

## Editorial

### \*Corresponding author

Glen N. Gaulton, PhD

Department of Pathology and  
Laboratory Medicine

Center for Global Health

University of Pennsylvania

Philadelphia, PA 19104, USA

E-mail: [gaulton@mail.med.upenn.edu](mailto:gaulton@mail.med.upenn.edu)

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# It's Time to Examine the Impact of Genetic Susceptibility on the Incidence of Diabetes among HIV-Infected Individuals

Kyle J. Gaulton, PhD<sup>1</sup>; Glen N. Gaulton, PhD<sup>2\*</sup>

<sup>1</sup>Department of Pediatrics, University of California, San Diego, San Diego, CA 92121, USA

<sup>2</sup>Department of Pathology and Laboratory Medicine, Center for Global Health, University of Pennsylvania, Philadelphia, PA 19104, USA

The remarkable advances in application of anti-retroviral therapy (ART) to treat HIV-infection has had a profound impact on the HIV epidemic as well as improved the quality and longevity of life for those who receive such treatment. Nonetheless, as individuals receiving ART live longer, they may develop chronic non-communicable disease at an increased incidence and/or severity when compared to non-infected and/or untreated individuals. Prime examples of this include cardiovascular and neurological disease, as well as metabolic syndrome and diabetes mellitus. Whether these growing disease burdens are identical in origin and outcome to disease in uninfected individuals, and whether ART impacts disease incidence and severity in addition to limiting HIV infection is often poorly distinguished. The data on type 2 diabetes mellitus (T2DM) provides a welcome case in point for this discussion.

There is now a wealth of data documenting the increased incidence of T2DM in HIV-infected subjects under ART. While the range of this increase varies by study population, location, and drug therapy, the most comprehensive studies typically show an increase of 2.25- 4.7 fold in the incidence of T2DM in HIV positive subjects on ART at four years after diagnosis and treatment.<sup>1,2</sup> Related studies have more recently tied these effects to an increase in the prevalence of dyslipidemia and metabolic syndrome,<sup>3,4</sup> to elevated BMI and hypertension as opposed to the level of HIV or CD4 count,<sup>5</sup> and lastly to an increase in the rate of death from the complications of diabetes.<sup>6</sup>

While the impact of HIV infection on T2DM in the absence of ART remains in debate,<sup>7</sup> there is ample evidence that various protease inhibitors used for ART cause insulin resistance independent of increases in visceral adipose tissue or lipid and lipoprotein levels.<sup>8</sup> Thus, multiple factors likely bear on the increase in T2DM seen in HIV infected subjects, especially when undergoing ART. Diabetes mellitus is a complex disease, and risk factors such as family history, genetics, obesity, race/ethnicity, age, and dyslipidemia are all poorly understood in HIV-infected individuals. However, remarkable insights into the genetic factors that foster predisposition to T2DM are rapidly emerging.<sup>9</sup> These observations illustrate that risk of T2DM is mediated by hundreds of genetic factors, the majority of which commonly occur in the general population.

Although using genetic factors to predict individual risk of T2DM is a challenge, these findings have revealed new genes and processes involved in disease pathogenesis. For example, T2DM variants affect the activity of the melatonin receptor gene that functions in circadian regulation of glucose homeostasis.<sup>10</sup> Many T2DM genetic factors—such as *TCF7L2*—cause defects in insulin secretion and alter pancreatic islet function, other factors—such as *PPARG* and *FTO*—contribute to insulin resistance,<sup>11</sup> and additional factors influence BMI and dyslipidemia.<sup>12</sup> Collectively these genes have profoundly informed the underlying causes of T2DM.

One key insight from these studies is that genetic factors for T2DM do not typically alter the protein product of a gene, and instead predominantly lie in non-coding sequences.<sup>9,10</sup> Detailed maps of the epigenome in disease-relevant tissues such as pancreatic islets, adipose,

skeletal muscle and liver have helped uncover precise genetic elements affected by T2DM risk variants.<sup>9</sup> These data suggest that much of the genetic risk of T2DM is encoded in regulatory elements activated in these tissues that affect tissue-specific gene expression. These genetic elements are thus critical to target in at-risk individuals.

Whether HIV infected subjects display an enhanced disposition and/or altered pattern of origin in T2DM that is linked to these genetic components has not been studied. This warrants immediate investigation as the populations and samples are well defined, and the tools now in place to accomplish this goal in a cost-effective manner. As the relative effect of HIV infection and/or ART on the incidence of T2DM is not absolute, studies of genetic associations and gene expression in these populations might provide clues to help decipher the relative effects of various genetic elements in predisposition to T2DM. Under the best circumstances these results might also provide a means to enhanced monitoring of certain individuals with a predisposition to develop diabetes—the ultimate goal being better preparedness and improved management of long-term health in these patients.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this manuscript.

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