Translating Knowledge from Research to Outcomes: Pharmacogenomics in the Treatment of HIV/AIDS

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Although therapeutic medicines are frequently prescribed to improve health, individual responses are often inconsistent, unpredictable and potentially harmful. Recognising that individual genetic variation can influence response, pharmacogenomics aims to identify clinically relevant medicine/genome relationships, and use this knowledge to improve the safe and effective use of medicines. To facilitate the translation of new pharmacogenomic knowledge from the scientific laboratories where it is generated, into the clinical health services where it can be applied, Khoury et al developed a framework outlining a continuum of translation research. This framework must be embedded within a social and political environment conducive to supporting translational research if the desired outcomes are to be achieved. Drawing on the example of one pharmacogenomic test that is now well integrated into clinical practice, this article traces the contemporaneous social and political factors that facilitated translational pharmacogenomic research, and enabled the safe use of a vital medicine.

INTRODUCTION

The use of medicines[1] is a common feature of many treatment regimens designed to maintain health and treat disease.[2] Unfortunately, individual therapeutic responses are not universally consistent. In some instances, use of a particular medicine will result in the desired response and outcome, while in others the response may be sub-therapeutic or, in fact, harmful.[3] The uncertainty associated with a potential response to medicines presents an ongoing challenge for their safe and efficacious use.

Researchers and clinicians have long been aware that, along with environmental and developmental factors,[4] individual genetic variation can contribute to individual variability in medicine response.[5] Without specific genetic or genomic knowledge, however, this could only be determined after exposure. More recently, building on the increasing knowledge of the human genome, researchers have begun to identify specific alleles that contribute to this variability. Termed pharmacogenomics,[6] to date this research has successfully identified more than 100 genomic variants that could help predict individual response to medicines.[7]

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[1] *Therapeutic Goods Act 1989* (Cth) s 3 defines medicine as a therapeutic good "represented to achieve … their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human".

[2] T Morgan et al, "A National Census of Medicines Use: A 24-hour Snapshot of Australians Aged 50 Years and Older" (2012) 196(1) *Medical Journal of Australia* 50, 50.

[3] K Hakkarainen et al, "Percentage of Patients with Preventable Adverse Drug Reactions and Preventability of Adverse Drug Reactions – A Meta-analysis" (2012) 7(3) *PLoS ONE* e33236.

[4] P Ward-Smith, "Individual Variations in Drug Responses" (2010) 30(1) *Urologic Nursing* 22; D Wolbrette, "Antiarrhythmic Drugs: Age, Race, and Gender Effects" (2010) 2(3) *Cardiac Electrophysiology Clinics* 369.

[5] W Kalow, "Human Pharmacogenomics: The Development of a Science" (2004) 1(5) *Human Genomics* 375.

[6] Pharmacogenomics includes the study of variations in the whole genome that influence pharmacological function and response.

[7] PharmGKB, *Well-Known Pharmacogenomic Associations* <https://www.pharmgkb.org/search/knownPairs.action>.

In order for new pharmacogenomic knowledge to enhance the safe use of medicines, it must move beyond the laboratory and into clinical practice. Referred to as knowledge translation,[8] the process has traditionally relied on the assumption that clinicians would actively seek new knowledge and integrate it into their practice. In this model, the new knowledge unilaterally flows from the researchers to clinicians.[9] Evidence suggests that this assumption is flawed;[10] explaining why relatively few improved health outcomes based on pharmacogenomic knowledge have so far been demonstrated.[11]

Recognising that pharmacogenomic knowledge requires active efforts to facilitate translation into clinical practice, frameworks to support the process have been developed.[12] Building on the successful translation of new knowledge in other areas of medicine, Khoury et al describe an expanded continuum of translation research specific to genomic medicine.[13] With the aim of improving health at a population level, they classify different types of multidisciplinary research into one of four phases. These phases provide a framework that ultimately supports the production of evidence-based recommendations and guidelines that can be used in the clinical setting.[14] During the final phase of Khoury et al's framework, research identifies the benefits of genomics on "real-world health outcomes" to demonstrate the successful translation of new knowledge.[15]

What this framework does not make explicit is the relevance of the context in which the research takes place. Without the opportunity to identify the social and political factors, and the diverse influence they exert, gaps and barriers to translation cannot be addressed and may be allowed to persist.[16] Equally, it can also highlight the social and political factors that positively influence translational research, resulting in changes in clinical practice and improved health outcomes. It is in this context that the integration of the pharmacogenomic test associated with the antiretroviral medicine abacavir is situated.[17] Used in the treatment of human immunodeficiency virus (HIV), the test has become standard clinical practice prior to prescribing abacavir, and a noteworthy exception to the generally slow uptake of pharmacogenomics. Given that this has been described as an example of the successful translation of pharmacogenomics into clinical practice,[18] it provides a unique opportunity to illustrate the social and political factors that preceded, and promoted, the research required by Khoury et al to successfully translate new knowledge.

The article is structured as follows: it begins by describing the phases of Khoury et al's translational research framework, and providing examples of the types of pharmacogenomic research that could be included in each. As any translational research is predicated on a foundational scientific finding, the article then outlines the controversy associated with the discovery of the retrovirus responsible for causing HIV/AIDS. In the years following this discovery, the communities most

[8] E Oborn, M Barrett and G Racko, "Knowledge Translation in Healthcare: Incorporating Theories of Learning and Knowledge from the Management Literature" (2013) 27(4) *Journal of Health Organisation and Management* 412, 413.

[9] Oborn, Barrett and Racko, n 8, 415.

[10] Oborn, Barrett and Racko, n 8, 415.

[11] D Carr, A Alfirevic and M Pirmohamed, "Pharmacogenomics: Current State-of-the-Art" (2014) 5(2) *Genes* 430, 434.

[12] M Khoury et al, "The Continuum of Translation Research in Genomic Medicine: How Can We Accelerate the Appropriate Integration of Human Genome Discoveries into Healthcare and Disease Prevention" (2007) 9(10) *Genetics in Medicine* 665; W Burke and D Korngiebel, "Closing the Gap Between Knowledge and Clinical Application: Challenges for Genomic Translation" (2015) 11(2) *PLoS Genetics* e1004978.

[13] Khoury et al, n 12.

[14] Khoury et al, n 12, 666.

[15] Khoury et al, n 12, 671.

[16] V Ward, A House and S Hamer, "Developing a Framework for Transferring Knowledge into Action: A Thematic Analysis of the Literature" (2009) 14(3) *Journal of Health Services Research and Policy* 156, 157.

[17] Abacavir (trade name, Ziagen) is a nucleoside analogue reverse transcriptase inhibitor used as part of a combination antiretroviral regime for people with HIV/AIDS. It can be prescribed as either an oral tablet or solution.

[18] E Phillips and S Mallal, "Succesful Translation of Pharmacogenetics into the Clinic" (2009) 13(1) *Molecular Diagnosis and Therapy* 1.

affected by the virus organised to influence the societal response. The impact of this activism is outlined before describing the specific regulatory outcomes that eventuated. After highlighting the consequences of these changes, the article describes how the research that led to the test's successful integration into clinical practice aligns with the phases of translational research offered by Khoury et al. The article concludes by emphasising the impact of disparate social and political factors on the translation of new knowledge, and ultimately, the successful translation of this pharmacogenomic test into clinical practice.

A Framework to Support the Translation of New Knowledge

The principles of evidence-based medicine emerged during the 1980s as a response to the inconsistent practices resulting from consensus-based methods of medical decision-making.[19] Since that time, clinicians have increasingly relied on findings of rigorously conducted and reviewed research to develop evidence-based guidelines that inform treatment decisions.[20] This goal can only be achieved on the basis of sound research. Emphasising the importance of different types of research conducted at different times to provide this solid foundation, Khoury et al advance a framework describing the translational research process. The framework consists of four phases.

In relation to genomic medicine, research conducted in the first phase (T1) is designed to move a basic genome-based discovery into a candidate health application.[21] Pharmacogenomics research in this phase could therefore include identifying an allele responsible for variability in the metabolism of different medicines. Findings from this type of research also support the knowledge required to develop a potential screening test that could be used in the clinical setting. Acknowledging that the ability to identify a particular allele, and a test that screens for it, does not fundamentally change health outcomes, subsequent research will evaluate the integration of a test into clinical practice and contribute to the second phase (T2) of translational findings.[22]

As the next part of the translational research continuum, phase three (T3) research aims to disseminate knowledge about innovative evidence-based interventions effectively and encourage their widespread adoption.[23] In this phase, pharmacogenomics studies could, for example, evaluate the benefits of, and barriers to pharmacogenomic screening in the clinical setting. The fourth and final phase (T4) in Khoury et al's translation framework assesses the effect of evidence-based guidelines on population outcomes. Undertaking multicentre surveillance of adverse medicine reactions associated with pharmacogenomic screening would be included as T4 research. In addition to informing sound health policy,[24] T4 research demonstrating the benefit of genomic medicine infers that translation of new knowledge is complete.

The value of efficiently translating new knowledge into clinical practice is not, however, unique to genomic medicine generally, or pharmacogenomics specifically. As with translational research proposed for any area of medicine or public health, there must first be a basic scientific discovery.[25] In terms of pharmacogenomics, the discovery includes a particular genetic variation; in infectious diseases, it may be the discovery of a new infectious agent. As previously stated, abacavir is an antiretroviral developed for the treatment of HIV/AIDS. So even before considering the discovery of a genetic variation that may be relevant for HIV treatment, the discovery of the retrovirus responsible for causing HIV also constituted new knowledge that needed to be translated. Despite, or perhaps

[19] D Eddy, "Evidence-Based Medicine: A Unified Approach" (2005) 24(1) *Health Affairs* 9, 12.

[20] Eddy, n 19, 13.

[21] Khoury et al, n 12, 667.

[22] S Grosse and M Khoury, "What is the Clinical Utility of Genetic Testing?" (2006) 8(7) *Genetics in Medicine* 448, 449. Grosse and Khoury acknowledge that outcomes other than those associated with health may also have value and could be considered as an evaluative measure. For example, the benefit of having information available, even if not relied upon to change clinical treatment, or the cost-effectiveness of a test.

[23] Khoury et al, n 12, 670.

[24] Khoury et al, n 12, 671.

[25] Khoury et al, n 12, 666.

because of the urgent need to find a cause of HIV, the controversy associated with the discovery illustrates that translating even foundational scientific discoveries can be tortuous.

DISCOVERING HIV

The disease that was to become known as HIV was first identified by the United States Center for Disease Control and Prevention in 1981, following reports of five cases of *Pneumocystis carinii* pneumonia[26] in homosexual men living in Los Angeles.[27] Additional cases of other life-threatening opportunistic infections, and a rare malignancy known as *Kaposi Sarcoma*, were reported shortly after.[28] The serious nature of the disease meant that determining the cause was imperative if any form of effective treatment was to be developed and instituted.

During the 1970s, researchers believed that viruses, particularly retroviruses, could cause some cancers. In both France and the United States, researchers were actively engaged in finding these retroviruses.[29] A decade later when young, previously healthy, homosexual men began presenting with symptoms of viral infection suggestive of a new infectious agent, the same groups of researchers thought that a retrovirus could be responsible, and sought to isolate it.[30]

In 1983, the French researchers succeeded in identifying a previously unknown retrovirus, a lentivirus[31] which they named lymphadenopathy-associated virus (LAV).[32] Demonstrating that LAV killed CD4+ T-cells, they believed that they had discovered the agent responsible for causing AIDS.[33] These findings were presented at a scientific meeting in September 1983. However, the concept of a new family of retroviruses was controversial, and the findings were received with much scepticism.[34]

In contrast to the French experience, the United States researchers were (initially) successful at convincing the scientific community that a retrovirus they had identified was the cause of AIDS.[35] Using cell culture samples supplied by the French group, the United States researchers were able to grow CD4+ T-cells and reveal that they contained two distinct viral forms. One was a retrovirus they had previously identified as the human T-cell leukaemia virus (HTLV); the other they assumed was an aberrant form of this virus, and responsible for the infection leading to AIDS.[36] Believing that they had isolated the causative agent, the United States researchers published four scientific papers in quick succession.[37] Successful peer review and publication facilitated public acceptance of this "new"

[26] J Stringer et al, "A New Name for Pneumocystis from Humans and New Perspectives on the Host-Pathogen Relationship" (2002) 8(9) *Emerging Infectious Diseases* 891, 891. *Pneumocystis carinii* pneumonia was renamed *Pneumocystis jiroveci* in 1999 after DNA analysis demonstrated that *Pneumocystis* organisms differ between host organisms.

[27] M Gottlieb et al, "Pneumocystis Pneumonia – Los Angeles" (1981) 30(21) *Morbidity and Mortality Weekly Report* 250.

[28] AE Friedman-Kien et al, "Kaposis Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California" (1981) 30(25) *Morbidity and Mortality Weekly Report* 305.

[29] L Montagnier, "A History of HIV Discovery" (2002) 298(5599) *Science* 1727; R Gallo, "The Early Years of HIV/AIDS" (2002) 298(5599) *Science* 1728.

[30] Montagnier, n 29, 1727.

[31] A Karpas, "Human Retroviruses in Leukaemia and AIDS: Reflections on their Discovery, Biology and Epidemiology" (2004) 79(4) *Biological Reviews* 911, 919. Lentiviruses are any one of a family of non-oncogenic retroviruses that can infect both dividing and non-dividing cells and produce diseases with long incubation periods.

[32] F Barré-Sinoussi et al, "Isolation of a T-lymphotropic Retrovirus From a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)" (1983) 220(4599) *Science* 868.

[33] Montagnier, n 29, 1728.

[34] L Montagnier, "25 Years after HIV Discovery: Prospects for Cure and Vaccine" (2010) 397(2) *Virology* 248, 250.

[35] M Popovic et al, "Detection, Isolation, and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS" (1984) 224(4648) *Science* 497

[36] Gallo, n 29, 1729.

[37] Popovic, n 35; R Gallo et al, "Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS" (1984) 224(4648) *Science* 500; M Sarngadharan et al, "Antibodies Reactive with Human

knowledge.[38] A widely broadcast announcement made by the United States Secretary of the Department of Human Services reinforced that the United States researchers were the discoverers of the virus that caused AIDS.[39] Naming the virus HTLV-III, it was also proclaimed that a commercial test to detect the virus would soon be available. When it later became apparent that the aberrant HTLV was the same virus that the French team had previously identified, and that it was present in the cells sent to the United States by the French researchers,[40] an international controversy erupted.[41]

The dissension about which team was the first to discover the virus culminated in an international dispute when in 1985, patents were to be issued for the blood test that would identify the virus.[42] As a highly profitable undertaking, the French researchers believed they were the first to discover the causative agent, and were entitled to the significant revenues that would flow from use of the test.[43] The magnitude of the dispute was reflected in the fact that the resolution involved significant political intervention.[44] It was eventually decided that the two research groups were "co-discoverers" of the virus and that patent royalties would be equally divided.[45]

More than 30 years later, the knowledge that HIV/AIDS is caused by a readily identifiable retrovirus is widely accepted.[46] The process of knowledge translation, which involved publications in peer reviewed journals, conference presentations, public announcements, and ultimately political "resolution" of the French/United States conflict, has been described as "a disorderly history of contingency, controversy, and uncertainty".[47] In this context, the fact that the new causative retrovirus was isolated and identified within three years is remarkable, as it is not unusual for new scientific knowledge to take a decade or longer to translate into clinical practice.[48] The comparatively short translation time, however, was little consolation for the increasing number of people who were developing HIV and dying from AIDS in the interim.[49] It also meant that during this time, clinicians charged with assessing and treating people who were presenting with life-threatening symptoms, had little understanding of the virus responsible, much less an effective treatment.

T-lymphotropic Retroviruses (HTLV-III) in the Serum of Patients with AIDS" (1984) 224(4648) *Science* 506; J Schüpbach et al, "Serological Analysis of a Subgroup of Human T-lymphotropic Retroviruses (HTLV-III) Associated with AIDS" (1984) 224(4648) *Science* 503.

[38] M Fagan, "Collective Scientific Knowledge" (2012) 7(12) *Philosophy Compass* 821, 823.

[39] D Rogowska-Szadkowska, "2008 Nobel Prize for Medicine or Physiology for Discovery of HPV and HIV Viruses – Short History of Discovery of HIV" (2008) 7(4) *HIV & AIDS Review* 5, 6.

[40] Karpas, n 31, 911.

[41] U Ranga, "The Saga of the HIV Controversy" (2009) 14(5) *Resonance* 472, 491.

[42] H Singer, "Institut Pasteur v United States: The AIDS Patent Dispute, the Contract Disputes Act and the International Exchange of Scientific Data" (1989) 15 *American Journal of Law & Medicine* 439, 440.

[43] Singer, n 42, 440.

[44] Singer, n 42, 439. Unsuccessful attempts to settle the dispute over the patent application for an AIDS blood test kit were held in the United States courts. Shortly after, President Reagan and Prime Minister Chirac announced an agreement where the United States and French researchers were to share credit for having discovered the AIDS virus and both parties would share patent rights.

[45] J Cohen and M Enserink, "HIV, HPV Researchers Honored, but One Scientist Is Left Out" (2008) 322(5899) *Science* 174.

[46] There is a persistent group of academics who question whether AIDS is caused by HIV. See, eg P Duesberg (ed), *AIDS: Virus- or Drug Induced?* (Springer Science & Business Media, 2012).

[47] S Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge* (University of California Press, 1996) 28.

[48] Z Slote Morris, S Wooding and J Grant, "The Answer is 17 Years, What is the Question? Understanding Time Lags in Translational Research" (2011) 104(12) *Journal of the Royal Society of Medicine* 510, 510; Oborn, Barrett and Racko, n 8, 413.

[49] Centers for Disease Control, *Weekly Surveillance Report*, 31 December 1984. At the end of 1984 there had been 7,699 AIDS cases and 3,665 AIDS deaths in the United States, and 762 cases had been reported in Europe: <http://www.cdc.gov/hiv/pdf/statistics_surveillance84.pdf>.

One consequence of this knowledge gap was that many different "theories" about the cause of AIDS began to surface. For example, faced with a disease "uniquely"[50] affecting homosexual men, the cluster of symptoms was initially referred as "Gay Related Immune Deficiency" (GRID).[51] On this basis, Epstein observes that epidemiologists and clinicians fastened upon the most sensational markers of homosexual difference to pejoratively medicalise the lifestyles of those affected.[52] Other groups vulnerable to HIV infection, such as intravenous drug users, were similarly unpopular and shunned by the political mainstream.[53] Despite the fact that there were reports of women and people who had not had any homosexual contact presenting with symptoms of HIV, moral disapprobation toward the more visible groups resulted in a societal response perceived as unconscionably slow.[54] A direct response to the inaction of organisations and institutions charged with driving research that would lead to effective treatments, was the formation of activist organisations to support the unique and disparate needs of the community affected by HIV/AIDS.[55]

The expectation that the scientific research community would ardently seek to develop treatments for this new disease reflects a traditional "knowledge driven model" of knowledge translation that is common in the natural sciences.[56] In this model, new knowledge is anticipated to flow in a unidirectional linear fashion. The fact that it is typically anchored in asymmetrical power relations between theoretical and applied researchers means the process is exceedingly slow and inefficient.[57] Efforts of AIDS activists, who were most invested with efficiently translating any new knowledge about the new virus, sought to circumvent traditional processes and rebalance these entrenched power relations. To achieve this, a suite of strategies that influenced every aspect of the translational process were employed.

ACTIVISM AND HIV/AIDS

In 1981, a small group of men concerned about the new disease affecting their friends, established an information hotline and referral service.[58] From relatively modest beginnings, Gay Men's Health Crisis (GMHC) quickly expanded to providing psychosocial support and advocacy for thousands of people affected by, and living with, AIDS.[59] While this type of support was welcomed, it was apparent that access to medicines that would slow or halt the spread of the virus was imperative if the ever-increasing deaths were to be avoided. To this end, foundational members of the GMHC began to form activist groups with more practically directed goals.

Aware that some potentially promising medicines marketed in other jurisdictions had yet to receive marketing approval in the United States, one group of AIDS activists sought to establish other

[50] Epstein, n 47, 47. GRID was in fact not restricted to gay men. According to the Center for Disease Control's task force on the syndrome, 8% of the 159 cases were among heterosexuals, one of whom was a woman. See also H Masur et al, "An Outbreak of Community-acquired Pneumocystis Carinii Pneumonia" (1981) 305(24) *New England Journal of Medicine* 1431.

[51] JH Fujimura and DY Chou, "Dissent in Science: Styles of Scientific Practice and the Controversy Over the Cause of AIDS" (1994) 38(8) *Social Science & Medicine* 1017, 1030.

[52] Epstein, n 47, 49. Epstein notes that cases of men with histories of thousands of sexual partners were highlighted, while those of monogamous men were mostly ignored.

[53] MD Greenberg, "AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process" (1999) 3 *New York University Journal of Legislation & Public Policy* 295, 310.

[54] Greenberg, n 53, 309.

[55] D Hodel, *At the Crossroads: A Study of Federal HIV/AIDS Advocacy* (Funders Concerned About AIDS, 2004) [12] <http://www.fcaaids.org/Portals/0/Uploads/Documents/Public/HIV_entire_book.pdf>. In this 2004 study, more than 18 policy advocacy groups were identified.

[56] Oborn, Barrett and Racko, n 8, 415.

[57] Oborn, Barrett and Racko, n 8, 415.

[58] M Oberlink, "The Gay Men's Health Crisis: Working on the Front Line" (1988) 2(5) *AIDS Patient Care* 19, 19.

[59] Oberlink, n 58. Oberlink reports that GMHC would receive more than 5,000 calls each month.

ways of accessing the medicines that they hoped would slow the progression of the disease.[60] In 1987, the New York-based "People With AIDS Health Group" (PWA Health Group) formed the first buyers' club. The sole purpose of the Group was to import unapproved medicines into the United States and make them available to those with HIV. The group began to import and provide medicines such as AL721, which was derived from eggs and, based on some preliminary studies, believed to have some effect against HIV.[61] Substances from Japan[62] and the United Kingdom[63] were also sourced and supplied, deliberately avoiding the usual regulatory requirements.

The actions of the PWA Health Group were unique in that they entirely circumvented traditional processes involved in the translation of new knowledge. Not only did the knowledge not flow from researchers to clinicians, the PWA Health Group did not rely on the outcomes of approved clinical trials, or published literature supporting the use of a particular medicine. Instead, they relied on alternative and unconventional sources, and made their own treatment decisions on this basis. Ultimately, the medicines that were sourced were found to have had limited effect.[64] Yet, the PWA Health Group was responsible for developing an alternative, unorthodox knowledge translation model that met the needs of a select group of people with AIDS at a time when few accessible options existed.

For those unable to access the "underground", effective HIV/AIDS therapies remained elusive. As the development of, approval and access to medicines to impede the rapid replication of the virus was imperative, any regulatory process perceived as obstructive became the object of fervent criticism. In the United States, the agency responsible for approving safe and efficacious medicines for marketing is the Food and Drug Administration (FDA), and it was this organisation that became the target of resolute political activism.

"AIDS Coalition to Unleash Power" (ACT UP) soon emerged as a provocative activist group, committed to achieving political and regulatory reform through confrontational tactics.[65] ACT UP's fundamental contention was that, with a new epidemic disease such as AIDS, lengthy testing through multiple phases of clinical trials of experimental medicines resulted in long delays in their marketing approval and caused unnecessary deaths.[66] Consequently, ACT UP sought to ensure that people infected with HIV/AIDS would receive timely access to antiretroviral therapy by softening government regulatory policy on approvals. While the motivation for ACT UP's confrontational action was benevolent, it failed to acknowledge the central tension in relation to clinical trials for experimental AIDS medicines. Traditionally, the purpose of clinical trials was to demonstrate evidence of a potential new medicine's safety and efficacy. Investigators therefore perceived trials for experimental AIDS therapies as research designed to provide generalisable knowledge that may help others. Conversely, in the setting of debilitating disease that, with no viable treatment option would lead to death, most individuals suffering with AIDS saw the trials as forms of therapy designed to

[60] L Terrizzi, "The Need for Improved Access to Experimental Drug Therapy: AIDS Activists and Their Call for a Parallel Track Policy" (1991) 4(3) *Administrative Law Journal* 589, 610.

[61] P Reichertz and M Friend, "Hiding Behind Agency Discretion: The Food and Drug Administration's Personal Use Drug Importation Policy" (2000) 9 *Cornell Journal of Law & Public Policy* 493, 500.

[62] Reichertz and Friend, n 61, 500. Dextran sulphate was approved in Japan to treat high cholesterol, and displayed potential for combating the AIDS virus.

[63] J-M Andriote, *Victory Deferred: How AIDS Changed Gay Life in America* (University of Chicago Press, 1999) 177. Fluconazole and aerosol pentamidine used to treat pneumocystis pneumonia were imported from England.

[64] Andriote, n 63, 177.

[65] Greenberg, n 53, 312; Epstein, n 47, 221.

[66] D Crimp, "Before Occupy: How AIDS Activists Seized Control of the FDA in 1988", *The Atlantic*, 6 December 2011 <http://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302>.

benefit them.[67] It was on this basis that AIDS activists strongly agitated for accelerated access to medicines, despite the fact that their safety and efficacy may not have been demonstrated to the standards traditionally required.[68]

Accelerating the approval of new medicines, however, could only occur if new medicines were being developed. Recognising that this would require the successful completion of clinical trials, activists turned their attention to the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. The AIDS Clinical Trials Group was the government entity responsible for administering publically funded clinical trials of AIDS treatments.[69] In contrast to the confrontational tactics directed toward the FDA, these activists sought to work collaboratively with biomedical scientists and researchers to achieve their goal. For example, the New York chapter of ACT UP developed a "National AIDS Treatment Research Agenda" that they presented at the 5th International Conference on AIDS.[70] Included in this agenda was the principle that, in contrast to current practices, the use of placebos in any clinical trial should be avoided.[71] At the time this was considered extreme, but acknowledging the mutual interdependency of researchers and people affected by HIV/AIDS, it was given due consideration by AIDS treatment researchers.[72] By 1992, activists focused on the development of new treatments had developed expert knowledge on the stages of viral replication, the pathogenesis of HIV, the methodology of randomised clinical trials, and were working collaboratively with researchers to determine the most productive research directions.[73]

In the decade following the discovery of HIV as the cause of AIDS, the multifaceted efforts of AIDS activists effectively influenced the way that research around the disease was conducted. They also influenced the development of, and ultimately access to, new medicines. An integral element of this achievement was the ability to successfully challenge traditional models of knowledge translation. This allowed people, other than the scientific community which typically orchestrated its translation, to engage authoritatively and influence the translation with potentially life-saving results. In this context, however, the tension between access to new medicines that may or may not be beneficial, and the overarching need to ensure their safety remained the ultimate responsibility of government regulators. This meant that a degree of caution was still required.

Regulatory Reform Improving Access to Medicines

History has shown that regulatory oversight of medicines has increased incrementally in response to concerns about their safety.[74] The inherent teratogenic effects of the anti-nausea drug thalidomide is the most notable example, and resulted in regulatory bodies requiring manufacturers to demonstrate the safety and efficacy of any new drug prior to marketing approval.[75] Although the ground swell of AIDS activism may have been perceived as initiating regulatory reform, the United States administration had been aware of, and begun taking steps to address the criticism aimed at FDA

[67] G Annas, "Faith (Healing), Hope and Charity at the FDA: The Politics of AIDS Drug Trials" (1989) 34 *Villanova Law Review* 771, 773.

[68] Terrizzi, n 60, 600.

[69] S Epstein, "The Construction of Lay Expertise: AIDS Activism and the Forging of Credibility in the Reform of Clinical Trials" (1995) 20(4) *Science, Technology and Human Values* 408, 416.

[70] D Byar et al, "Design Considerations for AIDS Trials" (1990) 323(19) *New England Journal of Medicine* 1343, 1343.

[71] ACT UP, *A National AIDS Treatment Research Agenda: V International Conference on AIDS* (1989) [3] <http://joeclark.org/dossiers/actup/agenda/agenda-edited.pdf>. On the basis that placebo trials in AIDS are a "medically sanctioned form of Russian roulette".

[72] Byar, n 70, 1343.

[73] Epstein, n 69, 416; M Harrington, "From HIV to Tuberculosis and Back Again: A Tale of Activism in 2 Pandemics" (2010) 50(Supp 3) *Clinical Infectious Diseases* S260, 262.

[74] J Abraham, "Sociology of Pharmaceuticals Development and Regulation: A Realist Empirical Research Programme" (2008) 30(6) *Sociology of Health & Illness* 869, 872.

[75] J Greene and S Podolsky, "Reform, Regulation, and Pharmaceuticals-The Kefauver-Harris Amendments at 50" (2012) 367(16) *New England Journal of Medicine* 1481, 1481.

processes that impeded marketing of new pharmaceuticals prior to the AIDS epidemic.[76] Together these societal and political influences resulted in a series of regulatory changes directed at ensuring people with HIV would have access to safe antiretroviral medicine in a timely manner. The first incremental regulatory change resulted in applications for marketing approval of new medicines being addressed more efficiently by the FDA.[77] Shortly after, this was extended to specifically address investigational new drug applications (INDs). Restructured processes were designed to assist sponsors to prepare and submit high-quality applications, thus permitting the FDA to review them efficiently and reduce delay.[78]

Having streamlined the processes involved in attaining market authorisation, procedures to make medicines available to seriously ill patients as early in the development process as possible were subsequently advanced. Known as treatment investigational new drugs (Treatment INDs),[79] the new procedures permitted access to medicines still in the clinical investigation phase to people with immediately life-threatening or other serious diseases for which no satisfactory alternative therapies existed.[80] A mandated requirement in this process was the early and continued consultation between the FDA and sponsors that, it was anticipated, would accelerate the ordinary clinical trial process.[81] Despite their stated aim, critics asserted that the process was implemented inconsistently.[82] When combined with the necessity of an immediately life-threatening condition that in many circumstances limited rather than expanded access to experimental treatments,[83] the program did not translate into significantly improved access to experimental drugs for people infected with HIV.[84] Consequently, the Treatment IND program was largely discredited, providing the impetus for further activism-led reform.[85]

Almost a decade after HIV was identified as the virus responsible for causing AIDS, the only FDA method of experimental medicine distribution exclusively targeted at AIDS and HIV-related conditions was introduced.[86] Known as a "parallel track" mechanism, this policy permitted a sponsor to develop a "parallel" protocol for expanded access to antiretroviral medicine in collaboration with special interest groups. Under a parallel track, medicines could be distributed at the inception of phase

[76] C Davis and J Abraham, "Desperately Seeking Cancer Drugs: Explaining the Emergence and Outcomes of Accelerated Pharmaceutical Regulation" (2011) 33(5) *Sociology of Health & Illness* 731, 736. Davis and Abraham report that in 1981 President Reagan enounced a commitment to radical deregulatory agendas. As part of this process, Congress convened a Commission on the Federal Drug Approval Process to address regulatory overkill at the FDA. In 1982, the Commission recommended reforms designed to promote more rapid approval of new drugs, which were subsequently endorsed by the National Academy of Sciences on the grounds that such reforms would boost market innovation. See also *New Drug Regulations; Public Meeting*, 44 Fed Reg 58919 (October 1979).

[77] *New Drug and Antibiotic Regulations*; (October 1982), which sought to amend 21 CFR § 310, 312, 314, 430, 431 and 433.

[78] *New Drug and Antibiotic Regulations; Proposed Rule*, 47 Fed Reg 46 622.

[79] Terrizzi, n 60, 601. Prior to the introduction of Treatment INDs, it was possible for some people to access experimental medications on a "compassionate basis". Terrizzi describes two significant problems with the compassionate use program that provided the impetus for development of Treatment INDs.

[80] Terrizzi, n 60; W Appler, "The FDA's Treatment IND Rule – A Glimpse Into the Future of Drug Regulation in the US?" (1988) 43(4) *Food, Drug, Cosmetic Law Journal* 649, 651. Appler notes that the Treatment IND rule is not unique or original; the FDA had been informally allowing treatment use of non-approved drugs for many years. Azidothymidine (AZT) was in fact authorised for treatment use in 1986, seven months before its new drug application was approved, and coincidentally, seven months before the Treatment IND rule was re-proposed in March 1987.

[81] *Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illness*, 53 Fed Reg 41516 (October 1988).

[82] Terrizzi, n 60, 609.

[83] Greenberg, n 53, 321. Greenberg describes the example of trimetrexate, which was limited to patients who had had an adverse reaction to conventional treatments, yet was denied to those who merely failed to respond positively to conventional treatment.

[84] Terrizzi, n 60, 609.

[85] B Rossen, "FDA's Proposed Regulations to Expand Access to Investigational Drugs for Treatment Use: The Status Quo in the Guise of Reform" (2009) 64(1) *Food & Drug Law Journal* 183; Terrizzi, n 60, 601.

[86] *Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People Infected with AIDS and Other HIV Related Disease*, 57 Fed Reg 13250 (April 1992).

two of the clinical testing process and would not require the same level of evidence for effectiveness as generally required for a Treatment IND, reducing the initial burden on sponsors conducting the trials further.[87]

The "parallel track" policy also failed to provide the panacea for access to effective HIV medicines, but the momentum and motivation for regulatory change inspired by the ongoing efforts of AIDS activists continued.[88] A notable outcome occurred in 1992 when the FDA initiated an accelerated approval pathway to marketing approval.[89] In a significant change from traditional approval requirements, it would now be possible for new medicines to be assessed on the basis of surrogate end-points that were seen as reasonably likely to predict clinical benefits, rather than end-points such as the development of an opportunistic infection or death.[90] The change would permit phase III clinical trials to be completed more quickly, and subsequently expedite marketing approval.[91] Initially, a rise in CD4+ T-cell count was suggested as an appropriate surrogate. This was subsequently replaced by decreases in plasma HIV-1 RNA levels that were assessed as being more closely aligned with improved clinical outcomes.[92] In order to legitimise the selection of the surrogate end-point, medicines authorised for marketing after "accelerated approval" would still be required to demonstrate the traditional safety and efficacy requirements through post-marketing surveillance.[93] Of the regulatory changes designed to ensure that people infected with HIV would have timely access to safe and effective medicines, the change to the conduct of clinical trials and accelerated approval was one of the most effective.[94]

Continued efforts of AIDS activists were instrumental in directing and accelerating the pace of research and consequently access to treatments that would effectively stem the progress of the lethal disease.[95] Successfully achieving a series of incremental regulatory changes ensured that access to these treatments would not unnecessarily be delayed. In 1998, it was within this new regulatory context that the new antiretroviral medicine, abacavir, sought marketing approval.[96]

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[87] US Food and Drug Administration, *Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS* <http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm134331.htm>. Interestingly, the FDA reports that only one drug was ever submitted for consideration under the parallel track policy. The protocol for stavudine (d4T) was allowed to proceed on 5 October 1992. Approximately 12,000 patients received stavudine through the parallel track mechanism. An accelerated new drug application for stavudine was approved on 17 June 1994. The application received full marketing approval on 21 December 1995. While the parallel track policy is still technically available, it has not been used since stavudine was approved in 1994. Treatment INDs have proven to be a more practical mechanism to provide treatment access.

[88] J Eigo, "Expedited Drug Approval Procedures; Perspectives from an AIDS Activisit" (1990) 45(4) *Food, Drug, Cosmetic Law Journal* 377, 381.

[89] 21 CFR § 314.H (2009).

[90] L Naeger et al, "Running a Tightrope: Regulatory Challenges in the Development of Antiretrovirals" (2010) 85(1) *Antiviral Research* 232, 234. Naeger et al report that in the clinical trials conducted to determine the safety and efficacy of AZT, marketing approval was delayed while researchers waited for clinical end-points to be reached.

[91] Naeger et al, n 90, 234.

[92] S Shulman and J Brown, "The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked" (1995) 50 *Food & Drug Law Journal* 503; Naeger et al, n 90, 234. When first introduced, CD4+ T-cell counts were relied upon as surrogate end-points. However, this was changed when it appeared that this biomarker was a weaker predictor of clinical outcomes than originally anticipated.

[93] Davis and Abraham, n 76, 732.

[94] J Darrow et al, "Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs" (2015) 372(3) *New England Journal of Medicine* 279; Shulman and Brown, n 92.

[95] J Killen, M Harrington and A Fauci, "MSM, AIDS Research Activism, and HAART" (2012) 380(9839) *Lancet* 314; Darrow et al, n 94. Not all commentators agree that it was solely the influence of activists that were responsible for these changes. See, eg, Davis and Abraham, n 76, 879 who contend that the changes should be regarded primarily as part of a deregulatory regime driven by the interests of the pharmaceutical industry in partnership with all major aspects of the state.

[96] Letter from US Food and Drug Administration to Martha Moore, Glaxo Wellcome Inc, 17 December 1998, regarding the approval of the drug applications NDA 20-997 and NDA 20-978 for Ziagen (abacavir sulphate) <http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20-977_ZIAGEN_APPROV.PDF>. The drug applications were submitted on 24 June 1998.

The then pharmaceutical company Burroughs Wellcome received marketing approval for the first antiretroviral medicine, azidothymidine (AZT), in 1987.[97] Seven years later, the company merged with Glaxo to form GlaxoWellcome. During the interceding years, the company had significant experience navigating the regulatory mechanisms designed to provide early access to its medicines.[98] Consequently, less than three years after submitting the new drug application, approval was granted for abacavir.[99] The original accelerated approval was based on safety data that was obtained from more than 578 trial participants.[100] The traditional approval required substantially more clinical trial data.[101] The remaining clinical trial data would be collected when abacavir was prescribed as part of an expanded access program. This program was instituted across 68 sites in the United States, 11 in Canada and 58 in Europe and Australia, ultimately enrolling more than 11,000 patients.[102]

ABACAVIR AND HYPERSENSITIVITY

The beginning of the new millennium brought with it the much anticipated announcement that an international consortium had successfully mapped the human genome,[103] and in so doing, provided the foundational scientific knowledge for pharmacogenomic research.[104] Around the same time, and during the course of the clinical trials conducted as part of the expanded access program, it became apparent that 4-5% of patients experienced signs of an adverse reaction to abacavir. The symptoms most commonly reported were fever, rash, diarrhoea, nausea with vomiting, and headache.[105] In most cases, these symptoms resolved quickly once abacavir was ceased.[106] At a meeting of the FDA Antiviral Drugs Advisory Committee where this information was presented, it was proposed that the cluster of symptoms suggested a hypersensitivity reaction (HSR).[107] Responding to questions about the safety of abacavir in light of the potential for this reaction, GlaxoWellcome affirmed that it would continue to collect and analyse data on abacavir hypersensitivity.[108] As it would be impossible for treating doctors to predict the likelihood of a hypersensitivity to abacavir, the importance of prompt recognition and discontinuation once identified was paramount.[109]

In contrast to the social and political influences responsible for translating new knowledge around HIV/AIDS and access to medicines, the recognition of the potential for HSR in response to abacavir, and identification of the responsible allele, is more closely aligned with the translational research framework advanced by Khoury et al. However, rather than initiating T1 research after the discovery of a genomic variation, and seeking to develop an appropriate clinical application, in this case, the

[97] K Kaitin, "Case Studies of Expedited Review: AZT and L-dopa" (1991) 19(3-4) *Journal of Law, Medicine & Ethics* 242, 242.

[98] D Barry, "A Perspective on Compassionate Parallel Category C Treatment Track IND Procedures" (1990) 45 *Food, Drug, Cosmetic Law Journal* 347, 353.

[99] US Food and Drug Administration, "Ziagen", *Drugs@FDA* <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>. Original approval 17 December 1998.

[100] Antiviral Drugs Advisory Committee, Transcript of Meeting, 2 November 1998, 43 <http://www.fda.gov/ohrms/dockets/ac/cder98t.htm#>. Dr Smiley, Vice President HIV/OI Clinical Development Glaxo Wellcome, presented data in support of the pharmaceutical company's application for accelerated approval.

[101] H Kessler et al, "Abacavir Expanded Access Program for Adult Patients Infected with Human Immunodeficiency Virus Type 1" (2002) 34(4) *Clinical Infectious Diseases* 535, 536.

[102] Kessler et al, n 101.

[103] National Human Genome Research Institute, *International Consortium Completes Human Genome Project* (April 2003) <https://www.genome.gov/11006929>.

[104] G Emilien et al, "Impact of Genomics on Drug Discovery and Clinical Medicine" (2000) 93(7) *Quarterly Journal of Medicine* 391.

[105] Kessler et al, n 101, 537.

[106] Kessler et al, n 101, 537.

[107] Antiviral Drugs Advisory Committee, n 100, 51-58. Dr Seth Hetherington, Senior Clinical Research Physician, presented information about abacavir hypersensitivity to the Committee.

[108] Antiviral Drugs Advisory Committee, n 100, 194.

[109] Antiviral Drugs Advisory Committee, n 100, 194.

clinical application was readily apparent; a need to avoid the HSR. The recent regulatory changes that supported expanded access to newly developed medicines had highlighted this. Research to identify the allele responsible was therefore required.

Conditions imposed by the FDA on the accelerated approval of abacavir were prescriptive and specific, including the ongoing commitment from the manufacturer to evaluate abacavir HSR and undertake the study of the biologic mechanism/immunological basis of the reaction.[110] Indicative of the explicit attempts of the FDA to balance early and easy access to a new antiretroviral medicine with ongoing efforts to ensure public safety, these conditions also influenced the dissemination of knowledge about abacavir HSR. The understanding that abacavir HSR was an "idiosyncratic reaction and a distinct clinical syndrome" characterised by systemic involvement[111] was disseminated widely to treating clinicians; and further, that the appearance of clinical symptoms consistent with this "syndrome" mandated immediate discontinuation of abacavir treatment.[112]

In 2001, the 1st International AIDS Society Conference on HIV Pathogenesis and Treatment was convened. At the conference, representatives from GlaxoWellcome presented their risk factor analysis for hypersensitivity reactions to abacavir. Analysing data from 25 clinical trials, researchers concluded that prior therapy and African ethnicity were associated with a reduced risk of HSR.[113] These preliminary findings suggested that there might be a genetic component involved in the development of the reaction. At the same conference, findings from a study that involved genotyping a group of homosexual men in Western Australia who had been recruited for a prospective longitudinal study of immune function were presented.[114] A short time later, using the same cohort of research participants, the Western Australian research group actively sought to identify an allele responsible for the HSR reaction.[115] In 2002, this group published its finding that the majority of people exhibiting the reaction carried the HLA-B*5701 allele.[116] The GlaxoWellcome research team replicated these findings in a retrospective clinical study and published the results in the same journal three weeks later.[117] Having made these initial findings, additional studies to determine whether the results could be extended to more diverse populations were conducted.[118]

As a precursor to T1 research, Khoury et al suggest that the discovery of a genetic variation with clinical applicability is required.[119] However, at the time when HSR to abacavir was identified, methods of identifying human leukocyte antigen (HLA) variants were still being developed. This meant that rather than T1 research following a basic scientific discovery, both types were being conducted concurrently.[120] In the interim, to assist identifying those at risk of developing HSR prior to

[110] Letter from US Food and Drug Administration, n 96.

[111] S Hetherington et al, "Hypersensitivity Reactions During Therapy with the Nucleoside Reverse Transcriptase Inhibitor Abacavir" (2001) 23(10) *Clinical Therapeutics* 1603, 1604.

[112] Hetherington et al, n 111, 1604.

[113] S Hetherington et al, *Risk Factor Analysis of Hypersensitivity Reactions to Abacavir: Retrospective Analysis of 25 Clinical Trials* (Poster Presentation, 1st International AIDS Society Conference on HIV Pathogenesis and Treatment, Buenos Aires, 2001) Abstract 527.

[114] G Stewart et al, *Determination of the Influence of Chemokine/Chemokine Receptor Genetic Variation on HIV Disease Progression in a Well-defined Cohort of HIV-1 Seroconverters* (Poster Presentation: 1st International AIDS Society Conference on HIV Pathogenesis and Treatment, Buenos Aires, 2001) Abstract 627.

[115] S Mallal et al, "Association between Presence of HLA-B5701, HLA-DR7, and HLA-DQ3 and Hypersensitivity to HIV-1 Reverse-Transcriptase Inhibitor Abacavir" (2002) 359(9308) *Lancet* 727.

[116] Mallal et al, n 115.

[117] S Hetherington et al, "Genetic Variations in HLA-B Region and Hypersensitivity Reactions to Abacavir" (2002) 359(9312) *Lancet* 1121.

[118] A Hughes et al, "Association of Genetic Variations in HLA-B Region with Hypersensitivity to Abacavir in Some, But Not All, Populations" (2004) 5(2) *Pharmacogenomics* 203.

[119] Khoury et al, n 12, 667.

[120] AR Hughes et al, "Pharmacogenetics of Hypersensitivity to Abacavir: From PGx Hypothesis to Confirmation to Clinical Utility" (2008) 8(6) *Pharmacogenomics Journal* 365, 367.

commencing abacavir, researchers developed a skin patch test that would produce a localised visible skin reaction that mimicked the systemic reaction.[121] While the skin patch test could confirm immunologically mediated abacavir hypersensitivity, the procedure had not been validated for routine clinical use and was used only as a research tool.[122] In lieu of an accurate and efficient method of identifying the responsible allele, skin patch testing represented T1 research that would later support the clinical validity HLA-B*5701 testing.

Over the course of the next couple of years, laboratory tests that could accurately detect the presence of HLA-B*5701 allele were developed[123] and allele screening commenced in a series of single-site studies.[124] Subsequently, the deliberate avoidance of abacavir in adults carrying the HLA-B*5701 allele resulted in a significant reduction in the incidence of HSR.[125] Although several T1 and T2 studies demonstrated the clinical utility of HLA-B*5701 screening, its implementation into clinical practice could not be guaranteed without confidence in reported laboratory results and widespread acceptance by clinicians. Recognising the importance of analytical validity, studies demonstrated that among four international laboratories, analytic specificity of detecting the HLA-B*5701 allele was greater than 99%.[126] A similar result was found in European laboratories.[127] These findings suggested that clinicians could be confident that results from testing laboratories would accurately predict the potential for HSR prior to prescribing abacavir.

While the methodologies employed in these studies were able to confirm the clinical utility of HLA-B*5701 allele screening, randomised controlled trials are considered to provide the highest level of evidence.[128] To this end, the Prospective Randomised Evaluation of DNA Screening in a Clinical Trial (known as PREDCIT-1) was designed to test the hypothesis that prospective pharmacogenomic screening for the HLA-B*5701 allele, and the exclusion of those patients carrying the allele from abacavir treatment, reduces the incidence of hypersensitivity reaction as compared with that in an unscreened population.[129] The PREDICT-1 Study Team enrolled nearly 2,000 HIV patients from 19 countries. The study demonstrated that screening for the HLB-B*5701 allele could completely eliminate immunologically confirmed HSRs. Representing the culmination of T2 translational research, the results that confirmed the efficacy of this pharmacogenomic screening test were published in the *New England Journal of Medicine* in 2008.[130]

Translation into Clinical Practice

Having identified the allele responsible for initiating the HSR to abacavir, and a clinically valid test, screening to eliminate the risk of it developing was incorporated into many of the international

[121] Hughes et al, n 120, 367.

[122] AR Hughes et al, "Genetic Association Studies to Detect Adverse Drug Reactions: Abacavir Hypersensitivity as an Example" (2009) 10(2) *Pharmacogenomics* 225, 228.

[123] D Nolan, "HLA-B*5701 Screening Prior to Abacavir Prescription: Clinical and Laboratory Aspects" (2009) 46(3) *Critical Reviews in Clinical Laboratory Sciences* 153.

[124] D Nolan et al, "Prospective Genetic Screening Decreases the Incidence of Abacavir Hypersensitivity Reactions in the Western Australian HIV Cohort Study" (2006) 43(1) *Clinical Infectious Diseases* 99; L Waters et al, "Prospective HLA-B*5701 Screening and Abacavir Hypersensitivity: A Single Centre Experience" (2007) 21(18) *Aids* 2533; D Zucman et al, "Prospective Screening for Human Leukocyte Antigen-B*5701 Avoids Abacavir Hypersensitivity Reaction in the Ethnically Mixed French HIV Population" (2007) 45(1) *Journal of Acquired Immune Deficiency Syndromes* 1.

[125] Waters et al, n 124; A Rauch et al, "Prospective Genetic Screening Decreases the Incidence of Abacavir Hypersensitivity Reactions in the Western Australian HIV Cohort Study" (2006) 43(1) *Clinical Infectious Diseases* 99.

[126] E Hammond et al, "External Quality Assessment of HLA-B*5701 Reporting: An International Multicentre Survey" (2007) 12(7) *Antiviral Therapy* 1027.

[127] C Orkin et al, "An Epidemiologic Study to Determine the Prevalence of the HLA-B*5701 Allele among HIV-positive Patients in Europe" (2010) 20(5) *Pharmacogenetics & Genomics* 307.

[128] Hughes et al, n 120, 372.

[129] S Mallal et al, "HLA-B*5701 Screening for Hypersensitivity to Abacavir" (2008) 358(6) *New England Journal of Medicine* 568.

[130] Mallal et al, n 129.

guidelines on the use of antiretroviral therapy in HIV-infected people.[131] The expectation that screening would occur was also reinforced by product information provided with abacavir-containing medicines authorised for sale in the United States, Europe, Australia and Japan.[132] As with the majority of prescription medicines, abacavir is dispensed with a monograph that describes the indication for use, usual doses and route of administration as well as contraindications or warnings. Highlighting the potential severity of the hypersensitivity reaction to abacavir, the warning is prominently displayed as "boxed" or a "black box warning". The format of the warning differs among jurisdictions, but all prescribers and patients are alerted to the need to consider screening for the HLA-B*5701 allele prior to commencing abacavir treatment.

Since the publication of the PREDCIT-1 findings, T3 research demonstrating the uptake of HLA-B*5701 testing has been conducted. These studies generally reinforce the clinical utility and associated benefits of testing.[133] They also demonstrate that the test is cost-effective, and relatively easy to access and interpret.[134] The overarching theme in these studies suggests that the changes to clinical practice, required for new knowledge to successfully be translated, have occurred. However, an important component of T3 translational research identified by Khoury et al is research that more broadly engages with factors such as marketing, regulation and policy-making.[135] Recognising that this represents an "inherently non-linear" aspect of the framework, studies describing the use of genetic information on medicine labels generally,[136] rather than abacavir specifically, can be included in this phase.

The final Khoury et al phase in the research translation framework assesses how the adoption of evidence-based guidelines has impacted on "real-world" outcomes.[137] In this phase, the overlap with T3 research is clearly apparent, and could include, for example, the decisions to (or to avoid) subsidising the cost of HLA-B*5701 testing. To date, T4 research in relation to this specific pharmacogenomic test has yet to be conducted. It is possible, however, that the successful translation of this one test could be relied upon to inform the translation of future pharmacogenomic testing and ultimately improve the safety and efficacy of many medicines.

CONCLUSION

To facilitate the integration of new genomic research into clinical practice, Khoury et al developed a framework that describes a continuum of translation research. Retrospectively applying this framework to one pharmacogenomic test, the analyses in this article demonstrate that successful

[131] See, eg US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, *AIDSinfo: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>; Australasian Society for HIV Medicine, *Australian Commentary to the US DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents* <http://arv.ashm.org.au>; D Asboe et al, "British HIV Association Guidelines for the Routine Investigation and Monitoring of Adult HIV-1 Infected Individuals 2011" (2012) 13(1) *HIV Medicine* 1.

[132] European Medicine Agency, *Find Medicine – Ziagen Product Information* <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000252/WC500050343.pdf>; US Food and Drug Administration, *FDA Online Label Repository: Abacavir* <http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020977s028,020978s032lbl.pdf>; Therapeutic Goods Administration, *Product and Consumer Medicine Information Licence Ziagen* <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-019633&d=20150810161146224 12>; Y Otsubo et al, "Similarities and Differences between US and Japan as to Pharmacogenomic Biomarker Information in Drug Labels" (2011) 27(1) *Drug Metabolism & Pharmacokinetics* 142.

[133] See, eg T Kauf et al, "Economic Efficiency of Genetic Screening to Inform the Use of Abacavir Sulfate in the Treatment of HIV" (2010) 28(11) *PharmacoEconomics* 1025; M Watson et al, "A Study of HIV Provider Attitudes Toward HLA-B 5701 Testing in the United States" (2009) 23(11) *AIDS Patient Care & STDs* 957.

[134] D Hughes, "The Economics of Personalised Medicine and Pharmacogenetic Testing" (2013) 35(8) *Clinical Therapeutics* e118; R Kapoor et al, "Reducing Hypersensitivity Reactions with HLA-B*5701 Genotyping before Abacavir Prescription: Clinically Useful But Is It Cost-Effective in Singapore?" (2015) 25(2) *Pharmacogenetics & Genomics* 60.

[135] Khoury et al, n 12, 671.

[136] R Tutton, "Pharmacogenomic Biomarkers in Drug Labels: What Do They Tell Us?" (2014) 15(3) *Pharmacogenomics* 297.

[137] Khoury et al, n 12, 671.

translation depends on a range of studies, using a variety of methodologies and widely disseminated findings. Relying on this knowledge to inform the development of evidence-based guidelines, and evaluating outcomes based on compliance with guidelines, is believed to be integral to delivering improved, safe and efficient health outcomes.

The article goes further though, by highlighting the importance of the context in which this translational research is situated. In the example of pharmacogenomic testing for abacavir, traditional models of knowledge generation and translation were challenged by the unique circumstances created by the HIV/AIDS epidemic in the early 1980s. This resulted in restructured, innovative and unprecedented changes to the regulatory process that would permit expanded access to novel treatments for the deadly virus. Consequently, more people were exposed to abacavir much sooner in the development process than would have occurred prior to the changes. This meant that there were more people presenting with symptoms of HSR, providing an unprecedented opportunity to explore the genetic factors responsible for the unwanted and harmful response.

These circumstances provided fertile ground for the subsequent development and integration of a new pharmacogenomic test for several reasons. First, the outcome of research directed at finding the cause was that a single genetic variant, HLA-B*5701, was highly predictive of an adverse clinical outcome. Further, as research and development of rapid and accurate methods for identifying genetic variants was also occurring, the ability to detect the presence or absence of a specific allele, in contrast to wider genotyping, meant that any test ordered would deliver information that was easily interpreted and actioned. Clinicians could confidently either include or withhold abacavir or abacavir-containing medicines on the basis of a single test. Importantly, for those people carrying the HLA-B*5701 allele, viable and effective alternative treatment options were available.

While this article has highlighted the positive social and political influences on the translation of one pharmacogenomic test into clinical practice, it is unlikely that these exceptional circumstances are a necessary condition for the successful translation of any new or subsequent pharmacogenomic test. What the analysis has demonstrated is that, in this case, they did create an environment conducive to supporting a wide variety of different research. Consistent with the phases of translational research outlined by Khoury et al, the breadth of research effectively contributed to the effective translation of new pharmacogenomic knowledge, and improved health outcomes.