, various study designs should be pursued in parallel, not sequentially (eg, observational and prospective studies, studies of clinical outcomes and intermediate phenotypes, studies in different populations and contexts, etc). (2) When observational evidence of genetic association is sufficiently strong, prospective clinical trials to test genetic predictors may not be required. However, treatment guidelines are most strongly affected by prospective trials, and information in different populations is required to define generalizability. (3) Cost-effectiveness modeling plays an important role in assessing genetic markers and the feasibility of application to clinical practice. (4) Both positive and negative findings from genetic association studies should be presented. (5) Genetic studies should consider nongenetic and ecological factors (eg, nutritional status, medication adherence, concomitant medications, and concomitant illnesses). (6) The most relevant phenotypes should be carefully chosen based on clinical impact. Considerations include drugs that are widely used, and populations in which they are prescribed. (7) Identifying genetic predictors of adverse events is most critical, but predictors of virologic response would also be of considerable interest. (8) Pharmacogenomics studies should incorporate pharmacokinetic analyses. Pharmacokinetic data enhance interpretation of genetic association studies, and predictors of drug disposition could inform dosing schedules. (9) Pharmacogenomics research benefits from an understanding of pharmacokinetic-pharmacodynamic relationships. (10) As much information as possible should be gleaned from extant data and specimens through association analyses, cost-effectiveness analyses, and value-of-information analyses. (11) Merging data from various clinical trials and cohorts would be facilitated if studies routinely and uniformly collected minimum sets of key variables. (12) Results,
implications, and generalizability of genetic association studies may be context dependent. For example, some studies relevant to resource-limited countries may not be relevant to other countries. (13) A potential application of pharmacogenomics in resource-limited countries is to predict whether drugs are likely to be safe for their population. For example, if a reliable genetic predictor of drug toxicity is identified, that drug could be avoided in populations with high allelic frequencies of the predictor. (14) Although most genetic markers may not reach clinical application, much may be learned from genetic studies that elucidate underlying mechanisms of disease pathogenesis.

ACKNOWLEDGMENTS
The views expressed in written conference materials or publications and by speakers and moderators at HHS-sponsored conferences do not necessarily reflect the official policies of the US Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the US Government. This project has been funded in whole or in part with federal funds from the National Institute of Allergies and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under contract no. HHSN272200800014C.

Potential Conflicts of Interest
David W. Haas: Principal Investigator for research grants to Vanderbilt from Bristol Myers Squibb, Boehringer Ingelheim, Merck, Gilead Sciences. Daniel Kuritzkes: Consultant to and/or received research support from Abbott, Aveza, Boehringer-Ingelheim, Gilead, GlaxoSmithKline (GSK), Merck, Oncolyx, Roche, Siemens, Tobira, Vertex, ViiV, Viro-Statics and VIRxSYS. Marylyn D. Ritchie: Consultant for Boehringer Ingelheim. Elizabeth Phillips: Honoraria and consulting fees from ViiV Australia, Merck Pty Ltd, and Tibotec. Christos Petropoulos: Employee of Monogram Biosciences, South San Francisco, CA. Roy M. Gulic: Ad hoc consultant for Bristol-Myers, Gilead, GSK, MedImmune, ViiV, and Virostatics, and as Principal Investigator for research grants to Weil Cornell from Merck and Pfizer. Richard Haubrich: Received honoraria or consultant fees from Abbott, Bristol-Myers Squibb, Gilead Sciences, GSK, Merck, Monogram, Pfizer, Roche, Tibotec, and ViiV and research support (to UCSD) from Abbott, GlaxoSmithKline, Merck, Pfizer, and ViiV. No potential conflicts of interest: Shashi Amur, Brian Gage, Gary Maartens, Dan Masys, Jacques Fellay, Heather J. Ribaudo, Kenneth A. Freedberg, Teri A. Manolio, Peter Kim, Marjorie Dehlinger, Rahel Abebe, and Amalio Telenti.

Funding
The workshop entitled, Pharmacogenomics – A Path Towards Personalized HIV Care, was supported by the National Institute of Allergy and Infectious Diseases and the NIH Office of AIDS Research. This work was supported in part by the AIDS Clinical Trials Group (grants AI68636, AI38858, AI68634, and AI38855). Participants were also supported by the following: grants AI069439, RR024975, and AI54999 (DWI); AI51966 (RMG); RR024996 (Cornell CTSC); RR69419 (CTU); Swiss National Foundation 324730–124943 (AT); HL097036 (BFG); AI64086, AI69432, and CHRP MC08-SD-700 (RH); AI69472 (DK); HL065962 and AI077505 (MDR); AI42006 and AI085736 (KAF).

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