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Meiring de Villiers

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# Foreseeability Decoded

Meiring de Villiers\*

## ABSTRACT

*This Article reviews the conceptual and doctrinal roles of the foreseeability doctrine in negligence law, and analyzes its application in cases where a new technology or unexplored scientific principle contributed to a plaintiff's harm. It adopts the common law definition of foreseeability as a systematic relationship between a defendant's wrongdoing and the plaintiff's harm, and demonstrates translation of the concept into the language of science so that the common law meaning of the foreseeability doctrine is preserved. An analysis of the foreseeability of HIV/AIDS as a blood-borne risk illustrates application of the concept to contemporary issues in medical science.*

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## I. INTRODUCTION

Foreseeability is a pervasive and vital ingredient of the law of torts.<sup>1</sup> Although jurists have lamented foreseeability as an elusive and frequently manipulated concept, the doctrine plays important conceptual and doctrinal roles in negligence law, and is considered the dominant test of proximate cause.<sup>2</sup> The basic test of foreseeability can be described as “whether one can see a systematic relationship between the type of accident that the plaintiff suffered and . . . the defendant’s [wrongdoing].”<sup>3</sup>

This Article reviews the conceptual and doctrinal roles of the foreseeability doctrine in negligence law, and analyzes its application in cases where a new technology or unexplored scientific principle contributed to a plaintiff’s harm. The foreseeability issue in such cases is governed by the Reasonable Ignorance of the Relationship doctrine of proximate causality.<sup>4</sup> Under the doctrine a defendant escapes liability if scientists could not predict, *ex ante*, the systematic relationship between the defendant’s wrongdoing and plaintiff’s harm.<sup>5</sup>

The Reasonable Ignorance doctrine is illustrated by *Doughty v. Turner Manufacturing Co.*<sup>6</sup> In *Doughty*, a technician negligently knocked the cover of a vat made of sindanyo, a combination of cement and asbestos, into liquid

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1. See David G. Owen, *Figuring Foreseeability*, 44 WAKE FOREST L. REV. 1277, 1277 (2009).

2. MICHAEL S. MOORE, *PLACING BLAME: A THEORY OF THE CRIMINAL LAW* 363 (Clarendon Press 1997) (“The dominant test of proximate cause in torts makes a defendant liable when but only when the harm he in fact caused was, at the time he acted, foreseeable to him . . .”).

3. Mark F. Grady, *Proximate Cause Decoded*, 50 UCLA L. REV. 293, 323 (2002).

4. *Id.* at 328.

5. See *id.* (describing that in the limited set of cases where “scientists would not have predicted this relationship *ex ante*,” no liability exists).

6. *Doughty v. Turner Mfg. Co.*, [1964] 1 Q.B. 518, 518 (C.A. 1963).

sodium cyanide.<sup>7</sup> A chemical reaction between the liquid and the sindanyo cover caused an eruption that resulted in burn injuries to the plaintiffs.<sup>8</sup> The fact that sindanyo could undergo this reaction at was unknown to scientists at the time.<sup>9</sup> The type of harm suffered by the plaintiff (burning due to splashing of hot liquid) was a foreseeable consequence of the defendant's reckless handling of the liquid, yet the defendant escaped liability.<sup>10</sup> The systematic relationship between the defendant's misconduct and the plaintiff's harm (splashing due to an obscure chemical reaction) was not only unknown to the defendant but also materially different from what was known and foreseeable (splashing due to mechanical action).<sup>11</sup>

The foreseeability issue is often resolved without controversy in cases where the science is established.<sup>12</sup> For example, the link between mesothelioma and protracted exposure to asbestos fibers is generally accepted.<sup>13</sup> Medical opinion is near unanimous that lung cancer is a foreseeable consequence of tobacco smoke, based on clinical evidence that carcinogens in tobacco smoke interact with human DNA to cause genetic mutations that result in lung cancer.<sup>14</sup> Novel and complex scientific phenomena present greater difficulties, notably in the field of medicine.<sup>15</sup> The Human Immunodeficiency Virus (HIV) and the mechanisms by which it causes the degenerative disease known as Acquired Immunodeficiency Syndrome (AIDS) have presented

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7. *Id.* at 519.

8. *Id.*

9. *Id.* at 518 ("In the present case the potential eruptive qualities . . . were not suspected and they were not a known source of danger . . .").

10. *Id.*

11. *Id.* ("[I]t would be quite unrealistic to describe this accident as a variant of the perils from splashing.").

12. See Grady, *supra* note 3, at 329 (comparing *Doughty v. Turner Manufacturing Co.* to a case where the science was more understood).

13. See, e.g., *Borel v. Fibreboard Paper Prod. Corp.*, 493 F.2d 1076, 1105 (1973) (explaining that the scope of an asbestos manufacturer's duty to warn includes foreseeable dangers related to exposure to asbestosis, mesothelioma, and other cancers); Jenny Steele & Nick Wikeley, *Dust on the Streets and Liability for Environmental Cancers*, 60 MOD. L. REV. 265, 268 (1997).

14. Stephen S. Hecht, *Tobacco Smoke Carcinogens and Lung Cancer*, 91 J. NAT'L CANCER INST. 1194, 1194 (1991).

15. See Ross D. Eckert, *The AIDS Blood-Transfusion Cases: A Legal and Economic Analysis of Liability*, 29 SAN DIEGO L. REV. 203, 204 (1992).

challenges, not only to medical researchers striving for a cure or at least better understanding,<sup>16</sup> but also to lawyers litigating issues related to the syndrome.<sup>17</sup> In particular, HIV-related diseases caused by negligently ordered or administered blood transfusions have triggered an avalanche of lawsuits.<sup>18</sup>

Common AIDS-defining opportunistic infections and diseases were known blood-borne risks even before the AIDS epidemic.<sup>19</sup> This fact appears to suggest that AIDS was a foreseeable blood-borne risk before and during the early stages of the epidemic. The general common law rule is that the type of injury must be foreseeable, rather than its extent or manner of occurrence.<sup>20</sup> Defendants who negligently ordered or administered blood transfusions that resulted in AIDS nevertheless escaped liability during the early stages of the epidemic.<sup>21</sup> The analysis in this Article supports these verdicts.

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16. See *id.* (describing AIDS as "the public health crisis of our time").

17. See Beth Rabkin & Michael Scott Rabkin, *Individual and Institutional Liability for Transfusion-Acquired Diseases: An Update*, 256 JAMA 2242, 2242 (1986); David Stevens, *Negligence Liability for Transfusion-Associated AIDS Transmission*, 12 J. LEGAL MED. 221 (1991); see also Osborn v. Irwin Mem'l Blood Bank, 7 Cal. Rptr. 2d 101, 104 (1992).

18. Eckert, *supra* note 15, at 204; Donald H.J. Hermann, *AIDS: Malpractice and Transmission Liability*, 58 U. COLO. L. REV. 63 (1987); Michael Trebilcock et al., *Do Institutions Matter? A Comparative Pathology of the HIV-Infected Blood Tragedy*, 82 VA. L. REV. 1407, 1407-09, 1483-84 (1996).

19. See Alexandra M. Levine, *Acquired Immunodeficiency Syndrome: The Facts*, 65 S. CAL. L. REV. 423, 424 (1991) ("AIDS is diagnosed when an individual is found to have one or more of the following illnesses: (1) opportunistic infection (2) Kaposi's sarcoma (3) high-grade, B-cell lymphoma (4) AIDS-dementia/encephalopathy syndrome (5) wasting syndrome (slim disease)."). These common AIDS-defining opportunistic infections and diseases such as cytomegalovirus infection, lymphomas including non-Hodgkin's lymphoma, human T-lymphotropic virus infection, and toxoplasmosis were known and foreseeable blood-borne risks before the AIDS epidemic. Yao-Chang Chen et al., *Infection of Human T-cell Leukemia Virus Type I and Development of Human T-cell Leukemia/Lymphoma in Patients with Hematologic Neoplasms: A Possible Linkage to Blood Transfusion*, 74 BLOOD 388 (1989); S. Gerald Sandier & F. Carl Grumet, *Posttransfusion Cytomegalovirus Infections*, 69 PEDIATRICS 650, 650 (1982) ("[C]ytomegalovirus has been recognized as a potential hazard of blood transfusion since 1966 . . .").

20. RESTATEMENT (SECOND) OF TORTS § 435 (1965).

21. See, e.g., *Hoemke v. New York Blood Ctr.*, 912 F.2d 550 (2d Cir. 1990); *Kozup v. Georgetown Univ.*, 663 F. Supp. 1048, 1054 (D.D.C. 1987), *aff'd in relevant part*, 851 F.2d 437 (D.C. Cir. 1988).

The *type* of harm, AIDS-defining opportunistic infections, was indeed foreseeable but scientists could not predict the *systematic relationship* between blood transfusions and AIDS. In addition, HIV/AIDS was not a *mere variant* of known blood-borne risks.<sup>22</sup>

Analysis of the foreseeability of HIV/AIDS as blood-borne risk requires a translation of the foreseeability doctrine into the language of medicine that preserves the common law meaning of the doctrine.<sup>23</sup> The essence of the doctrine is the concept of a systematic relationship between a defendant's wrongdoing and the plaintiff's harm.<sup>24</sup> The systematic relationship between a tort such as medical malpractice and a disease is defined by the *etiology* and *pathogenesis* of the disease.<sup>25</sup> The etiology of a disease is the cause or set of causes of the disease.<sup>26</sup> The pathogenesis is the mechanism by which an etiologic agent produces the disease.<sup>27</sup> For instance, the etiology of lung cancer includes carcinogens such as tobacco smoke.<sup>28</sup> The pathogenesis of lung cancer includes mechanisms such as the interaction of carcinogens with human DNA to

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22. See Mark Woolhouse et al., *Human Viruses: Discovery and Emergence*, 367 PHIL. TRANS. ROYAL SOC'Y 2864, 2864, 2867–68 (2012); see also Mark F. Grady, *Causation and Foreseeability*, in RESEARCH HANDBOOK ON THE ECONOMIC ANALYSIS OF TORTS 114 (Jennifer Arlen ed., 2013) (“The basic purpose of reasonable-foresight proximate cause is to cut off liability for . . . accidents that are not mere variants of those that were ex ante foreseeable.”).

23. Cf. LAWRENCE LESSIG, CODE AND OTHER LAWS OF CYBERSPACE 165 (1999) (“When dealing with [new technologies], judges are to be translators; different technologies are the different languages; and the aim is to find a reading of [legal principles] that preserves [their] meaning from one world's technology to another. This is fidelity as translation.”).

24. Benjamin C. Zipursky, *Foreseeability in Breach, Duty, and Proximate Cause*, 44 WAKE FOREST L. REV. 1247, 1271 (2009) (“[T]he plaintiff's injury must correlate with that aspect of the defendant's conduct that was negligent.”).

25. See generally A DICTIONARY OF EPIDEMIOLOGY 132 (John M. Last ed., 4th ed. 2001); RICHARD SLOANE, THE SLOANE-DORLAND ANNOTATED MEDICAL-LEGAL DICTIONARY 268 (1987).

26. SLOANE, *supra* note 25.

27. *Id.* at 535 (defining pathogenesis as “the cellular events and reactions and other pathologic mechanisms occurring in the development of disease.”); Bernard N. Fields, *Pathogenesis of Viral Infections*, in EMERGING VIRUSES 70 (Stephen S. Morse ed., 1996) (“Pathogenesis is the interaction of a microbe with a host resulting in an outcome by which a disease occurs.”).

28. Hecht, *supra* note 14, at 1194.

cause genetic mutations that result in lung cancer.<sup>29</sup> Lung cancer is a foreseeable consequence of human exposure to tobacco smoke because medical evidence shows that tobacco smoke contains an etiologic agent that initiates the pathogenesis of lung cancer in the exposed person.<sup>30</sup>

HIV is the etiologic agent of the mechanisms that culminate in AIDS-defining diseases and infections.<sup>31</sup> The foreseeability of AIDS as a blood-borne risk therefore depends on (1) awareness in the medical profession of HIV and its essential features, and (2) whether HIV is a mere variant of known disease-causing viruses and their pathogenesis.<sup>32</sup>

In the early stages of the AIDS epidemic, medical science was ignorant of the systematic relationship between AIDS and blood transfusions.<sup>33</sup> The etiologic agent of AIDS, HIV, was first identified and isolated only in 1983, and medical research confirmed the pathogenetic relationship between HIV and AIDS in 1984.<sup>34</sup>

The systematic relationship is not a mere variant of what is known and foreseeable because the etiology and pathogenesis of AIDS both differ materially from those of other viral diseases.<sup>35</sup> The etiologic agent (HIV) has a complex genetic structure and novel molecular mechanisms controlling its viral

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29. *Id.*

30. *Id.*

31. Eckert, *supra* note 15, at 204, 226; *see also infra* note 370 and accompanying text.

32. *See* Eckert, *supra* note 15, at 246–60 (discussing requirements to establish causation in “blood cases”); *see also* Grady, *supra* note 22, at 114 (“The basic purpose of reasonable-foresight proximate cause is to cut off liability for . . . accidents that are not mere variants of those that were ex ante foreseeable.”).

33. *See* Janice E. Clements & M. Christine Zink, *Molecular Biology and Pathogenesis of Animal Lentivirus Infections*, 9 CLINICAL MICROBIOLOGY REV. 100, 101 (1996); Kent A. Sepkowitz, *AIDS—The First 20 Years*, 344 NEW ENG. J. MED. 1764, 1764–65 (2001) (discussing the many early theories for the cause of AIDS, and that there was “doubt about a viral cause . . . until the actual virus was detected”).

34. Sepkowitz, *supra* note 33, at 1765 (outlining the major timeline of events in first decade of the AIDS epidemic); *see also infra* note 370 and accompanying text.

35. Sepkowitz, *supra* note 33, at 1765 (discussing how early hypotheses that AIDS was caused by cytomegalovirus was not upheld after observing pathogenesis in patients with the disease, and that over time “a novel viral cause of the disease” became a favored theory).

gene expression that distinguish it from other human viruses.<sup>36</sup> The pathogenesis of AIDS is distinctive as well, as discussed below.<sup>37</sup>

The distinctive features of HIV are material because they confer on HIV unique abilities that play a central role in the distinctive pathogenesis of AIDS.<sup>38</sup> Three prominent features of HIV are (1) extreme genetic variability, (2) a capacity to infect nondividing cells, and (3) unique genetic and molecular structure.

36. For instance, in addition to the *gag*, *pol* and *env* genes common to all retroviruses, the HIV genome contains six additional genes, namely *tat*, *rev*, *vif*, *vpr*, *nef*, and *vpu*. Daniel A. Eckstein et al., *HIV-1 Vpr Enhances Viral Burden by Facilitating Infection of Tissue Macrophages but Not Nondividing CD4+ T Cells*, 194 J. EXPERIMENTAL MED. 1407, 1407 (2001) (“In addition to the *gag*, *pol* and *env* genes found in all retroviruses, the HIV-1 genome contains six additional genes: *tat*, *rev*, *vif*, *vpr*, *vpu*, and *nef*. These genes confer upon HIV-1 a number of unique abilities, including the capacity to infect non-cycling cells.”); Anthony S. Fauci, *The Human Immunodeficiency Virus: Infectivity and Mechanisms of Pathogenesis*, 239 SCIENCE 617, 617 (1988) (“HIV also has at least five additional genes, three of which have known regulatory functions, and the expression of these genes almost certainly has an impact on the pathogenic mechanisms exerted by the virus.”).

37. See Part V.C.3. Professors Narayan and Clements describe features that distinguish the pathogenesis of HIV from those of other disease-causing viruses, calling HIV “the antithesis of [the] general concept of pathogenesis of viral disease.” Opendra Narayan & Janice E. Clements, *Biology and Pathogenesis of Lentiviruses*, 70 J. GEN. VIROLOGY 1617, 1618 (1989); see also C. Harold Mielke, Jr., *The Uniqueness of HIV Infection*, 8 J. CLINICAL APHERESIS 2, 4 (1993) (“HIV is indeed a unique infection; it is able to directly infect specific cells of the human immune system to produce immune abnormalities that lead to the development of opportunistic infections, host compromise, morbidity, and mortality. The retrovirus is able to directly infect cells of the immune system, especially the cells that contain the CD4 surface receptors. The virus contains reverse transcriptase, which is able to reverse the flow of genetic information by converting RNA into proviral DNA that is incorporated into the host cell’s DNA.”); Xiping Wei et al., *Antibody Neutralization and Escape by HIV-1*, 422 NATURE 307 (2003) (describing a strategy by HIV-1 to avoid attack by antibodies, not seen in other viruses); see also Margaret I. Johnston & Anthony S. Fauci, *An HIV Vaccine—Challenges and Prospects*, 359 NEW ENG. J. MED. 888, 888 (2008) (describing the unique pathogenesis of HIV).

38. Martin A. Nowak & Andrew J. McMichael, *How HIV Defeats the Immune System*, SCI. AM., Aug. 1995, at 58, 60–62 (describing the unique process of HIV infection and disease progression).



## A. GENETIC VARIABILITY

Three unique properties combine to make HIV the most variable human virus: a high mutation rate, a high replication frequency, and a high recombination frequency.<sup>39</sup>

1. HIV has a high mutation rate.<sup>40</sup> The genetic information of HIV is encoded in RNA rather than DNA, but it inserts a DNA copy of its genome into a host cell in order to replicate.<sup>41</sup> This process requires the action of the enzyme reverse transcriptase, which copies the viral RNA genome into a DNA sequence.<sup>42</sup> The virus mutates during this process because reverse transcriptase is error prone and has no editing mechanism for transcriptional errors.<sup>43</sup> HIV reverse transcriptase is one of the most error prone reverse transcriptase enzymes known.<sup>44</sup>

2. HIV has an exceptionally high replication frequency,<sup>45</sup> which contributes to AIDS pathogenesis in at least two ways. The sheer volume of viral replication inside the host immune cell overwhelms and kills the cell by monopolizing the cell's resources and disrupting the cell membrane.<sup>46</sup> Rapid viral

39. Charles R.M. Bangham & Rodney E. Phillips, *What Is Required of an HIV Vaccine?*, 350 LANCET 1615, 1615 (1997) (attributing difficulty of treatment and prevention of HIV infection to the "high rates of replication, mutation, and recombination of HIV").

40. Nowak & McMichael, *supra* note 38, at 59–60 ("The virus mutates readily . . . because reverse transcriptase is rather error prone.").

41. *Id.*

42. *Id.*

43. *Id.* ("It has been estimated that each time the enzyme copies RNA into DNA, the new DNA on average differs from that of the previous generation in one site."); John D. Roberts et al., *The Accuracy of Reverse Transcriptase from HIV-1*, 242 SCIENCE 1171, 1171 (1988) ("[T]he HIV-1 enzyme does not correct errors by exonucleolytic proofreading.").

44. Lori H. Conlan et al., *Localization, Mobility and Fidelity of Retrotransposed Group II Introns in rRNA Genes*, 33 NUCLEIC ACIDS RES. 5262, 5268 (2005) ("HIV-1 RT [reverse transcriptase] is the most error-prone RT known."); Susan M. Schader & Mark A. Wainberg, *Insights into HIV-1 Pathogenesis Through Drug Discovery: 30 Years of Basic Research and Concerns for the Future*, 10 HIV & AIDS REV. 91, 91 (2011) ("HIV-1 reverse transcriptase was observed to be remarkably error-prone relative to other retrovirus reverse transcription enzymes . . .").

45. Nowak & McMichael, *supra* note 38, at 60.

46. *Id.* at 58 ("In the initial stage of HIV infection, the virus colonizes . . . cells and macrophages. It also replicates unchecked for a while. As the amount of virus soars, the number of helper cells falls; macrophages die

replication also combines with and amplifies the high mutation rate to make HIV the most variable human virus known.<sup>47</sup>

3. HIV is the most recombinogenic known human virus.<sup>48</sup> Recombination is a process that enhances genetic variability of HIV within an infected individual during RNA to DNA transcription by scrambling the genetic content from two nonidentical RNA copies to generate a hybrid DNA mosaic.<sup>49</sup>

The resulting genetic variability of HIV contributes to AIDS pathogenesis by allowing the virus to escape recognition by the immune response and evade the effects of anti-retroviral therapies and vaccines.<sup>50</sup>

## B. CAPACITY TO INFECT NONDIVIDING CELLS

The second distinctive feature of HIV, the ability to infect nondividing cells such as macrophages<sup>51</sup> is, like its extreme mutability, central to AIDS pathogenesis.<sup>52</sup> Macrophages serve

as well . . . The infected [c]ells perish as thousands of new viral particles erupt from the cell membrane.”)

47. *Id.* at 60.

48. Etienne Simon-Loriere et al., *RNA Structures, Genomic Organization and Selection of Recombinant HIV*, 8 *RNA BIOLOGY* 280, 280 (2011) (“[I]n retroviruses and notably in the case of HIV, recombination is so frequent that it can be considered as part of its mode of replication.”).

49. *Id.* RNA carries two copies of RNA in each particle, both of which are used as a template to insert DNA into the host. *Id.* If the two RNA copies are not perfectly identical, a “scrambling” or recombination of the RNA templates creates a “new” DNA sequence. *See id.*; *see also* Wenfeng An & Alice Telesnitsky, *HIV-1 Genetic Recombination: Experimental Approaches and Observations*, 4 *AIDS REV.* 195, 196 (2002) (“[R]etroviruses differ from other viruses in that each contains duplicate RNAs. Retroviruses are sometimes considered to be diploid . . . Co-packaging two RNAs in a single virion provides two templates to the reverse transcriptase machinery and is a critical factor in the high frequency of retroviral recombination.”).

50. *Id.* (“This process . . . [is] involved in immune escape and development of resistance to antiviral treatments.”).

51. Macrophages are white blood cells within tissues that play an important role in the human immune response; their role is to phagocytize (engulf and then digest) cellular debris and pathogens, and to stimulate lymphocytes and other immune cells to respond to the pathogen. *See* GABRIEL VIRELLA, *MEDICAL IMMUNOLOGY* 2 (5th ed. 2001); PAUL A. VOLBERDING ET AL., *GLOBAL HIV/AIDS MEDICINE* 40 (2008); Stephanie Forrest et al., *Computer Immunology*, 40 *COMM. ACM* 88, 90 (1997).

52. Most retroviruses can enter the nucleus of a cell only while the cell is dividing. Masahiro Yamashita et al., *Evidence for Direct Involvement of the Caspid Protein HIV Infection of Nondividing Cells*, 3 *PLOS PATHOGENS* 1502,

as viral targets and reservoirs, facilitate pathogenesis of AIDS-related neurological disorders, and contribute to the development of AIDS-defining opportunistic infections.<sup>53</sup>

### C. UNIQUE HIV GENETIC STRUCTURE AND MOLECULAR MECHANISMS

The unique and powerful pathogenesis of HIV is directly attributable to distinctive aspects of its genetic structure. For instance, the six genes that are unique to HIV—which distinguish it from other retroviruses—play a central role in its high mutation rate and ability to infect and replicate in macrophages.<sup>54</sup> The *tat* and *nef* genes amplify and maintain the replication rate of HIV, a key contributor to genetic diversity.<sup>55</sup>

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1502 (2007) (“[M]ost retroviruses, such as murine leukemia virus, require cell division for efficient infection.”). HIV, in contrast, possesses genetic features that enable it to infect and replicate efficiently in non-dividing cells, including immune cells known as macrophages. *Id.* (“One of the properties that set HIV-1 . . . apart from most of the other retroviruses is the ability to infect cells independent of the cell cycle. This ability allows HIV-1 to propagate in nondividing cells . . .”) (citation omitted).

53. See Narayan & Clements, *supra* note 37, at 1619–22, 1630 (“Since macrophages constitute the main non-specific cellular defence system of the host, lentivirus [HIV] replication undoubtedly subverts this arm of the defence system and results in failure of the host to eliminate the virus.”); *infra* note 418.

54. See Clements & Zink, *supra* note 33, at 102 (“The additional gene products of the [HIV] lentiviruses contribute to a more complex pattern of gene expression and may also contribute to the pathogenesis of disease.”); Jay A. Levy, *Pathogenesis of Human Immunodeficiency Virus Infection*, 57 MICROBIOLOGICAL REV. 183, 188 (1993).

55. Bangham & Phillips, *supra* note 39, at 1616–17 (“The kinetics of HIV-1 replication are complicated by the regulatory genes *tat*, *nef*, *vpu*, *vpr*, and *vif*. . . . The Nef protein is particularly important in maintaining the high replication rate of HIV-1—and therefore its pathogenicity—in vivo. Also, the virus weakens the immune defenses by steadily depleting the CD4<sup>+</sup> T-cell population . . . .”); Fauci, *supra* note 36, at 617; John L. Foster & J. Victor Garcia, *Role of Nef in HIV-1 Replication and Pathogenesis*, 55 ADV. PHARMACOLOGY 389, 389–90 (2007) (“Nef is a pathogenic factor of HIV . . . . The enhancement of viral replication and pathogenesis by Nef [may be explained by] . . . the ability of Nef to enhance viral particle infectivity.”); see Paul U. Cameron & Mark Kelly, *HIV Immunopathology, in HIV MANAGEMENT IN AUSTRALASIA: A GUIDE FOR CLINICAL CARE* 19, 26 (Jennifer Hoy et al. eds., 2009), available at [http://www.som.uq.edu.au/media/418950/hiv\\_aus\\_guide.pdf](http://www.som.uq.edu.au/media/418950/hiv_aus_guide.pdf) (discussing how “a number of HIV proteins interfere with critical cellular processes that facilitate the host immune response,” including

The *rev* gene has been described as “absolutely essential” for viral replication,<sup>56</sup> in addition to its other contributions to HIV functionality and pathogenicity.<sup>57</sup> The *vpr* gene confers upon HIV the capacity to infect and replicate efficiently in nondividing cells such as macrophages.<sup>58</sup> The *vif*<sup>59</sup> and *vpu*<sup>60</sup> genes also play important roles in the pathogenesis of HIV.

In summary, the risk of HIV/AIDS was unforeseeable in the early stages of the AIDS epidemic. The etiology and pathogenesis of HIV/AIDS were discovered only in 1983 and

the Nef protein); Eric O. Freed, *HIV-1 Replication*, 26 SOMATIC CELL & MOLECULAR GENETICS 13, 29 (2001).

56. Thomas J. Hope & Didier Trono, *Structure, Expression, and Regulation of the HIV Genome*, HIV INSITE (Nov. 2000), <http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-02-01-02> (“Rev is absolutely required for HIV-1 replication: proviruses that lack Rev function are transcriptionally active but do not produce viral late genes and thus do not produce virions.”).

57. Clements & Zink, *supra* note 33, at 100 (“The regulatory genes *tat* and *rev* control viral transcription and RNA transport and translation . . .”); Freed, *supra* note 55, at 13 (“Rev plays a major role in the transport of viral RNAs from the nucleus to the cytoplasm.”); Miranda Shehu-Xhilaga & Robert Oelrichs, *Basic HIV Virology*, in HIV MANAGEMENT IN AUSTRALASIA: A GUIDE FOR CLINICAL CARE, *supra* note 55, at 9, 10 (“[T]he Rev responsive element . . . assists export of spliced RNA transcripts from the nucleus of the cell.”).

58. Eckstein et al., *supra* note 36, at 1407 (“Viral protein R (Vpr) in particular is known to play an important role in facilitating infection of non-dividing tissue macrophages as well as inducing G<sub>2</sub> cell cycle arrest in dividing T cells.”); Louis M. Mansky, *The Mutation Rate of Human Immunodeficiency Virus Type 1 Is Influenced by the vpr Gene*, 222 VIROLOGY 391, 394 (1996); Hengli Tang et al., *Lentivirus Replication and Regulation*, 33 ANNUAL REV. GENETICS 133, 154 (1999) (“HIV-1 vpr also has a role in the nuclear import of HIV-1 preintegration complexes (PICs) into the nucleus of infected cells. This makes vpr an important player in HIV infection of nondividing cells, such as macrophages.”).

59. Koji Sakai et al., *Recombinational Analysis of a Natural Noncytopathic Human Immunodeficiency Virus Type 1 (HIV-1) Isolate: Role of the vif Gene in HIV-1 Infection Kinetics and Cytopathy*, 65 J. VIROLOGY 5765, 5770 (1991); Shehu-Xhilaga & Oelrichs, *supra* note 57, at 11 (“Viral proteins perform a variety of roles to subvert normal cellular function and facilitate viral replication . . . . Vif is necessary for subsequent efficient infectivity of the newly produced viral particles.”).

60. John W. Balliet et al., *Distinct Effects in Primary Macrophages and Lymphocytes of The Human Immunodeficiency Virus Type 1 Accessory Genes, vpr, vpu, and nef: Mutational Analysis of a Primary HIV-1 Isolate*, 200 VIROLOGY 623 (1995); Freed, *supra* note 55, at 28; Shehu-Xhilaga & Oelrichs, *supra* note 57 (“Vpu promotes degradation of CD4 in the endoplasmic reticulum . . .”).

1984, respectively.<sup>61</sup> Furthermore, the risk was not a mere variant of what was known and foreseeable. HIV has a complex genetic structure and novel molecular mechanisms controlling its viral gene expression that distinguish it from other human viruses. These distinctive features are material because they confer on HIV unique abilities that play a central role in the distinctive pathogenesis of AIDS, a pathogenesis that the human immune response can neither contain nor defeat.

The analysis in this Article supports the common law evolution of the foreseeability issue in HIV/AIDS blood transfusion cases. Courts in early cases such as *Quinones v. Long Island College Hospital*<sup>62</sup> and *Fox v. Estrada*<sup>63</sup> held that HIV/AIDS is not a foreseeable blood-borne risk. Eventually, after scientists had isolated the virus and discovered the pathogenesis of AIDS, courts began to resolve the foreseeability issue in favor of plaintiffs.<sup>64</sup>

The Article is organized as follows. Part II reviews the foreseeability doctrine and its conceptual and doctrinal roles in negligence law. Part III discusses the legal definition of foreseeability. Part IV introduces the Reasonable Ignorance of the Relationship doctrine and analyzes its common law foundations. Part V presents an analysis of the foreseeability of HIV/AIDS as a blood-borne risk.

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61. Sepkowitz, *supra* note 33.

62. *Quinones v. Long Island Coll. Hosp.*, 607 N.Y.S.2d 103 (N.Y. App. Div. 1994).

63. *Fox v. Estrada*, No. 14-97-00821-CV, 1998 WL 831666, at \*2 (Tex. App. Dec. 3, 1998) (“[T]he contraction of AIDS was not a foreseeable proximate result of a blood transfusion known within the medical community in 1982 . . .”).

64. *See infra* note 345 and accompanying text.

## II. THE FORESEEABILITY DOCTRINE

Foreseeability is a pervasive and vital ingredient of the law of torts.<sup>65</sup> Professor David Owen describes foreseeability as “the dark matter of tort” that permeates and connects its various components, and that “gives moral content to the law of negligence, controlling how each element fits together and, ultimately, whether one person is bound to pay another for harm.”<sup>66</sup>

Foreseeability plays several conceptual roles in the law of negligence. The degree to which a defendant could foresee the consequences of a wrongful act is a factor in assigning blameworthiness and moral responsibility for any harmful consequences.<sup>67</sup> Furthermore, limiting a defendant’s liability to reasonably foreseeable harm promotes deterrence and economic efficiency.<sup>68</sup> Foreseeability places reasonable boundaries on the scope of a defendant’s liability by limiting liability to

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65. See Owen, *supra* note 1.

66. *Id.* at 1277.

67. *Id.* at 1280 (“For a person’s actions to be wrongful, the person must have had a choice of alternative courses of action and also must have chosen, by some standard, incorrectly. If an actor chooses to act in a manner that violates some community norm, of proper behavior, tort law holds the actor accountable for harmful consequences that result from that choice. Thus, tort responsibility normally implies that the actor ought to have considered and chosen to avoid the kind of harm he caused—that he or she wrongfully failed to avoid the harm. So, ascribing moral character (blame or praise) to a choice to risk or avoid the risk of harm implies the actor’s ability to conceive (foresee) its consequences. Foreseeability thus is bound up, inextricably, in notions of both wrongfulness and how far responsibility for wrongfulness should extend.”); see W. Jonathan Cardi, *Reconstructing Foreseeability*, 46 B.C. L. REV. 921, 943 (2005) (“[O]utcome-responsibility depends on the notion of control. Only an agent who is in control of his or her actions, and to a certain degree, of the consequences of those actions, may be said to be outcome-responsible. [T]he necessary degree of control over the outcome is defined by whether the outcome was avoidable, and avoidability exists only in the presence of a general capacity to foresee an outcome and to take steps to avoid its occurrence.”) (internal quotation marks omitted).

68. See Cardi, *supra* note 67, at 955 (“Only an injury that is foreseeable is capable of being deterred.”); see also WILLIAM A. LANDES & RICHARD A. POSNER, *THE ECONOMIC STRUCTURE OF TORT LAW* 247 (1987) (“[A dog owner] is liable only if he has reason to suspect the dog’s vicious disposition . . . Even if the probability of the dog’s biting is very high, the owner will not be liable unless he has reason to know it is high.”).

consequences reasonably related to the alleged wrongdoing;<sup>69</sup> and courts frequently employ foreseeability as an instrument to achieve policy goals, such as obtaining an appropriate balance between conflicting interests of the parties to a dispute.<sup>70</sup>

In addition to its conceptual role, foreseeability plays an important doctrinal role in negligence law. The general rule is that a defendant is liable only when the harm she in fact caused was foreseeable at the time of wrongdoing.<sup>71</sup> Foreseeability plays specific roles in several elements of negligence.<sup>72</sup> The plaintiff in a negligence action has to prove the following elements:<sup>73</sup>

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69. See MIRKO BAGARIC ET AL., TORTS: COMPENSATION FOR HARM 233 (2011) (“[T]he defendant will not be liable if the harm caused is too remote. Harm will be too remote where it was not reasonably foreseeable as a result of the act of the defendant.”); Cardi, *supra* note 67, at 927 (“[F]oreseeability . . . aids in the decision of whether the actual consequences of the defendant’s conduct were so . . . far-removed from the risks that made the conduct negligent that the defendant, though blameworthy, should not be held liable for them.”); Owen, *supra* note 1, at 1278 (“[B]ecause the effects of all behavior extend forever, no coherent conception of responsibility can suppose that a person is responsible for everything that could be called a consequence of his or her actions . . . . [A] defendant is responsible for and only for such harm as he could reasonably have seen and prevented.”) (internal quotation marks omitted).

70. Cardi, *supra* note 67, at 983 (“To the extent that a court imposes atypical boundaries on a jury’s determination of foreseeability in order to effect a policy-based limitation on liability, such a determination lies squarely within the province of the court to delineate the standard of care or to define the legal standard for proximate cause.”). Cardi refers to the use of foreseeability “as a proxy for decisions of policy.” *Id.* at 938. In cases involving liability of a business owner for assault of a customer on its premises, “many courts have imposed a duty, limited . . . by foreseeability. In some jurisdictions, for example, a business owner owes a duty to protect patrons only if he is aware of specific, imminent harm about to befall them . . . . [But all] test[s] represent a balance between the security interest of customers and the liberty interest of owners.” *Id.* at 984.

71. See, e.g., MOORE, *supra* note 2; Grady, *supra* note 22 (“U.S. courts have held that a defendant will be immune from liability for an accident otherwise caused by negligence if it was not ‘reasonably foreseeable.’”).

72. See Cardi, *supra* note 67, at 921 (“The concept of foreseeability is fast devouring the negligence cause of action.”).

73. See generally DAN B. DOBBS, LAW OF TORTS § 114, 269 (2001) (stating that the prima facie case for negligence consists of the following elements: duty, breach, actual cause, proximate cause, and actual damage); David G. Owen, *Idea: The Five Elements of Negligence*, 35 HOFSTRA L. REV. 1671, 1671–72 (2007); Owen, *supra* note 1.

1. A duty of care to prevent unreasonable risks of harm.
2. A breach of duty.
3. A causal connection between the defendant's conduct and the plaintiff's harm.<sup>74</sup>
4. Actual damage resulting from the defendant's negligence.

Foreseeability features in three elements. Foreseeability defines whether the defendant owed a duty to the plaintiff,<sup>75</sup> whether the defendant breached a duty,<sup>76</sup> and whether the defendant's breach proximately caused the plaintiff's injury.<sup>77</sup>

Negligence liability of a defendant depends first and foremost on the existence of a duty of care to the plaintiff,<sup>78</sup> defined as a legally mandated obligation to take reasonable care to avoid a risk of harm to another.<sup>79</sup> A duty of care may be

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74. This element includes actual, as well as proximate, cause. A defendant's negligence is the actual cause of the plaintiff's harm if but for the breach the harm would not have occurred. Owen, *supra* note 73, at 1680. The proximate causation element requires the defendant's conduct to be reasonably related to the plaintiff's harm. *Id.* at 1681 (defining proximate cause as "a reasonably close connection between a defendant's wrong and the plaintiff's injury, a connection that is not remote").

75. W. Jonathan Cardi, *Purging Foreseeability: The New Vision of Duty and Judicial Power in the Proposed Restatement (Third) of Torts*, 58 VAND. L. REV. 739, 758 (2005) ("[P]laintiff-foreseeability frequently makes a dual appearance, influencing both duty and proximate cause analyses."); Cardi, *supra* note 67, at 923 ("[F]oreseeability remains a pervasive consideration in many courts' duty analyses.").

76. RESTATEMENT (THIRD) OF TORTS § 4 (Discussion Draft 1999) ("Primary factors to consider in ascertaining whether conduct lacks reasonable care are the foreseeable likelihood that it will result in harm, the foreseeable severity of the harm that may ensue, and the burden that would be borne by the actor and others if the actor takes precautions that eliminate or reduce the possibility of harm."); Cardi, *supra* note 67, at 921 ("Foreseeability of risk has for centuries rested at the heart of courts' determinations of whether a defendant breached its duty of care.").

77. See, e.g., WILLIAM PROSSER & W. PAGE KEETON, ON THE LAW OF TORTS 281 (5th ed. 1984); *supra* note 3 and accompanying text.

78. Owen, *supra* note 1, at 1301 ("Every negligence claim must pass through the duty portal that bounds the scope of tort recovery for accidental harm.").

79. See William L. Prosser, *Palsgraf Revisited*, 62 MICH. L. REV. 1, 12–15 (1953).



imposed by common law tort principles.<sup>80</sup> A duty may also be imposed by statute, either expressly<sup>81</sup> or by legal precedent, if the statute does not expressly provide for civil liability.<sup>82</sup>

Foreseeability is a fundamental consideration in the duty analysis,<sup>83</sup> and has been described as duty's "unified theory."<sup>84</sup> It is a necessary, and perhaps the most important, factor in determining whether a duty exists.<sup>85</sup> Courts have denied a duty based on absence of foreseeability, even where the defendant's conduct created a risk of physical harm.<sup>86</sup>

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80. See, e.g., Michael L. Rustad & Thomas H. Koenig, *Extending Learned Hand's Negligence Formula to Information Security Breaches*, 3 I/S: J.L. & POL'Y INFO. SOC'Y 237, 239–40 (2007) ("[C]ompanies have a duty to provide reasonable information security practices under the common law of torts."); Vincent R. Johnson, *Cybersecurity, Identity Theft, and the Limits of Tort Liability*, 57 S.C. L. REV. 255, 272–82 (2005) (discussing various examples of common law derived duties).

81. E.g., CAL. CIV. CODE § 1798.81.5 (West 2005) ("A business that owns or licenses personal information about a California resident shall implement and maintain reasonable security procedures and practices appropriate to the nature of the information, to protect the personal information from unauthorized access, destruction, use, modification, or disclosure.").

82. E.g., RESTATEMENT (THIRD) OF TORTS § 12 (Discussion Draft 1999) ("An actor is negligent if, without excuse, the actor violates a statute that is designed to protect against the type of accident the actor's conduct causes, and if the accident victim is within the class of persons the statute is designed to protect."); VINCENT R. JOHNSON & ALAN GUNN, *STUDIES IN AMERICAN TORT LAW* 305–06 (3d ed. 2005).

83. See, e.g., *J.S. v. R.T.H.*, 714 A.2d 924, 928 (N.J. 1998) ("Foreseeability of the risk of harm is the foundational element in the determination of whether a duty exists."); Zipursky, *supra* note 24, at 1258 ("[F]oreseeability [is] a significant factor (and frequently the most significant factor) in analyzing whether the duty element is met in a negligence claim."). *But see* *Gipson v. Kasey*, 150 P.3d 228, 231 (Ariz. 2007) ("[W]e now expressly hold that foreseeability is not a factor to be considered by courts when making determinations of duty, and we reject any contrary suggestion in prior opinions.").

84. *Cardi*, *supra* note 67, at 922; see also Peter F. Lake, *Revisiting Tarasoff*, 58 ALA. L. REV. 97, 121–23 (1994).

85. See HAROLD LUNTZ ET AL., *TORTS CASES AND COMMENTARY* 129 (6th ed. 2009); Arthur Ripstein, *Justice and Responsibility*, 17 CAN. J.L. & JURISPRUDENCE 361, 374 (2004) ("Other factors may be relevant to the existence of a duty, but foreseeability provides an outer bound beyond which there can be no liability because there can be no duty.").

86. E.g., *Herrera v. Quality Pontiac*, 73 P.3d 181, 187 (N.M. 2003) (stating that there is no duty unless the plaintiff was within the scope of risk created by the defendant); see also *Cardi*, *supra* note 67, at 930 ("[F]oreseeability has

Foreseeability is sufficient to create a duty when a defendant has committed an affirmative act that created a risk of harm to others.<sup>87</sup> In this limited set of cases, the defendant owes a duty of care to all plaintiffs foreseeably within the scope of the risk.<sup>88</sup> Foreseeability by itself is not sufficient in all circumstances to trigger a duty. The California Supreme Court<sup>89</sup> as well as the courts of most other states,<sup>90</sup> list foreseeability prominently among the factors to be balanced in determining whether a duty exists, but make it clear that other factors also play a role.<sup>91</sup>

“Breach of duty” refers to a violation of the duty to avoid unreasonable risks of harm to others.<sup>92</sup> Common law rules require the plaintiff to prove breach of duty by identifying and pleading an untaken precaution that would have prevented the accident, had it been taken.<sup>93</sup> The defendant will be in breach if the benefits of risk reduction provided by the pleaded precaution exceed its cost.<sup>94</sup> The plaintiff must further show

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become so central a concept in may courts’ duty analyses that a ruling on foreseeability is outcome-determinative.”).

87. *See, e.g.*, *Brennen v. City of Eugene*, 591 P.2d 719, 723 (Or. 1979) (concluding that “the agent’s duty should be defined in terms of foreseeability,” and that “the agent was required to perform this duty so as to avoid creating a foreseeable risk of harm to others”).

88. *See, e.g., id.*; Jill M. Fraley, *Comment: Knowledge Circles and the Duty of Care*, 71 WASH. & LEE L. REV. 789, 790–91 (2010) (citing RESTATEMENT (THIRD) OF TORTS: PHYS. & EMOT. HARM § 7 (2010)).

89. *E.g.*, *Rowland v. Christian*, 443 P.2d 561, 564 (Cal. 1968) (“[T]he foreseeability of harm to the plaintiff, the degree of certainty that the plaintiff suffered injury, the closeness of the connection between the defendant’s conduct and the injury suffered, the moral blame attached to the defendant’s conduct, the policy of preventing future harm, the extent of the burden to the defendant and consequences to the community of imposing a duty to exercise care with resulting liability for breach, and the availability, cost, and prevalence of insurance for the risk involved.”).

90. *See* Peter F. Lake, *Common Law Duty in Negligence Law: The Recent Consolidation of a Consensus on the Expansion of the Analysis of Duty and the New Conservative Liability Limiting Use of Policy Considerations*, 34 SAN DIEGO L. REV. 1503, 1524 (1997) (concluding from a survey of duty in fifty states that foreseeability has become prominent in determining the existence of a duty of care); Zipursky, *supra* note 24, at 1258.

91. *See Rowland*, 443 P.2d at 564.

92. DOBBS, *supra* note 73, § 115, at 270.

93. *See id.*

94. *Delisi v. St. Luke’s Episcopal-Presbyterian Hosp., Inc.*, 701 S.W.2d 170 (Mo. Ct. App. 1985) (explaining that the plaintiff had to prove physician’s

that the precaution is technically feasible; namely, that there were reasonable practical means by which it could have been implemented.<sup>95</sup>

Foreseeability plays a crucial role in breach analysis.<sup>96</sup> The breach calculus weighs the cost of the untaken precaution against the value of the reduction in all foreseeable risks that the precaution would have provided, not just the risk that actually materialized.<sup>97</sup>

Foreseeability is the touchstone of the element of proximate cause.<sup>98</sup> Professor Michael S. Moore formulates the

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breach of duty by specifying the treatment that should have been administered); Mark F. Grady, *Untaken Precautions*, 18 J. LEGAL STUD. 139, 143 (1989) (“[Courts] take the plaintiff’s allegations of the untaken precautions of the defendant and ask, in light of the precautions that had been taken, whether some particular precaution promised benefits (in accident reduction) greater than its associated costs.”). For a numerical example of breach analysis, see Meiring de Villiers, *Information Security Standards and Liability*, 13 J. INTERNET L. 24, 28–29 (2010).

95. See, e.g., *Martin v. Michelin N. Am., Inc.*, 92 F. Supp. 2d 745, 754 (E.D. Tenn. 2000) (defining feasibility in terms of technological and scientific realities of the time); see also David G. Owen, *Design Defects*, 73 MO. L. REV. 291, 331 (2008).

96. RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL HARM § 3 (Proposed Final Draft No. 1, 2005) (“A person acts negligently if the person does not exercise reasonable care under all the circumstances. Primary factors to consider in ascertaining whether the person’s conduct lacks reasonable care are the foreseeable likelihood that the person’s conduct will result in harm, the foreseeable severity of any harm that may ensue, and the burden of precautions to eliminate or reduce the risk of harm.”); KENNETH S. ABRAHAM, *THE FORMS AND FUNCTIONS OF TORT LAW* 59–60 (2d ed. 2002) (describing the role of foreseeability in breach); MARC A. FRANKLIN & ROBERT L. RABIN, *TORT LAW AND ALTERNATIVES* 399 (7th ed. 2001); Zipursky, *supra* note 24, at 1249–50.

97. RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL HARM § 3 cmt. b (Proposed Final Draft No. 1, 2005) (“[A]ll the risks foreseeably resulting from the actor’s conduct are considered in ascertaining whether the actor has exercised reasonable care.”); Cardi, *supra* note 75, at 746 (“The brand of foreseeability associated with breach is one of general focus. That is, it does not examine the foreseeability of the particular injury suffered by the plaintiff, but the foreseeable likelihood and severity of injuries that might have occurred.”); Grady, *supra* note 94, at 146; Owen, *supra* note 1, at 1292.

98. *Tetro v. Town of Stratford*, 458 A.2d 5, 7–8 (Conn. 1983) (“The test for finding proximate cause is whether the harm which occurred was of the same general nature as the foreseeable risk created by the defendant’s negligence.”); RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL HARM (BASIC PRINCIPLES) § 29, cmt. j (Tentative Draft No. 23, 2002); K. BARKER ET AL., *THE LAW OF TORTS IN AUSTRALIA* 565 (5th ed. 2012) (“The basic test of

basic rule succinctly: “[t]he dominant test of proximate cause in torts makes a defendant liable when but only when the harm he in fact caused was, at the time he acted, foreseeable to him.”<sup>99</sup> Commenting on the role of foreseeability, Professor Jonathan Cardi states: “[A] plaintiff may fail to survive the proximate cause inquiry where the defendant’s actions resulted in 1) an unforeseeable type of injury, 2) an injury occurring in an unforeseeable manner, or 3) injury to an unforeseeable plaintiff.”<sup>100</sup>

### III. LEGAL DEFINITION OF FORESEEABILITY

Despite, or perhaps due to, its prominence in the law of negligence, commentators have described the concept of foreseeability as elusive and confounding,<sup>101</sup> frequently manipulated and co-opted by the judiciary,<sup>102</sup> and undermining the perceived legitimacy of the judicial process.<sup>103</sup> These

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remoteness of damage . . . is foreseeability.”); DOBBS, *supra* note 73, § 187, at 463 (“[C]ourts usually reduce the tests of proximate cause . . . to a question of foreseeability.”); FRANKLIN & RABIN, *supra* note 96, at 399; B. RICHARDS ET AL., *TORT LAW IN PRINCIPLE* 305 (5th ed. 2009) (“In the issue of remoteness, the court is not judging whether the defendant has been negligent (that has already been established); it is merely deciding what are the foreseeable consequences of that negligence.”); Grady, *supra* note 3, at 322–32 (discussing the reasonable foresight paradigms of proximate cause); Owen, *supra* note 1, at 1293 (“[T]he concept of ‘foreseeability’ . . . is the ‘touchstone’ or ‘cornerstone’ of proximate cause.”).

99. MOORE, *supra* note 2; *see also* BAGARIC ET AL., *supra* note 69, at 233 (“[T]he defendant will not be liable if the harm caused is too remote. Harm will be too remote where it was not reasonably foreseeable as a result of the act of the defendant.”); DOBBS, *supra* note 73, § 180, at 443; Owen, *supra* note 1, at 1294 (“[P]roximate cause limits negligence responsibility to the scope of risks that are foreseeable.”).

100. Cardi, *supra* note 75, at 749.

101. *Id.* at 744 (“[T]he term [foreseeability] is surely among the most confounding in the common law.”); Benjamin C. Zipursky, *The Many Faces of Foreseeability*, 10 KAN. L.L. & PUB. POL’Y 156, 156 (2000) (“Foreseeability is undoubtedly a muddle in the law of negligence.”).

102. *See* Cardi, *supra* note 75, at 740–43 (“[Foreseeability has] been bent, muddled, and co-opted to such a degree that it has lost any real meaning.”); *id.* at 743 (“In many courts, the foreseeability lens seems to expand, contract or change focus at the will of the judge. Indeed . . . some have argued that the doctrine of foreseeability has lost any fixed meaning and instead acts as a mere surrogate for judicial discretion.”).

103. *Id.* at 741 (“[T]o the extent that reference to foreseeability masks the actual reasons for a judge’s decision to impose or deny negligence liability,

concerns notwithstanding, a clear and precise definition of foreseeability can be distilled from the noise of common law patterns. An event is the foreseeable result of an action if the action *ex ante* created or enhanced the risk of the event.<sup>104</sup> An equivalent definition describes foreseeability as a systematic relationship between a defendant's wrongdoing and the type of harm that had befallen the plaintiff.<sup>105</sup> The following case provides an illustration.

In *Weirum v. RKO General, Inc.*,<sup>106</sup> the defendant, a popular Los Angeles radio station that broadcast to a predominately teenage audience, started a promotional to increase its listener base.<sup>107</sup> One of its disk jockeys, "The Real Don Steele," drove a red muscle car to various locations in the Los Angeles area, while another disk jockey back at the station announced his changing destinations.<sup>108</sup> Under the rules of the contest, the first listener who caught up with the traveling disk jockey won a cash prize.<sup>109</sup> Two teenagers independently pursued Don Steele, reaching speeds up to eighty miles per hour.<sup>110</sup> In their zeal to catch up with Steele, one of them "forced [the] decedent's car on to a center divider where it overturned."<sup>111</sup> In the lawsuit that inevitably followed, the jury returned a verdict against the two teenagers and the radio

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foreseeability obfuscates the judicial process and likely undermines its perceived legitimacy.").

104. See RESTATEMENT (THIRD) OF TORTS, § 29 (2010) ("An actor's liability is limited to those harms that result from the risks that made the actor's conduct tortious."); DOBBS, *supra* note 73, § 187, at 463–64 ("[The essence of foreseeability is that] the scope of the defendant's liability is determined by the scope of the risk he negligently created . . . . When courts say that [a] risk is unforeseeable what they mean is that it is not a risk enhanced or created by the defendant's conduct."); Grady, *supra* note 3, at 323 (stating that a plaintiff must show that the untaken precaution would have reduced the risk of the accident at issue to prevail on proximate cause grounds).

105. Grady, *supra* note 3, at 323–24; Zipursky, *supra* note 24, at 1271 ("[T]he plaintiff's injury must correlate with that aspect of the defendant's conduct that was negligent.").

106. *Weirum v. RKO Gen., Inc.*, 539 P.2d 36 (Cal. 1975).

107. *Id.* at 38.

108. *Id.*

109. *Id.*

110. *Id.*

111. *Id.* at 39.

station as joint tortfeasors.<sup>112</sup> The California Supreme Court affirmed the judgment, finding that the accident was a foreseeable consequence of the contest and the way it was conducted.<sup>113</sup> The accident and injuries suffered by the plaintiffs were foreseeable because of a systematic relationship between an opportunity designed to appeal to teenagers and the predictable recklessness of the youngsters.<sup>114</sup> The teens who lacked maturity and the assets to pay a judgment were more susceptible to such behavior than responsible adults.<sup>115</sup>

Coincidental harm is generally unforeseeable, even where factually caused by the defendant's wrongdoing. For instance, suppose a driver exceeded a speed limit and arrived at a spot just in time to be struck by a falling tree. Although the driver's speeding caused the accident, the accident is outside the scope of risk created by the speeding.<sup>116</sup> The driver's speeding created risks of certain types of traffic accidents, but it neither created nor enhanced the risk of falling trees.<sup>117</sup> The accident is coincidental and not systematically related to the driver's negligence, hence unforeseeable.<sup>118</sup> The outcome would likely have been different if instead a tree had fallen in front of the speeding driver, and the car collided with it.<sup>119</sup> If the accident could have been avoided had the driver travelled at a reasonable speed, the driver's speeding may in those circumstances have been a proximate cause of the accident.<sup>120</sup>

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112. *Id.*

113. *Id.* at 40 ("We conclude that the record amply supports the finding of foreseeability.").

114. *Id.* ("It was foreseeable that defendant's youthful listeners, finding the prize had eluded them at one location, would race to arrive first at the next site and in their haste would disregard the demands of highway safety.").

115. See Mark F. Grady, *The Free Radicals of Tort*, 11 SUP. CT. ECON. REV. 189, 189–91 (2004).

116. See, e.g., *Berry v. Sugar Notch Borough*, 43 A. 240 (Pa. 1899).

117. *Id.*

118. See, e.g., DOBBS, *supra* note 73, § 187, at 463–64 ("When courts say that [a] risk is unforeseeable what they mean is that it is not a risk enhanced or created by the defendant's conduct."); Grady, *supra* note 3, at 324.

119. *Berry*, 43 A. at 240 ("It might have been otherwise if the tree had fallen before the car reached it, for in that case a high rate of speed might have rendered it impossible for the plaintiff to avoid a collision which he either foresaw or should have foreseen.").

120. *Id.*

Failure to stop within a short time window to avoid a collision is a foreseeable risk of speeding.<sup>121</sup>

Intervening events between the defendant's wrongdoing and the plaintiff's harm, however complex or bizarre, do not deny foreseeability as long as there is no intervening tort or crime, and as long as the ultimate harm is systematically related to the defendant's wrongdoing.<sup>122</sup> The exact concatenation of events need not be foreseeable.<sup>123</sup> The type of injury suffered by the plaintiff must be foreseeable, rather than its extent or manner of occurrence.<sup>124</sup> Two famous cases, *Bunting v. Hogsett*<sup>125</sup> and *Palsgraf v. Long Island Railroad Co.*,<sup>126</sup> provide good illustrations.

In *Bunting*, the defendant owned a furnace, and used a small railroad to carry supplies to his furnace on a dinky train.<sup>127</sup> The small railroad formed a circle that crossed the

121. See *id.*; see also Grady, *supra* note 3, at 324.

122. See Grady, *supra* note 3, at 304–05.

123. See, e.g., *Stodola v. Grunwald Mech. Contractors, Inc.*, 422 N.W.2d 341, 344 (Neb. 1988) (“The law does not require precision in foreseeing the exact hazard or consequence which happens. It is sufficient if what occurs is one of the kind of consequences which might reasonably be foreseen.”); *Hughes v. Lord Advocate*, [1963] A.C. 837 (H.L.) 850 (appeal taken from Scot.) (“It is true that the duty of care expected in cases of this sort is confined to reasonably foreseeable dangers, but it does not necessarily follow that liability is escaped because the danger actually materializing is not identical with the danger reasonably foreseen and guarded against.”); DOBBS, *supra* note 73, § 189, at 467 (explaining the risk rule of foreseeability to say, “if I foresee the risk in general, I need not foresee the details”); see also JOHN W. SALMOND, *THE LAW OF TORTS: A TREATISE ON THE ENGLISH LAW OF LIABILITY FOR CIVIL INJURIES* 719 (4th ed. 1965) (“Type of damage must be foreseen . . . [P]recise details of the accident need not be foreseen . . . The question is, was the accident a variant of the perils originally brought about by the defendant's negligence?”).

124. DOBBS, *supra* note 73, § 189, at 466 (“The defendant is liable for harms he negligently caused so long as a reasonable person in his position should have recognized or foreseen the general kind of harm the plaintiff suffered. He is not ordinarily relieved of liability merely because the manner of injury or its details were unforeseeable.”); Owen, *supra* note 1, at 1298 (“[R]esponsibility requires only that an actor foresee the type of harm, not the manner of harm nor the extent of harm.”); see also Grady, *supra* note 3, at 298 (“[T]he type of intervening event and the type of intervening actor are often much more significant to the issues of proximate cause than the mere ex ante probability of the intervening event, whatever it was.”).

125. *Bunting v. Hogsett*, 21 A. 31 (Pa. 1891).

126. *Palsgraf v. Long Island R.R. Co.*, 162 N.E. 99 (N.Y. 1928).

127. *Bunting*, 21 A. at 31.

Southwest Pennsylvania mainline tracks twice.<sup>128</sup> The plaintiffs were traveling on a passenger train on the Southwest Pennsylvania mainline tracks.<sup>129</sup> The driver of the dinky train failed to maintain a proper lookout and did not see the passenger train approaching the intersection with the dinky tracks until it was too late to avoid a collision.<sup>130</sup> When the dinky driver realized a collision was inevitable, he reversed the engine, shut off the steam, and jumped out.<sup>131</sup> The driverless dinky train collided with the rear end of the passenger train.<sup>132</sup> This collision did not cause any injuries to the passengers, but it reopened the throttle on the dinky train, causing it to reverse back along the dinky tracks.<sup>133</sup>

In the meantime the engineer on the passenger train had applied his airbrakes, which brought the passenger train to a halt exactly at the second intersection with the dinky tracks.<sup>134</sup> By now, the driverless dinky train was on its way back to the second intersection.<sup>135</sup> The engineer of the passenger train knew a second collision was imminent, but was unable to prevent it because his airbrakes had been applied.<sup>136</sup> The dinky engine crashed into the stationary passenger train, causing serious injuries to the plaintiffs.<sup>137</sup>

Injured passengers on the passenger train filed suit against the owner of the dinky line.<sup>138</sup> The jury found that the defendant's dinky engineer had been negligent in failing to keep a lookout.<sup>139</sup> The defendant appealed and the appellate court affirmed the trial court's judgment for the plaintiffs.<sup>140</sup> Although the accident resulted from a highly unforeseeable sequence of events, the plaintiffs' harm was a foreseeable

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128. *Id.*

129. *Id.*; see also Grady, *supra* note 3, at 304.

130. *Bunting*, 21 A. at 32.

131. *Id.*

132. *Id.*

133. *Id.*

134. *Id.*

135. *Id.*

136. *Id.*

137. *Id.*

138. *Id.*

139. *Id.*; Grady, *supra* note 3, at 304–05.

140. *Bunting*, 21 A. at 32.



consequence of the defendant's untaken precaution.<sup>141</sup> There was clearly a systematic relationship between the dinky driver's failure to keep a proper lookout in a traffic intersection and a collision in that intersection<sup>142</sup> Furthermore, no tort or crime intervened between the defendant's untaken precaution and the collision.<sup>143</sup>

In *Palsgraf v. Long Island Railroad Co.*,<sup>144</sup> as in *Bunting*, an unusual sequence of events intervened between the defendant's wrongful act and the plaintiff's injury. Unlike *Bunting* however, the defendant in *Palsgraf* escaped liability, not because of the intervening events, but because the type of accident was unforeseeable.<sup>145</sup>

Helen Palsgraf, a cleaning lady from Brooklyn, was standing on a platform of the defendant's railroad waiting to board a train.<sup>146</sup> A train departed from the station at the other end of the platform, and two men ran forward to catch it.<sup>147</sup> One of the men managed to board the moving train without mishap.<sup>148</sup> The other man, who was carrying a package, jumped aboard the car while a guard on the car held the door open and pulled him in and another guard on the platform pushed him from behind.<sup>149</sup> In the scuffle, the passenger dropped his package and it fell on the rails.<sup>150</sup> The package contained fireworks that ignited on impact and exploded.<sup>151</sup> The shock of the explosion toppled some mail scales at the other end of the platform.<sup>152</sup> The scales fell on the plaintiff, causing injuries for

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141. *Id.*; Grady, *supra* note 3, at 305 ("The type of harm that the plaintiffs sustained, namely, collision harm, was exactly the type that the dinky engineer should have predicted when he neglected to look out for the passenger train.").

142. Grady, *supra* note 3, at 305 ("[A] highly systematic relationship exists between a train collision and an engineer's failure to maintain a lookout.").

143. *Bunting*, 21 A. at 31.

144. *Palsgraf v. Long Island R.R. Co.*, 162 N.E. 99 (N.Y. 1928).

145. *Id.* at 99.

146. *Id.* at 100-01.

147. *Id.* at 99.

148. *Id.*

149. *Id.*

150. *Id.*

151. *Id.*

152. *Id.*

which she sued.<sup>153</sup> No one in the station, except the passenger with the package and his companion, had any reason to know that the package contained explosives.<sup>154</sup>

The trial court denied the defendant's motion to dismiss, and the jury found for the plaintiff.<sup>155</sup> The appellate division affirmed the judgment for the plaintiff.<sup>156</sup> The New York Court of Appeals reversed and dismissed the complaint.<sup>157</sup> Writing for the majority, Judge Cardozo ruled that the defendant's wrongful act created no foreseeable risk of injury to Mrs. Palsgraf.<sup>158</sup> There is only a minimal, if any, systematic relationship between pulling a passenger onto a moving train and a scale toppling onto a person some distance away.<sup>159</sup>

Natural events and unusual "acts of God" beyond the defendant's control preserve a defendant's liability, provided the type of harm is foreseeable and there is no intervening tort or crime.<sup>160</sup> In *Johnson v. Kosmos Portland Cement Co.*,<sup>161</sup> the defendant's negligence caused flammable gas to accumulate in

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153. *Id.*

154. *Id.*

155. *Id.* at 101.

156. *Id.*

157. *Id.*

158. *Id.* at 99 ("The conduct of the defendant's guard, if a wrong in its relation to the holder of the package, was not a wrong in its relation to the plaintiff, standing far away. Relative to her it was not negligence at all. Nothing in the situation gave notice that the falling package had in it the potency of peril to persons thus removed."); Thomas A. Cowan, *The Riddle of the Palsgraf Case*, 23 MINN. L. REV. 46, 48 (1938) ("[I]f negligent at all, [the defendant] had been negligent toward the passenger; [but] no duty of care was owed to Mrs. Palsgraf since no risk of injury to her was foreseeable."); Prosser, *supra* note 79, at 5 ("The conduct of the guards toward the passenger involved no foreseeable risk that the plaintiff might be injured.").

159. See Grady, *supra* note 22, at 114 ("The Court of Appeals of New York, in a famous majority decision by Justice Benjamin Cardozo, held that the plaintiff could not recover because the accident was not 'reasonably foreseeable' to the defendant."). According to dissenting Judge Andrews, the distance between the incident and the falling scales was "apparently twenty-five or thirty feet," but regarding this distance, "[t]here was no plat in evidence, and Andrews could not have known, unless there was some statement of counsel." Prosser, *supra* note 79, at 3 n.10.

160. See DOBBS, *supra* note 73, §191, at 475 (explaining that if a defendant is harmed as a result of a concurrence of an unforeseeable natural event and the defendant's negligence, the defendant remains liable for the harm); Grady, *supra* note 3, at 303.

161. *Johnson v. Kosmos Portland Cement Co.*, 64 F.2d 193 (6th Cir. 1933).

the hold of a barge on which the decedents were working.<sup>162</sup> Lightning struck and ignited the gas, killing the workers.<sup>163</sup> The defendant was held liable.<sup>164</sup> The harm suffered by the plaintiffs was a foreseeable consequence of the defendant's negligence.<sup>165</sup> There is a systematic relationship between an act of negligence that allows combustible gas to accumulate and a subsequent explosion when the gas is ignited.<sup>166</sup> The intervention of the lightning bolt did not cut off the defendant's liability, because it was a natural event.<sup>167</sup> An intervening event may affect the foreseeability analysis, however, if scientists could not have predicted the event—the topic of the next Part.

#### IV. REASONABLE IGNORANCE OF THE RELATIONSHIP

Foreseeability of an event is not necessarily a reflection of its objective probability. Rather, it is a reflection of what a reasonable person would foresee under the circumstances.<sup>168</sup> This degree of foresight may be equal to the objective probability of the event, or it may be a fraction thereof.<sup>169</sup> The fraction may be zero if the defendant is reasonably ignorant of the systematic relationship between her wrongful act and a

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162. *Id.* at 194.

163. *Id.* at 194–96.

164. *Id.* at 197.

165. DOBBS, *supra* note 73, § 189, at 470 (“Although it might not be foreseeable that lightning would strike the barge and ignite the gases, it was foreseeable that some intervening incendiary force would ignite them.”); *Johnson*, 64 F.2d at 197 (“The danger of the injurious result was over present, even though the manner in which, or the means by which, such result was brought about may have had in it some aspect of unusualness.”).

166. *See* Grady, *supra* note 3, at 299.

167. *Johnson*, 64 F.2d at 195–97 (“This case does not fall within that class of cases . . . where a secondary efficient cause intervenes to break the chain of causation and so becomes the sole proximate cause of the injury.”).

168. *See* ARTHUR RIPSTEIN, EQUALITY, RESPONSIBILITY, AND THE LAW 94 (1999); Lara Khoury & Stuart Smyth, *Reasonable Foreseeability and Liability in Relation to Genetically Modified Organisms*, 27 BULL. SCI. TECH. & SOC'Y 215, 224 (2007) (“The test [for foreseeability] is essentially objective, but knowledge available at the time of the events must be taken into account.”).

169. *Cardi*, *supra* note 67, at 939 (“[F]oreseeability measures the fragment of objective probability that a reasonable person could have or should have—depending on the context of the decision—foreseen under the circumstances.”).

plaintiff's injury.<sup>170</sup> The Reasonable Ignorance of the Relationship doctrine, proposed by Professor Mark Grady, formalizes this concept.<sup>171</sup> Under the doctrine, proximate causality is cut off due to absence of foreseeability when, even though *ex post* there is clearly a systematic relationship between the defendant's untaken precaution and the plaintiff's harm, "scientists would not have predicted the relationship *ex ante*."<sup>172</sup> In this special case, there is no liability.<sup>173</sup> The defendant's ignorance of the systematic relationship must be objectively reasonable to escape liability under the doctrine.<sup>174</sup> A defendant who was subjectively ignorant of a risk may nevertheless be held liable if a court finds that she should have known or investigated the risk.<sup>175</sup>

The remainder of this Part reviews the common law evolution of the Reasonable Ignorance doctrine and its application in negligence cases where the defendant's wrongdoing created a novel risk, such as when a new technology or unexplored scientific principle contributed to the plaintiff's harm.

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170. *See id.*

171. *See generally* Grady, *supra* note 3, at 328.

172. *Id.*

173. *Id.*; *see also* Khoury & Smyth, *supra* note 168, at 225–26 (discussing how uncertainty as to the impact of biotechnological activities makes it "less likely it is that the courts will find that [an] injury was foreseeable"); Zipursky, *supra* note 24, at 1257 ("Imagine a plaintiff arguing that a developer could have cheaply rendered the fireplace in a house more heat-resistant by using a specially engineered, low-cost resin. Is it relevant whether the technology for the resin was available or discoverable to a reasonable architect when the house was built? Of course it is.").

174. LUNTZ ET AL., *supra* note 85, at 132 ("The question is not what the defendant personally could have foreseen, but what a reasonable person *in the position of the defendant* could reasonably have foreseen.").

175. Owen, *supra* note 1, at 1292 ("[P]rudence sometimes requires actors to investigate and evaluate possibilities of hidden or inchoate risk."); Stephen R. Perry, *The Moral Foundations of Tort Law*, 77 IOWA L. REV. 449, 506 n.207 (1992) ("Blame is assignable not just where the agent acts with knowledge of fairly specific facts, say that a certain action will or might cause a certain harm. It is also assignable where the agent knows that he ought not to act without first obtaining knowledge of the specific facts (knows that he ought to know, for short).").

## A. CLASSIC CASES

In the classic case, *Overseas Tankship (U.K.) Ltd. v. Morts Dock & Engineering Co.*,<sup>176</sup> a tank ship, the Wagon Mound, was loading furnace oil at the Caltex Wharf in Sydney, Australia.<sup>177</sup> The Wagon Mound negligently discharged flammable oil into the water that spread over the bay and under the plaintiff's wharf.<sup>178</sup> The plaintiffs were ship builders and repairers, and their employees were doing welding work on a ship, the Corrimal.<sup>179</sup> The plaintiff's operations manager saw the oil on the water, and gave instructions that no welding was to be done.<sup>180</sup> He then discussed the situation with the manager of the Caltex Wharf, who assured him that it was safe for normal welding operations to continue because there was no apparent fire hazard.<sup>181</sup> The fuel oil floating on the water could not ignite because the oil could not normally reach its flashpoint of 170 degrees Fahrenheit (77 degrees Celsius) while floating on the surface of the water.<sup>182</sup> With this reassurance, welding operations resumed.<sup>183</sup>

After a while, the oil caught fire, causing substantial damage to the plaintiff's wharf, the Corrimal, and another ship docked in the vicinity.<sup>184</sup> The oil ignited in an unusual manner. Some debris attached to a piece of cotton had been floating on the water under the oil layer, invisible to any observer.<sup>185</sup> A welder's torch set off sparks that struck the cotton.<sup>186</sup> The cotton smoldered for a while and eventually acquired sufficient heat to ignite the oil, causing the fire that burned down the dock.<sup>187</sup>

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176. *Overseas Tankship (U.K.) Ltd. v. Morts Dock & Eng'g Co. (The Wagon Mound No. 1)*, [1961] A.C. 388 (P.C.) (appeal taken from N.S.W.) (U.K.).

177. *Id.* at 412.

178. *Id.* at 413.

179. *Id.*

180. *Id.*

181. *Id.*

182. See BARKER ET AL., *supra* note 98, at 559.

183. *Overseas Tankship*, [1961] A.C. at 413.

184. *Id.* at 413-15.

185. *Id.*

186. *Id.*

187. *Id.*

The dock owner sued the charterers of the Wagon Mound, alleging that the destruction of his wharf was caused by the negligence of the defendants' employees.<sup>188</sup> The Supreme Court of New South Wales found that the defendant was reasonably ignorant of the fact that the oil could ignite while spread on the water.<sup>189</sup> However, the Court was compelled to follow the precedent of *Polemis*,<sup>190</sup> which allowed recovery for direct consequences of a defendant's negligence, regardless of foreseeability.<sup>191</sup> The Supreme Court of New South Wales held the Wagon Mound defendants liable under *Polemis* because there were no intervening causes between the defendant's act and the plaintiff's damage.<sup>192</sup> Justice Manning nevertheless expressed the hope that the House of Lords or the Privy Council would "pronounce on the topic in terms that would facilitate its everyday application to current problems."<sup>193</sup>

Justice Manning got his wish. On appeal, the Privy Council overturned *Polemis*, and established a liability standard based on foreseeability.<sup>194</sup> The oil spill created several risks, including hazards associated with water pollution and fire.<sup>195</sup> The risk of pollution was foreseeable, but did not cause the harm complained of.<sup>196</sup> The fire hazard was unforeseeable, because of the physical nature of the oil and the fact that the debris and cotton were out of sight.<sup>197</sup> The court accepted the testimony of a "distinguished scientist" that the defendants could not reasonably have foreseen that the particular kind of oil would

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188. *Id.* at 412–13.

189. *Id.*

190. *See In re Polemis & Furness, Withy & Co.*, [1921] 3 K.B. 560 (C.A.).

191. *Id.*

192. *Overseas Tankship*, [1961] A.C. at 414.

193. *Id.* at 390.

194. *Id.* at 418–20 ("After the event, even a fool is wise. But it is not the hindsight of a fool; it is the foresight of the reasonable man which alone can determine responsibility . . . . But if it would be wrong that a man should be held liable for damage unpredictable by a reasonable man because it was 'direct' or 'natural,' equally it would be wrong that he should escape liability, however 'indirect' the damage, if he foresaw or could reasonably foresee the intervening events which led to its being done . . . . Thus foreseeability becomes the effective test.")

195. *Id.* at 388–89.

196. *Id.* at 389.

197. *Id.*

be flammable when spread on water.<sup>198</sup> The Privy Council therefore denied liability on foreseeability grounds, finding that the defendants were reasonably ignorant of the mechanism by which the plaintiff's harm occurred.<sup>199</sup>

In *Doughty v. Turner Manufacturing Co.*,<sup>200</sup> a technician negligently knocked the cover off a vat containing molten sodium cyanide into the liquid in the vat.<sup>201</sup> The cover was made of a combination of asbestos and cement known as sindanyo.<sup>202</sup> A chemical reaction between the molten liquid and the sindanyo caused an eruption that resulted in burn injuries to the plaintiffs.<sup>203</sup> The risk that the cover might splash the molten liquid onto bystanders was foreseeable, but the chemical reaction that actually caused the harm was unknown and unpredictable at the time of the accident.<sup>204</sup> Scientists later discovered that at sufficiently high temperatures the sindanyo compound would undergo a chemical change that creates steam.<sup>205</sup> Steam created in this manner caused the eruption that injured the plaintiff in *Doughty*.<sup>206</sup> This process was unknown to scientists at the time of the accident, and the compound of sindanyo was, until the accident occurred, thought to be safe for the purpose it was used for.<sup>207</sup>

The court held in favor of the defendant.<sup>208</sup> Even though *ex post* there was clearly a systematic relationship between the defendant's misconduct and the plaintiff's injuries, the defendant was unaware of the relationship at the time of the

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198. *Id.* at 413.

199. *Id.* ("The *raison d'être* of furnace oil is, of course, that it shall burn, but I find the [appellants] did not know and could not reasonably be expected to have known that it was capable of being set afire when spread on water.").

200. *Doughty v. Turner Mfg. Co.*, [1964] 1 Q.B. 518, 518 (C.A. 1963).

201. *Id.* at 519.

202. *Id.*

203. *Id.*

204. *Id.* at 522.

205. *Id.* at 519.

206. *Id.* at 519–20.

207. *Id.* at 518–19 ("Nobody supposed that if the covers were immersed into the cauldron, any serious consequences would result . . . . When the lid dropped into the liquid, nobody was alarmed, and two bystanders actually moved closer to peer into the bath.").

208. *Id.* at 524.

accident.<sup>209</sup> The defendant therefore escaped liability under the Reasonable Ignorance doctrine.<sup>210</sup>

In *Tremain v. Pike*,<sup>211</sup> the claimant, an employee of the defendant, contracted a rare disease known as Weil's disease, allegedly due to rat infestation on the defendant's farm.<sup>212</sup> Weil's disease is a form of leptospirosis that is caused by bacteria known as leptospire.<sup>213</sup> Leptospire are present in rats that are carriers of the disease, and are passed from the kidneys to the urine of infected rats.<sup>214</sup> Justice Payne held that the defendant had not breached his duty to the plaintiff in the circumstances of the case, but added that even if the defendant had been in breach, he would not be liable because the type of harm suffered by the plaintiff was not a reasonably foreseeable consequence of rat infestation.<sup>215</sup> Although the medical profession and officials in the Ministry of Agriculture were familiar with the condition known as Weil's disease, evidence before the court suggested that the defendants-farmers were reasonably ignorant of the disease.<sup>216</sup>

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209. *Id.* at 519–20.

210. *Cf.* *Doughty v. Turner Mfg. Co.*, [1964] 1 Q.B. 518, 520, 524–25 (C.A. 1963); DOBBS, *supra* note 73, § 189, at 468 (“The chemical reaction had been completely unknown up until that time, so the eruption by this means was entirely unforeseeable.”); Marc Stauch, *Risk and Remoteness of Damage in Negligence*, 64 MOD. L. REV. 191, 203 (“[E]ven where a general link between the faulty conduct and the harm is apparent, the presence of the further causal condition in the background environment, and its potential to combine with the faulty conduct in the causal set for harm, must have been known of at the time of the conduct.”).

211. *Tremain v. Pike*, [1969] 3 W.L.R. 1556 (Eng.).

212. *Id.* at 1559 (“It follows from the evidence that . . . an increase in the rat population on a farm increases the risk of infection with leptospirosis.”).

213. *Id.* at 1558.

214. *See, e.g.*, THE MERCK MANUAL OF MEDICAL INFORMATION 1104–05 (Mark H. Beers et al. eds., 2d Home ed. 2003) (describing of leptospirosis and Weil's disease).

215. *Tremain*, [1969] 3 W.L.R. at 1560–61 (“If, contrary to my view, it should be held that the defendants were in breach of duty . . . [defendants] are still immune from liability on the grounds that Weil's disease was at best a remote possibility which they could not reasonably foresee, and that the damage suffered by the plaintiff was, therefore, unforeseeable and too remote to be recoverable.”).

216. *Id.* at 1559 (“Knowledge of Weil's disease in this country is as rare as the disease itself. The evidence before me suggests that it is known to medical officers of health, public health inspectors and some officers of the Ministry of Agriculture, and a bulletin on the Control of Rats and Mice, published by the



If the risk at issue were described as “illness due to rat infestation,” the plaintiff’s harm would be foreseeable.<sup>217</sup> Rat infestation creates multiple risks, including foreseeable risks such as illness related to rat bites and poisoning by consumption of rat-contaminated food.<sup>218</sup> However, the court ruled that the foreseeability inquiry should be based on the specific risk of Weil’s disease, because it is distinct from the foreseeable class of rodent-borne diseases.<sup>219</sup> The defendants therefore escaped liability because they were reasonably ignorant of the specific disease contracted by the plaintiff and the mechanism by which it was transmitted.<sup>220</sup>

When scientific knowledge advances and new information becomes available, courts may decide that a once obscure risk has become foreseeable, and decline to allow a defendant the benefit of the Reasonable Ignorance doctrine.<sup>221</sup> Decades after

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Ministry in 1961, and reprinted in 1967, refers to this disease amongst others, but this booklet has not been issued to farmers or circulated through the National Farmers Union. There is no evidence before me to suggest that farmers know, or reasonably ought to know, of this disease. The defendant, Leonard Pike, had never heard of it . . . Two witnesses . . . had not heard of the disease, and did not know that one could get any disease by handling matter contaminated by rats.”).

217. See, e.g., MICHAEL JONES, TEXTBOOK ON TORTS 242 (6th ed. 1998) (“If the question had been: Was illness from some rat-transmitted disease foreseeable? The answer would surely have been yes. Rats are associated with disease but few people could specify which diseases are foreseeable.”).

218. See *Tremain*, [1969] 3 W.L.R. at 1560–61.

219. *Id.* at 1561 (“The kind of damage suffered here was a disease contracted by contact with rat’s urine. This, in my view, was entirely different in kind from [foreseeable harms such as] the effect of a rat-bite, or food poisoning by the consumption of food or drink contaminated by rats. I do not accept that all illness or infection arising from an infestation of rats should be regarded as of the same kind.”); *id.* at 1556 (noting that Weil’s disease is the only known rodent-borne disease that is not transmitted by rat bites or food contamination.).

220. *Id.* at 1556.

221. See, e.g., PROSSER, *supra* note 75, at 185 (“As scientific knowledge advances . . . what was excusable ignorance yesterday becomes negligent ignorance today.”); CAROLYN SAPPIDEEN ET AL., TORTS COMMENTARY AND MATERIALS 221 (11th ed. 2012) (“What is foreseeable can therefore change according to circumstances as knowledge develops.”); Khoury & Smyth, *supra* note 168, at 224 (“[T]he exchange of information within the research community as well as research efforts . . . are likely to have a direct impact on the courts’ [foreseeability analysis]. The level of knowledge prevalent in the industry may give courts some indication of what they can expect reasonable foresight to consist of at a particular point in time.”).

*Tremain*, in *Campbell v. Percy Bilton*, an employee of the defendants contracted Weil's disease after coming into contact with rat urine in water that had accumulated in crevices and steel girders on a building site.<sup>222</sup> This time the court held for the plaintiff.<sup>223</sup> The disease had become much more widespread than in 1969 when *Tremain* was decided, and the hazard was well known in the particular working environment.<sup>224</sup> The defendant could not rely on a pleading of reasonable ignorance of the risk because Weil's disease had become a known and foreseeable consequence of rat infestation.

#### B. LEVEL OF ABSTRACTION

The foreseeability of a risk depends on the level of abstraction at which it is defined. The risk at issue in *Doughty v. Turner*<sup>225</sup> may be described as "injury by splashing of molten metal," which is foreseeable.<sup>226</sup> At a lower level of abstraction, the risk may be described more precisely as "injury by splashing of molten metal due to an unknown chemical reaction."<sup>227</sup> A court that accepted the latter description would likely rule that the risk was unforeseeable.<sup>228</sup> A defendant has the apparent incentive to describe a risk as precisely as possible, while the plaintiff would want to describe it as generally as possible.<sup>229</sup> A defendant cannot, however, manipulate the foreseeability issue to its advantage by defining a risk arbitrarily precisely.<sup>230</sup> Regardless of how a risk is presented to a court, a defendant's liability will be preserved if the court finds that the specific risk at issue is substantially similar to, or a mere variant of a foreseeable risk or class of risks.<sup>231</sup> The following case provides an illustration.

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222. For a discussion of this case, see JOHN HODGSON & JOHN LEWTHWAITE, *TORT LAW* 73 (2d ed. 2012).

223. *Id.*

224. *Id.*

225. *Doughty v. Turner Mfg. Co.*, [1964] 1 Q.B. 518, 518 (C.A. 1963).

226. *See* DOBBS, *supra* note 73, § 189, at 468–69.

227. *Id.*

228. *Id.*

229. *See id.*

230. *Id.*

231. *See, e.g.*, *Stodola v. Grunwald Mech. Contractors, Inc.*, 422 N.W.2d 341, 344 (Neb. 1988) ("The law does not require precision in foreseeing the exact hazard or consequence which happens. It is sufficient if what occurs is

In *Bradford v. Robinson Rentals*,<sup>232</sup> the plaintiff was a fifty-seven-year-old mobile radio and television service engineer who frequently travelled in a small van in the course of his employment.<sup>233</sup> During the winter of 1963, his employer required him to travel to a distant location to exchange one van for another.<sup>234</sup> His employer knew the weather would be severe, with temperatures likely to dip below freezing point, and that he would have to drive at least twenty hours in these conditions.<sup>235</sup> Because of the plaintiff's protracted exposure to freezing weather and fatigue from driving under stressful conditions, circulation in his hands and feet stagnated and he suffered frostbite,<sup>236</sup> an unusual condition even in the cold winters of England.<sup>237</sup> The defendant argued that the plaintiff's injury was unusual and therefore not reasonably foreseeable.<sup>238</sup> The court disagreed and held that although the defendant

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one of the kind of consequences which might reasonably be foreseen."); *Parsons v. Uttley Ingham & Co. Ltd.*, [1978] Q.B. 791 (holding that the risk of intestinal disease in pigs included the unforeseeable risk of *E. coli* infection); *Rowark v. Nat'l Coal Bd.* [1978] R 480, 1986 WL 1255199 (finding that the plaintiff's unusual injury, tenosynovitis, is no more than a specific variant of foreseeable injuries such as strains or sprains.); *Bradford v. Robinson Rentals*, [1967] 1 W.L.R. 337 (Eng.) (holding that the risk of frostbite is unforeseeable but substantially similar to a foreseeable risk such as chilblains); SALMOND, *supra* note 123, at 719 ("Type of damage must be foreseen . . . [P]recise details of the accident need not be foreseen . . . The question is, was the accident a variant of the perils originally brought about by the defendant's negligence?"); Grady, *supra* note 22, at 114 ("The basic purpose of reasonable-foresight proximate cause is to cut off liability for . . . accidents that are not mere variants of those that were ex ante foreseeable.").

232. *Bradford*, [1967] 1 W.L.R. at 337.

233. *Id.*

234. *Id.*

235. *Id.* at 341.

236. See JOHN MARX, *ROSEN'S EMERGENCY MEDICINE: CONCEPTS AND CLINICAL PRACTICE* 1862 (7th ed. 2010) ("Frostbite is the medical condition where localized damage is caused to skin and other tissues due to extreme cold."); see also Alexander Golant et al., *Cold Exposure Injuries to the Extremities*, 16 J. AM. ACAD. ORTHOPAEDIC SURGEONS 704, 704-15 (2008).

237. *Bradford*, [1967] 1 W.L.R. at 342; see also *Rowark v. Nat'l Coal Bd.* [1978] R 480, 1986 WL 1255199 ("[In] *Bradford v. Robinson Rentals* . . . the injury suffered by the plaintiff was frost-bite, a condition which is very rare, if indeed it is known at all, to occur at the levels of temperature that we have in this country. It had been argued that frost-bite was not a foreseeable injury.").

238. *Bradford*, [1967] 1 W.L.R. at 342.

could not foresee the specific injury,<sup>239</sup> it was of the same “type and kind” as injuries that typically result from exposure to extreme cold, such as chilblains.<sup>240</sup> The plaintiff’s injury was therefore a foreseeable consequence of the defendants’ breach of duty.<sup>241</sup>

The court’s position appears logical. The conditions of frostbite and chilblains are similar and are in fact often confused.<sup>242</sup> Both are caused by exposure to extreme cold, although frostbite is more severe than chilblains—a chilblain is a nonfreezing tissue injury,<sup>243</sup> while frostbite is a freezing condition.<sup>244</sup> Neither the rarity of frostbite<sup>245</sup> nor its unusual severity<sup>246</sup> makes it unforeseeable. The defendant’s liability was therefore properly preserved.

In *Bradford*, the defendant was held liable—although the specific risk was unforeseeable, it was similar to a foreseeable

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239. *Id.* at 344.

240. *Id.* Chilblains is a painful, itching swelling on the skin, typically on a hand or foot, caused by poor circulation in the skin when exposed to cold. It is relatively common in Britain. See R. John Gourlay, *The Problem of Chilblains with a Note on Their Treatment with Nicotinic Acid*, BRITISH MED. J. 336, 336 (1948).

241. *Bradford*, [1967] 1 W.L.R. at 346.

242. *Homeopathy for Chilblains*, HOMEOPATHY FOR EVERYONE (May 16, 2014), <http://treatment.hpathy.com/homeo-medicine/homeopathy-chilblains/> (“Chilblains is a medical condition that is often confused with frostbite and trench foot.”).

243. THE MERCK MANUAL OF MEDICAL INFORMATION, *supra* note 214, at 1656.

244. C. Imray et al., *Cold Damage to the Extremities: Frostbite and Non-Freezing Cold Injuries*, 85 POSTGRADUATE MED. J. 481, 481 (2009) (“Frostbite is defined as true tissue freezing caused by heat loss sufficient to cause ice crystal formation in superficial or deep tissues.”).

245. Cf. BAGARIC ET AL., *supra* note 69, at 168, 233; Grady, *supra* note 22.

246. See, e.g., *Hughes v. Lord Advocate*, [1963] A.C. 837 (H.L.) 845 (appeal taken from Scot.) (“[A] defender is liable, although the damage may be a good deal greater in extent than was foreseeable. He can only escape liability if the damage can be regarded as differing in kind from what was foreseeable.”); DOBBS, *supra* note 73, § 188, at 464 (stating that a defendant’s liability is preserved “if he could reasonably foresee the nature of the harm done, even if the total amount of harm turned out to be quite unforeseeably large”) (citing RESTATEMENT (SECOND) OF TORTS § 435); LUNTZ ET AL., *supra* note 85, at 132 (stating that the defendant is liable for damage that is of the same kind as that which was reasonably foreseeable, “even though its extent may have been unforeseeable”).

class of risks.<sup>247</sup> In cases where a specific risk is unforeseeable as well as distinct from foreseeable risks, courts typically deny liability.<sup>248</sup> In *Fox v. Estrada*, the Court distinguished the unforeseeable risk of HIV/AIDS (at the time) from known and foreseeable blood-borne risks, based on the unique behavior of HIV inside the body of an infected person.<sup>249</sup> In *Doughty v. Turner*, the court distinguished the risk of splashing a hot liquid due to an unknown chemical reaction from the known risk of splashing due to mechanical action.<sup>250</sup> In *Tremain v. Pike*, the court distinguished an unknown bacterial disease that is transmitted through human contact with rodent urine from foreseeable rodent-transmitted diseases.<sup>251</sup> In *Estrada*, *Tremain*, and *Doughty*, the defendant's wrongdoing created multiple risks, some of which were foreseeable, some not.<sup>252</sup> The risk that injured the plaintiff was unforeseeable and distinct from the foreseeable risks.<sup>253</sup> Novel and unexpected factors such as an unknown chemical reaction in *Doughty* and obscure diseases in *Estrada* and *Tremain* distinguished the respective materialized risks, enabling the defendant to escape liability under the Reasonable Ignorance doctrine.<sup>254</sup>

The next Part presents an analysis of the common law evolution of the foreseeability issue and the Reasonable Ignorance doctrine in a special class of cases, namely HIV/AIDS as a blood-borne risk.

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247. *Bradford*, [1967] 1 W.L.R. at 344, 346.

248. DOBBS, *supra* note 73, § 189, at 468–69.

249. *Fox v. Estrada*, No. 14-97-00821-CV, 1998 WL 831666, at \*3–4 (Tex. App. Dec. 3, 1998) (describing distinctive features of HIV/AIDS).

250. *Doughty v. Turner Mfg. Co.*, [1964] 1 Q.B. 518, 522 (C.A. 1963).

251. *Tremain v. Pike*, [1969] 3 W.L.R. 1556, 1560–61 (U.K.).

252. *See Doughty*, [1964] 1 Q.B. at 522; *Fox*, 1998 WL 831666, at \*3–4; *Tremain*, [1969] 3 W.L.R. at 1560–61.

253. *See Doughty*, [1964] 1 Q.B. at 522; *Fox*, 1998 WL 831666, at \*3–4; *Tremain*, [1969] 3 W.L.R. at 1560–61.

254. *See Doughty*, [1964] 1 Q.B. at 522; *Fox*, 1998 WL 831666, at \*3–4; *Tremain*, [1969] 3 W.L.R. at 1560–61.

## V. HIV/AIDS BLOOD TRANSFUSION CASES

## A. INTRODUCTION TO HIV

The Human Immunodeficiency Virus is a retrovirus that causes progressive failure of the human immune response, culminating in the degenerative disease known as AIDS.<sup>255</sup> The major mechanisms of HIV transmission are exposure to body fluids of an infected person, use of contaminated needles, and perinatal (mother to newborn baby) transmission.<sup>256</sup> Two subtypes of HIV are known, HIV-1 and HIV-2.<sup>257</sup> HIV-1 is more virulent and infective, and is the major cause of the global AIDS epidemic.<sup>258</sup> HIV-2 is much less pathogenic and is mainly found in West African countries.<sup>259</sup>

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255. See MICHAEL D. JOHNSON, *HUMAN BIOLOGY: CONCEPTS AND CURRENT ISSUES* 199–200 (2d ed. 2003) (“A syndrome is a medical term for a group of symptoms that occur together, and acquired means that one catches it.”); Anna Forsman & Robin A. Weiss, *Why Is HIV a Pathogen?*, 16 *TRENDS MICROBIOLOGY* 555, 557 (“AIDS was named a syndrome because as an end-stage disease it is manifested by a variety of severe symptoms.”); Hermann, *supra* note 18, at 63–64 (“AIDS is an impairment of the human body’s natural immune system of defense against disease that renders a person vulnerable to infections and various illnesses. The damage to the immune system results . . . as a consequence of infection with HIV. AIDS is an acquired condition rather than an inherited one, and it is a syndrome in that it is constituted by a number of symptoms and conditions that characterize the disorder.”); see also *Doe v. Mut. of Omaha Ins. Co.*, 179 F.3d 557, 560–61 (7th Cir. 1999) (“The essential point to understand is that HIV doesn’t cause illness directly. What it does is weaken and eventually destroy the body’s immune system. As the immune system falters, the body becomes prey to diseases that the system protects us against. These ‘opportunistic’ diseases that HIV allows, as it were, to ravage the body are exotic cancers and rare forms of pneumonia and other infectious diseases. To refer to them as ‘complications’ of HIV or AIDS is not incorrect, but it is misleading, because they are the chief worry of anyone who has the misfortune to be afflicted with AIDS.”).

256. See JOHNSON, *supra* note 255, at 200–01; Keith A. Crandall, *Human Immunodeficiency Viruses (HIV)*, in *ENCYCLOPEDIA OF LIFE SCIENCES* 4 (2001); Viviana Simon et al., *HIV/AIDS Epidemiology, Pathogenesis, Prevention, and Treatment*, 368 *LANCET* 489, 496–98 (2006).

257. See Norman L. Letvin, *Strategies for an HIV Vaccine*, 110 *J. CLINICAL INVESTIGATION* 15, 15 (2002) (“The HIV responsible for causing AIDS in much of West Africa is referred to as HIV-2; the HIV that causes AIDS throughout the rest of the world is referred to as HIV-1.”).

258. See *id.*

259. *Id.*; M. Tersmette, *The Role of HIV Variability in the Pathogenesis of AIDS*, in *IMMUNOLOGY OF HIV INFECTION* 31, 31–32 (A.G. Bird ed. 1992).

The term “retrovirus”<sup>260</sup> refers to a virus family whose genetic information is encoded in RNA rather than DNA, but that inserts a DNA copy of its genome into a host cell in order to replicate.<sup>261</sup> Once integrated into the target cell’s chromosomes, the virus uses the host cell’s own genetic material to replicate itself.<sup>262</sup> Newly created copies of the virus are released and infect other cells in turn.<sup>263</sup> HIV belongs to a subgroup of the retrovirus family known as lentiviruses.<sup>264</sup> Lentiviruses derive their name from the Latin for “slow,” and are characterized by a long incubation period.<sup>265</sup> HIV-1 and HIV-2 are the only known human lentiviruses.<sup>266</sup>

### 1. The Stages of HIV Infection

The natural history of HIV infection proceeds through three well-defined phases: primary infection; an intermediate phase of clinical latency; and the end stage, clinical illness.<sup>267</sup> The primary infection phase may last from a few days to several weeks and can be clinically asymptomatic or characterized by influenza-like symptoms such as a fever, accompanied by a rash and swollen lymph glands.<sup>268</sup> At this stage, HIV replicates actively and kills cells of the immune system.<sup>269</sup> This viral assault is met by a highly targeted and

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260. The retrovirus family has three subgroups; HIV belongs to a subgroup of the retrovirus family known as lentiviruses. Tersmette, *supra* note 259, at 31–32.

261. M. CICHOKI, *LIVING WITH HIV: A PATIENT’S GUIDE* 34 (2009); LAUREN SOMPAYRAC, *HOW PATHOGENIC VIRUSES WORK* 59 (2002); Tang et al., *supra* note 58, at 135 (“The defining feature of a retrovirus is its ability to convert its RNA genome to a DNA intermediate . . . . A subsequent reaction . . . results in the integration of this DNA molecule into host chromosome DNA, where it resides as a provirus.”).

262. SOMPAYRAC, *supra* note 261, at 60.

263. Levine, *supra* note 19, at 428.

264. Tang et al., *supra* note 58, at 135 (describing HIV as the “prototype lentivirus”).

265. Narayan & Clements, *supra* note 37, at 1618.

266. A.S. Fauci & R.C. Desrosiers, *Pathogenesis of HIV and SIV*, in *RETROVIRUSES* 587, 587 (J.M. Coffin et al. eds., 1997), available at <http://www.ncbi.nlm.nih.gov/books/NBK19359/>.

267. Narayan & Clements, *supra* note 37, at 1617–18.

268. Nowak & McMichael, *supra* note 38, at 58.

269. *Id.*

powerful defensive immune response that initially contains the virus.<sup>270</sup>

Following primary infection, an intermediate phase of clinical latency may last several years without clinical symptoms.<sup>271</sup> The virus is active during this period and continues to replicate, but at a reduced rate.<sup>272</sup> In the early stages of the phase, the patient is asymptomatic, but can infect others with the virus.<sup>273</sup> Eventually, the balance of power between HIV replication and the immune response of the infected person shifts and HIV gains the upper hand.<sup>274</sup> HIV systematically weakens and ultimately defeats the immune system, paving the way for AIDS-defining opportunistic infections.<sup>275</sup>

## 2. How HIV Defeats the Immune Response

HIV has several unique features that allow it to evade and also attack, weaken, and ultimately destroy the immune system.<sup>276</sup> A high mutation rate<sup>277</sup> and rapid replication frequency<sup>278</sup> combine to make HIV the most variable human virus known.<sup>279</sup> The result is a powerful weapon against the immune response.<sup>280</sup>

270. *Id.*

271. *Id.*

272. *Id.*

273. *See id.*

274. *See id.*

275. Nowak & McMichael, *supra* note 38, at 58; Robin A. Weiss, *How Does HIV Cause AIDS?*, 260 *SCIENCE* 1273, 1273–74 (1993) (explaining that AIDS “is the end-stage disease of human immunodeficiency virus (HIV) infection” and that “various opportunistic infections” result).

276. *See supra* Part I.A; *see also* Mario Stevenson, *HIV-1 Pathogenesis*, 9 *NATURE MED.* 853, 853 (2003); B. Matija Peterlin & Didier Trono, *Hide, Shield and Strike Back: How HIV-Infected Cells Avoid Immune Eradication*, 3 *NATURE REV. IMMUNOLOGY* 97 (2003).

277. *See supra* note 40 and accompanying text; *see also* Letvin, *supra* note 257, at 15 (“[T]he inaccurate enzymatic machinery of this virus’s replication results in ongoing production of mutant virions.”).

278. *See supra* text accompanying notes 45–47; *see also* Stevenson, *supra* note 276, at 853 (“[V]iral replication is rapid and efficient.”).

279. *See supra* text accompanying notes 44, 47.

280. Johnston & Fauci, *supra* note 37, at 888 (“The extraordinary mutability and resulting genetic diversity of HIV, which is substantially more than that of other human viruses, also present a formidable obstacle to immune control.”); Nowak & McMichael, *supra* note 38, at 59 (“[The high



## i. Replication

The pathogenesis of HIV is a direct consequence of its rapid replication rate.<sup>281</sup> Once HIV enters the bloodstream of an infected person, it attaches to specialized cells of the immune system, such as the T-cell (CD4<sup>+</sup> lymphocyte).<sup>282</sup> The virus replicates inside the host immune cell, and eventually the sheer volume of viral replication overwhelms and kills the cell by monopolizing the cell's resources and disrupting the cell membrane.<sup>283</sup> When the expired host cell bursts open, newly created copies of the virus are scattered back into the blood stream to continue the process of infection and replication.<sup>284</sup> As a result of the systematic destruction of immune cells, the

genetic variability] increases the probability that some genetic change will give rise to an advantageous trait."); J. Zhuang et al., *Human Immunodeficiency Virus Type 1 Recombination: Rate, Fidelity, and Putative Hot Spots*, 76 J. VIROLOGY 11,273, 11,273 (2002) ("The . . . [HIV-1] genome in nature is characterized by its rapid evolution, which permits the virus to escape immune surveillance and to develop drug-resistant variants as well as making it difficult to produce an effective vaccine.").

281. John M. Coffin, *HIV Population Dynamics in Vivo: Implications for Genetic Variation, Pathogenesis, and Therapy*, 267 SCIENCE 483, 488 (1995) ("[T]he engine that is driving the [immunodeficiency] process is the constant repeated cycles of virus replication."); Stevenson, *supra* note 276, at 858 ("[V]iral pathogenicity is a consequence of both the direct effects of viral replication on infected cells and its indirect effects on uninfected cells.").

282. The human immune system consists of two basic cell types, B-cells and T-cells. B-cells are responsible for the production of antibodies, while T-cells play a central role in cell-mediated immune response, assist B-cells in producing antibodies, and kill infected cells in the body. See generally Nat'l Inst. of Allergy & Infectious Diseases, *How Vaccines Work*, VACCINES (Apr. 19, 2011), <http://www.niaid.nih.gov/topics/vaccines/understanding/pages/howwork.aspx>. Macrophages are immune cells that phagocytize (engulf and then digest) cellular debris and pathogens, and stimulate lymphocytes and other immune cells to respond to the pathogen. See sources cited *supra* note 51; see also Syed Z. Salahuddin et al., *Human T Lymphotropic Virus Type III Infection and Human Alveolar Macrophages*, 68 BLOOD 281, 281 (1986) ("Because macrophages are relatively long-lived cells capable of close interaction with lymphocytes . . . it is possible that infected macrophages in vivo could propagate viral infection in the hosts by transfer of virus to lymphocytes.").

283. Nowak & McMichael, *supra* note 38, at 58.

284. See *Bragdon v. Abbott*, 524 U.S. 624, 634 (1998) ("HIV is a retrovirus, which means it uses an enzyme to convert its own genetic material into a form indistinguishable from the genetic material of the target cell . . . . Once integrated [into the target cell's chromosomes], the virus can use the cell's own genetic machinery to replicate itself. Additional copies of the virus are released into the body and infect other cells in turn.").

immune response gradually weakens and becomes unable to regenerate or fight off infection.<sup>285</sup>

Viral replication also kills immune cells indirectly by inducing an aberrant reaction of the immune system to infected as well as uninfected bystander cells.<sup>286</sup> When an infected cell's regulatory functions become compromised because of HIV replication, the cell may commit suicide by a process known as programmed cell death, or apoptosis.<sup>287</sup> Uninfected cells in close proximity to HIV-infected cells may expire when they are erroneously identified as infected cells and, consequently, are destroyed by immune cells programmed to eliminate infected cells.<sup>288</sup>

## ii. Mutation

HIV has a high mutation rate.<sup>289</sup> The genetic information of HIV is encoded in RNA, rather than DNA, but the virus

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285. Hermann, *supra* note 18, at 64 (“AIDS is an impairment of the human body’s natural immune system of defense against disease that renders a person vulnerable to infections and various illnesses. The damage to the immune system results primarily from the destruction of certain crucial white blood cells—known as T lymphocytes—as a consequence of the infection with HIV.”); Nowak & McMichael, *supra* note 38, at 58 (“HIV replicates prodigiously and destroys cells of the immune system each day. But this growth is met . . . by a vigorous defensive response that [prevents] the virus from multiplying out of control. Commonly, however, the balance of power eventually shifts so that HIV gains the upper hand and causes the severe immune impairment that defines full-blown AIDS.”).

286. Stevenson, *supra* note 276, at 853 (“HIV-1 infection indirectly impairs cell function, perhaps because of an aberrant reaction to the infection by the host’s immune response.”).

287. Marie-Lise Gougeon, *Apoptosis as an HIV Strategy To Escape Immune Attack*, 3 NATURE REV. IMMUNOLOGY 392, 392 (2003) (“[I]ncreasing evidence points to HIV-driven lymphocyte apoptosis as an important contributor to the destruction of the immune system.”); Weiss, *supra* note 275, at 1274 (“HIV infection leads to early priming of lymphocytes for suicide . . . in culture. [Some scholars] argue that if apoptosis also occurs in vivo to a higher degree than normal, it could account for helper T cell depletion.”).

288. Gougeon, *supra* note 287, at 394 (“The mechanisms that are involved in HIV-associated apoptosis of lymphocytes include . . . death of bystander cells by pro-apoptotic virus proteins that are released by infected cells.”); Stevenson, *supra* note 276, at 858 (“[U]ninfected cells can also undergo apoptosis, suggesting that HIV-1 replication may be causing collateral damage.”).

289. See *supra* text accompanying notes 40–44; see also Letvin, *supra* note 257, at 15 (“Genetic diversity is also continuously generated in the course of

must insert a DNA copy of its genome into a host cell in order to replicate.<sup>290</sup> This process requires the action of the reverse transcriptase enzyme, which copies the viral RNA genome into a DNA sequence.<sup>291</sup> The virus mutates during this process because reverse transcriptase is error-prone and has no editing mechanism for transcriptional errors.<sup>292</sup> HIV reverse transcriptase is one of the most error-prone reverse transcriptase enzymes known.<sup>293</sup>

This high mutation rate helps HIV defeat the immune response.<sup>294</sup> When a disease-causing pathogen such as HIV enters the body, the immune response is activated to produce antibodies.<sup>295</sup> Antibodies are proteins that circulate in the blood of the infected person and bind to the invading pathogen by locking onto its surface.<sup>296</sup> The end of the antibody that binds with a pathogen varies to match the pathogen it is designed to recognize.<sup>297</sup> A pathogen marked with an antibody signals to the immune system that the pathogen must be eliminated, and

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an HIV infection in a single infected individual, as the inaccurate enzymatic machinery of this virus's replication results in ongoing production of mutant virions.”).

290. See sources cited *supra* note 261.

291. Tang et al., *supra* note 58, at 135 (“The defining feature of a retrovirus is its ability to convert its RNA genome to a DNA intermediate through the virally encoded reverse transcriptase.”).

292. Zhuang et al., *supra* note 280, at 11,273 (“[M]utations . . . can be introduced into the genome during viral DNA synthesis by the viral reverse transcriptase . . . owing in part to its lack of DNA proofreading activity.”); see also Roberts et al., *supra* note 43, at 1171 (noting that reverse transcriptase has no proof reading ability).

293. Schader & Wainberg, *supra* note 44.

294. Weiss, *supra* note 275, at 1277 (“HIV develops sequential escape mutants to keep one step ahead of the immune response . . .”).

295. See Julie Overbaugh & Lynn Morris, *The Antibody Response Against HIV-1*, 2 CSH PERSP. MED. 1, 2–3 (2012) (“B cell responses to HIV-1 infection first develop within ~1 week . . . as antigen-antibody complexes. This phase is followed by circulating . . . antibodies a few days later . . .”).

296. See *id.* at 1–10.

297. See generally Nowak & McMichael, *supra* note 38, at 58 (“Activated B lymphocytes secrete antibodies that recognize specific peptides on the viral surface. The antibodies mark free viral particles, those not yet sequestered in cells, for destruction.”); Peterlin & Trono, *supra* note 276, at 98–102 (discussing the antibody binding process).

the immune response then induces mechanisms that kill the pathogen.<sup>298</sup>

The mutation process disguises the virus by modifying its outer envelope protein, which is the key target for neutralizing antibodies.<sup>299</sup> By the time the body produces antibodies directed at the outer HIV envelope protein, the protein has mutated to a different form that the antibodies do not recognize.<sup>300</sup> New antibodies are produced in response, but new mutations repeatedly enable the virus to stay one step ahead of the immune response.<sup>301</sup> The virus effectively becomes a moving target by constantly changing its disguise, so that the antibodies never learn to recognize the latest version of the virus.<sup>302</sup>

A mutant virus that has escaped surveillance continues to replicate.<sup>303</sup> Once it infects a new cell, it mutates again.<sup>304</sup>

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298. Peterlin & Trono, *supra* note 276, at 102 (“Normally, cells that are infected by a virus are recognized and eliminated by the immune system. This is due mainly to the surface presentation of viral peptides . . . which allows for recognition and killing by virus-specific CTLs.”).

299. Johnston & Fauci, *supra* note 37, at 888 (“By the time the body produces antibodies directed at the outer HIV envelope protein, which is the key target for neutralizing antibodies, the protein has mutated in such a way that the circulating antibodies cannot neutralize it. New antibodies are induced, but new mutations repeatedly enable the virus to evade the immune system.”); Peterlin & Trono, *supra* note 276, at 102 (discussing how HIV interferes with the ability of cells to send antigen markers to the cell surface for recognition by the immune system).

300. Peterlin & Trono, *supra* note 276, at 97 (explaining how HIV evades the immune system “through mutations that alter recognition of the virus by virus-specific antibodies”).

301. Margaret I. Johnston & Anthony S. Fauci, *An HIV Vaccine—Evolving Concepts* 356 *NEW ENG. J. MED.* 2073, 2074 (“The effectiveness of the antibody response is subsequently thwarted by rapid genetic changes in the envelope protein that allow the virus to escape recognition by antibodies in circulation at that time.”); Peterlin & Trono, *supra* note 276, at 102 (discussing how HIV interferes with the ability of cells to send antigen markers to the cell surface for recognition by the immune system).

302. See generally John R. Mascola & David C. Montefiori, *HIV-1: Nature’s Master of Disguise*, 9 *NATURE MED.* 393 (2003).

303. *Id.* (“This [constant mutation] allows the virus to chronically replicate and to eventually wear down the body’s defenses by destroying the very cells necessary to coordinate an effective immune response.”).

304. See *SOMPAYRAC, supra* note 261, at 70; Nowak & McMichael, *supra* note 38, at 60 (estimating that mutations via reverse transcriptase occur at least once each time HIV integrates into a host cell genome).

Eventually, the genetic diversity of the viral population in an infected person overwhelms the immune system, and the threshold to full-blown AIDS is crossed.<sup>305</sup>

### iii. Genetic Variability

A high mutation rate and rapid replication frequency combine to make HIV the most variable human virus known.<sup>306</sup> The resulting genetic variability plays a central role in the ultimate defeat of the immune response.<sup>307</sup> It increases the likelihood that highly virulent and drug-resistant mutants may emerge in the viral population.<sup>308</sup> Drug-resistant mutants may be capable of evading the effects of anti-retroviral therapies and vaccines,<sup>309</sup> and virulent mutants typically accelerate the pace of AIDS-defining diseases.<sup>310</sup>

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305. Nowak & McMichael, *supra* note 38, at 62–65 (“Yet there comes a point, usually after many years, when there are too many HIV variants. When that threshold is crossed, the immune system becomes incapable of controlling the virus . . . . [T]he variability befuddles the patient’s immune system, which becomes less efficient and therefore enables the viral population to grow and to kill increasing numbers of helper cells.”).

306. *Id.* at 60; *see also* Krista Delviks-Frankenberry et al., *Mechanisms and Factors that Influence High Frequency Retroviral Recombinations*, 3 VIRUSES 1650, 1668 (2011) (“Retroviruses have one of the highest recombination rates among all viruses. Frequent recombination reassorts viral sequences to generate variants containing different combinations of polymorphic sequences, thereby generating high diversity in the viral population, which improve the odds that some variants in the population can survive the ever changing selection pressure in the environment . . . .”).

307. *See supra* note 302 and accompanying text.

308. *See* Nowak & McMichael, *supra* note 38, at 65.

309. Delviks-Frankenberry et al., *supra* note 306, at 1668 (“[Genetic variability through] recombination can also assort existing drug resistant mutations to generate a more resistant virus or a variant that is resistant to more than one drug.”); Letvin, *supra* note 257, at 15 (“HIV offers a uniquely difficult target for vaccine development . . . . [A]n antibody that can neutralize one HIV isolate may fail to neutralize another from the same individual. Such an extraordinary degree of genetic diversity among HIV isolates immeasurably complicates the process of HIV vaccine development.”); Louis M. Mansky, *Retrovirus Mutation Rates and Their Role in Genetic Variation*, 79 J. GEN. VIROLOGY 1337, 1337 (1998) (“[The genetic variation of HIV] has important implications not only on virus diversity and evolution, but also on virulence, pathogenesis and the ability to develop effective antiviral drugs and vaccines.”).

310. *See, e.g.*, Delviks-Frankenberry et al., *supra* note 306, at 1668 (stating that high diversity in the viral population “improve[s] the odds that some

## iv. Latency

HIV defends itself against the immune response by creating “cellular hideouts” and establishing proviral latency.<sup>311</sup> It establishes latency in some cells within days to weeks of infection, where it persists while shielded from the immune response.<sup>312</sup> CD4+ T-cells are the major cells that carry latent HIV,<sup>313</sup> but HIV can also be sequestered in macrophages<sup>314</sup> as well as anatomical reservoirs such as the

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variants in the population can survive the ever changing selection pressure in the environment”); Weiss, *supra* note 275, at 1276–67.

311. Sharon R. Lewin et al., *Finding a Cure for HIV: Will It Ever Be Achievable?*, 14 J. INT’L AIDS SOC’Y 1, 1 (2011) (“In latent HIV infection, the virus is able to integrate into the host cell genome, but does not proceed to active replication. As a consequence, antiviral agents, as well as the immune system, are unable to eliminate these long-lived, latently infected cells.”); Susan Moir et al., *Pathogenic Mechanisms of HIV Disease*, 6 ANNUAL REV. PATHOLOGY: MECHANISMS DISEASE 223, 228 (2010) (“The rapid establishment and persistence of various HIV reservoirs remain two of the most important impediments to achieving complete eradication of the virus in infected individuals . . .”); Peterlin & Trono, *supra* note 276, at 97 (“Not only does [HIV] mutate rapidly and make its surface components difficult to access by neutralizing antibodies, but it also creates cellular hideouts, establishes proviral latency, remove cell-surface receptors and destroys immune effectors to escape eradication.”).

312. Joel N. Blankson et al., *The Challenge of Viral Reservoirs in HIV-1 Infection*, 53 ANNUAL REV. MED. 557, 563 (2002) (“The persistence of [HIV] infection through the long latency period of AIDS . . . demonstrates the ability of HIV to avoid being eliminated by the host immune response.”); Johnston & Fauci, *supra* note 37, at 888 (“Because latency is established very early—within days to weeks after infection—the window of opportunity wherein HIV remains vulnerable to eradication through the immune response is very short.”); Vincent Piguët & Didier Trono, *Living in Oblivion: HIV Immune Evasion*, 13 SEMINARS IMMUNOLOGY 51, 52 (2001) (“HIV can apparently hide from cytotoxic T lymphocytes in at least two sites: the glial cell of the central nervous system . . . and the resting T lymphocyte.”); H.C. Slavin, *An Update on HIV/AIDS*, 127 J. AM. DENTAL ASS’N 1401, 1403 (1996) (“If living conditions become too hostile for the virus, HIV can go into hiding. Macrophages . . . represent a good hiding place and serve as a reservoir because they can harbor large quantities of HIV.”).

313. Alessandro Marcello, *Latency: The Hidden HIV Challenge*, 3 RETROVIROLOGY, no. 7, 2006, at 1 (describing resting memory CD4 T-cells as “the most prominent reservoir of transcriptionally silent provirus”).

314. Amit Kumar et al., *HIV-1 Latency in Monocytes/Macrophages*, 6 VIRUSES 1837 (2014).

brain and gastrointestinal tract.<sup>315</sup> Latent viruses may later be reactivated.<sup>316</sup> Latency during primary infection is unique to HIV.<sup>317</sup>

In summary, HIV defeats the immune response with unusual features that endow the virus with defensive strategies to evade the human immune response, as well as offensive strategies by which it weakens and ultimately destroys the immune system whose very function is to defend against it.

### 3. How Does HIV Cause AIDS?

HIV does not directly kill an infected individual—it weakens and eventually destroys the immune system of an infected person.<sup>318</sup> With little or no functioning immune system, opportunistic infectious organisms invade the body and latent infections are re-activated, causing diseases such as Kaposi's sarcoma, lymphoma and rare forms of pneumonia.<sup>319</sup> These diseases are referred to as "AIDS-defining infections"

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315. See Lewin et al., *supra* note 311, at 1 ("HIV can be sequestered in anatomical reservoirs, such as the brain, gastrointestinal tract and genitourinary tract.").

316. Johnston & Fauci, *supra* note 301, at 2076 ("[L]atently infected cells become activated, [and] produce virions that infect new cells before the initial cells die or are cleared.").

317. *Id.* at 2074 ("This aspect of HIV infection [latency] puts it in sharp contrast with almost all other viral infections, in which the initial rounds of viral replication do not establish a permanent reservoir of infection.").

318. Ashley T. Hasse, *Pathogenesis of Lentivirus Infections*, 322 NATURE 130, 133 (1986) ("Immunodeficiency is the hallmark of AIDS . . ."); Hermann, *supra* note 18, at 64 ("AIDS is an impairment of the human body's natural immune system of defense against disease that renders a person vulnerable to infections and various illnesses. The damage to the immune system [is] a consequence of the infection with HIV."); Nowak & McMichael, *supra* note 38, at 58 ("HIV replicates prodigiously and destroys cells of the immune system each day . . . [HIV] causes the severe immune impairment that defines full-blown AIDS.").

319. W. Kempf & V. Adams, *Viruses in the Pathogenesis of Kaposi's Sarcoma—A Review*, 58 BIOCHEMICAL & MOLECULAR MED. 1, 2 (1996) ("Kaposi's sarcoma remains one of the hallmarks of AIDS."); Mike May, *Playing Hide and Seek the Deadly Way*, 18 SCIENTIST, Feb. 2, 2004, at 16, 16 ("The person infected with HIV usually dies from . . . opportunistic infections."); Levine, *supra* note 19, at 424–27 (discussing how a microbe, which does not cause illness in the average patient, would cause pneumonia in an individual with an immunodeficiency, serving as a basis for an AIDS diagnosis).

because individuals with fully functioning immune systems are rarely susceptible to them.<sup>320</sup> When a person with an HIV-weakened immune system is found to have one or more of these opportunistic infections or has a T-cell count below a critical level (200 cells per milliliter of blood), the person is diagnosed as having AIDS.<sup>321</sup> The natural course of HIV is “relentlessly progressive,” and a spontaneous recovery is virtually unheard of.<sup>322</sup> Most untreated people infected with HIV eventually develop AIDS, for which there is no known cure.<sup>323</sup>

#### B. FORESEEABILITY OF HIV/AIDS AS A BLOOD-BORNE RISK

Blood transfusion is a very effective transmission mechanism for HIV.<sup>324</sup> Predictably, HIV-related injuries caused by negligent ordering or administration of transfusions have triggered numerous lawsuits.<sup>325</sup> In litigation arising from HIV-

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320. *Doe v. Mut. of Omaha Ins. Co.*, 179 F.3d 557, 561 (7th Cir. 1999) (“The principal opportunistic diseases of AIDS, such as Kaposi’s sarcoma, *Pneumocystis carinii* pneumonia, [and others], are rarely encountered among people who are not infected by HIV—so rarely as to be described frequently as ‘AIDS-defining opportunistic infections.’”); Hermann, *supra* note 18, at 63–64 (“Persons with AIDS are susceptible to contracting a number of diseases and opportunistic disorders caused by organisms commonly found in the environment but which are not harmful to a person whose immune system is functioning properly.”).

321. Levine, *supra* note 19, at 424–26 (defining AIDS by the presence of opportunistic infections); Nowak & McMichael, *supra* note 38, at 58 (“Patients are generally said to cross the line to AIDS when the helper cell count, which in healthy individuals measures 1,000 cells per microliter of blood, falls below 200.”).

322. D. R. Burton et al., *HIV Vaccine Design and the Neutralizing Antibody Problem*, 5 NAT. IMMUNOLOGY 233, 233–36 (2004) (explaining the difficulty of solving the neutralizing antibody problem); Johnston & Fauci, *supra* note 301, at 2074 (“HIV infection . . . as a rule is relentlessly progressive, even though only a small fraction of susceptible cells are infected at any point in time. Virtually no person clears HIV infection.”).

323. Levine, *supra* note 19, at 430 (“By 1986 and 1987 it became apparent that HIV infection was, in fact, a continuum of disease and that given enough time, the asymptomatic infected individuals would eventually go on to develop . . . full-blown AIDS.”); Simon et al., *supra* note 256, at 499 (noting that a cure and vaccine remain elusive).

324. Herbert A. Perkins et al., *Risk of AIDS for Recipients of Blood Components from Donors Who Subsequently Developed AIDS*, 70 BLOOD 1604, 1604–10 (1987) (estimating the probability of infection in an individual who has been transfused with the blood of an HIV-positive donor is in excess of ninety percent).

325. See *supra* note 18 and accompanying text.



tainted blood transfusions during the early 1980s, a crucial issue before the courts was the defendants' state of knowledge of the risk of HIV/AIDS.<sup>326</sup> Authorities differ on the point in time when the medical community had reached a consensus that HIV was a blood-borne risk. According to some, such a consensus had not been reached until 1984, while others believe it had been known as early as 1981.<sup>327</sup>

During the early stages of the epidemic while the risk was ill understood, defendants escaped liability based on absence of foreseeability.<sup>328</sup> In *Quinones v. Long Island College*

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326. Joseph Kelly, *The Liability of Blood Banks and Manufacturers of Clotting Products to Recipients of HIV-Infected Blood: A Comparison of the Law and Reaction in the United States, Canada, Great Britain, Ireland, and Australia*, 27 J. MARSHALL L. REV. 465, 468 (1995) ("Some of the crucial issues for litigation arising from transfusions between 1981 and March 1985 are: the defendants' knowledge about HIV/AIDS; when the defendants became aware of the risk of HIV/AIDS transmission through blood transfusions; and what the industry could have done to minimize HIV/AIDS transmission.").

327. See *Snyder v. Mekhjian*, 582 A.2d 307, 311 (N.J. Super. Ct. App. Div. 1990) ("By January 12, 1984 . . . the national medical community officially recognized . . . that AIDS was transmissible through blood and blood products.") (internal quotation marks omitted); LARA KHOURY, *UNCERTAIN CAUSATION IN MEDICAL LIABILITY* 186 (2006) ("The risk of transmission of HIV by blood had been known internationally since June 1981, and as early as October 1984, the efficiency of heating techniques for treating blood was recognized in the United States."); LUC MONTAGNIER, *VIRUS 9* (Steven Sartarelli trans., 1st ed. 1999) ("[AIDS] was identified in 1981, and two years later the causal agent was isolated for the first time."); Alinka F. Baker, *Liability Without Fault and the AIDS Plague Compel a New Approach to Cases of Transfusion-Transmitted Disease*, 61 U. COLO. L. REV. 81, 81 (1990) ("Some authorities say that the medical community had not reached a consensus that AIDS (Acquired Immune Deficiency Syndrome) was blood-borne until 1984, whereas others say that there was substantial evidence of that fact in 1982."); Hermann, *supra* note 18, at 78 ("By the end of 1982, evidence had developed that AIDS was associated with blood transfusions and with the antihemophile factor."); Mielke, *supra* note 37, at 3 ("Throughout 1983, the cause of AIDS remained unknown."); Schader & Wainberg, *supra* note 44, at 91 ("It was later that year [1983] that Luc Montangier and Françoise Barre-Sinoussi isolated a suspected retrovirus which was later confirmed to be the causative agent of AIDS by Robert Gallo in 1984.").

328. See, e.g., *Hicks v. City of New York*, 204 A.D.2d 516, 516 (N.Y. App. Div. 1994) ("[A]t that time it was not foreseeable that the blood might have been tainted by the virus which causes Acquired Immune Deficiency Syndrome . . ."); *Bieling v. Battle*, 434 S.E.2d 719, 722 (Ga. Ct. App. 1993) (granting the defendants' motion for summary judgment, holding that the plaintiff's contraction of AIDS was not a foreseeable result of the blood transfusion, because "the general medical community could not have

*Hospital*,<sup>329</sup> the Appellate Division of the Supreme Court of New York held that:

Even if it is assumed that negligent medical treatment by the defendant hospital resulted in the decedent's need for a series of blood transfusions in 1980, we are in agreement with the trial court that the risk of receiving blood tainted by the Human Immunodeficiency Virus which causes the Acquired Immune Deficiency Syndrome (AIDS) was not a legally foreseeable risk at the time in question.<sup>330</sup>

In *Fox v. Estrada*,<sup>331</sup> Carol H. Fox underwent gynecological surgery at Memorial City Medical Center in early 1982, where she was transfused with two units of blood.<sup>332</sup> In 1990, she became ill and was hospitalized.<sup>333</sup> While hospitalized, she and her daughter tested positive for HIV.<sup>334</sup> Carol Fox died in 1991 of AIDS-related complications, and the couple's daughter died five years later.<sup>335</sup> Carol Fox's husband brought a medical malpractice suit, as representative of the deceased, against appellee, Dr. William Estrada.<sup>336</sup> The trial court granted summary judgment in favor of Dr. Estrada.<sup>337</sup>

The plaintiff appealed the court's ruling that the deceased's HIV/AIDS was not a foreseeable consequence of the negligently ordered transfusion.<sup>338</sup> The defendant responded that the specific risk of HIV/AIDS was unforeseeable.<sup>339</sup> The plaintiff countered that the defendant's liability should depend on the foreseeability of the general risk of transmission of blood-borne pathogens, not the specific risk of HIV/AIDS.<sup>340</sup>

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anticipated in 1982 that AIDS was a natural, foreseeable risk associated with a blood transfusion as such connection had not been made at that time and was not a part of general medical knowledge.").

329. *Quinones v. Long Island Coll. Hosp.*, 200 A.D.2d 726 (N.Y. App. Div. 1994).

330. *See id.*

331. *See Fox v. Estrada*, No. 14-97-00821-CV, 1998 WL 831666, at \*1 (Tex. App. Dec. 3, 1998).

332. *Id.*

333. *Id.*

334. *Id.*

335. *Id.*

336. *Id.*

337. *Id.*

338. *Id.*

339. *Id.* at \*2.

340. *Id.*

The former characterization would be valid if HIV were a mere variant of known blood-borne pathogens.<sup>341</sup>

The appellate court agreed with the defendant.<sup>342</sup> It found that at the time of the decedent's transfusion the medical profession was unaware of HIV/AIDS as a blood-borne risk.<sup>343</sup> It held further that HIV/AIDS is distinct from known blood-borne diseases such as hepatitis, Epstein Barr virus, and malaria because of its unique behavior inside the body of an infected person.<sup>344</sup> Foreseeability should therefore be based on the specific risk of HIV/AIDS and not the general risk of blood-borne diseases.<sup>345</sup> The risk so characterized was unforeseeable and the defendant escaped liability.<sup>346</sup>

Eventually, when the medical community had achieved a better understanding of the nature of HIV and the mechanisms by which it causes AIDS, courts began to resolve the foreseeability issue in favor of plaintiffs.<sup>347</sup> In *Jeanne v. Hawkes Hospital of Mount Carmel*,<sup>348</sup> Dr. Gerald Drabyn, a plastic surgeon, performed elective breast reduction surgery on the plaintiff, H. Chrystal, in early 1985 at Hawkes Hospital of Mount Carmel.<sup>349</sup> During the procedure, Chrystal was transfused with blood collected by the Red Cross on March 7, 1985 from an unidentified donor who was HIV-positive.<sup>350</sup> The Red Cross represented the blood as safe,<sup>351</sup> and Mount Carmel

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341. *See id.* (discussing how other blood-borne pathogens cannot be compared to HIV because those diseases "do not have the devastating impact" of HIV); *see also* Grady, *supra* note 22, at 127 ("The basic purpose of reasonable-foresight proximate cause is to cut off liability for . . . accidents that are not mere variants of those that were ex ante foreseeable.").

342. *Fox*, 1998 WL 831666, at \*4.

343. *See id.* at \*2 ("The medical community did not reach a consensus that AIDS was in fact transmissible by blood until 1983.").

344. *Id.* at \*3.

345. *Id.*

346. *Id.* at \*4.

347. *See, e.g.*, *Snyder v. Am. Ass'n of Blood Banks*, 676 A.2d 1036, 1048 (N.J. 1996) (finding that the risk that patients may contract AIDS via contaminated blood transfusions is foreseeable, and that the defendant owed a duty to use reasonable precautions to avoid such infections).

348. *Jeanne v. Hawkes Hosp. of Mt. Carmel*, 598 N.E.2d 1174 (Ohio Ct. App. 1991).

349. *Id.* at 1175.

350. *Id.* at 1176.

351. *Id.*

conducted no further tests for hepatitis, venereal disease, or HIV.<sup>352</sup> It was later determined that Chrystal had been infected with HIV as a result of her blood transfusion.<sup>353</sup>

Chrystal filed a complaint against Mount Carmel and the Red Cross, alleging medical malpractice and negligence.<sup>354</sup> The jury returned a verdict in favor of the plaintiff, and awarded damages of \$12 million.<sup>355</sup> The defendants appealed, asserting that liability should be denied based on absence of foreseeability.<sup>356</sup> The appellate court confirmed the verdict for the plaintiff, finding that “it was foreseeable that if a person received a blood transfusion, one of the possible consequences of the transfusion was that the person could get AIDS.”<sup>357</sup>

### C. ANALYSIS

This section presents an analysis of the foreseeability of HIV/AIDS as a blood-borne risk. The risk may be described as infection by HIV and contraction of one or more opportunistic diseases that define AIDS. The AIDS syndrome is defined by a diagnosis of one or more of the following diseases: “(1) opportunistic infection (2) Kaposi’s sarcoma (3) high-grade B-cell lymphoma (4) AIDS-dementia/encephalopathy syndrome (5) wasting syndrome . . . .”<sup>358</sup>

Common AIDS-defining opportunistic infections and diseases such as cytomegalovirus infection, lymphomas including non-Hodgkin’s lymphoma, human T-lymphotropic virus infection and toxoplasmosis were known and foreseeable blood-borne risks before the AIDS epidemic.<sup>359</sup> This fact

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352. *Id.*

353. *Id.*

354. *Id.*

355. *Id.*

356. *See id.* at 1177.

357. *Id.* at 1178.

358. *See Levine, supra* note 19, at 424.

359. *See sources cited supra* note 19; *see also Kempf & Adams, supra* note 319, at 2 (noting that several blood-borne viruses are etiologic agents for Kaposi’s sarcoma, including cytomegalovirus and the herpes virus KSHV/HHV-8); S. Gerald Sandler et al., *Retroviral Infections Transmitted by Blood Transfusion*, 63 *YALE J. BIOLOGY & MED.* 353, 354, 356 (1990) (stating that human T-lymphotropic virus is a blood-borne risk); Siegfried Seidl & Peter Kühnl, *Transmissions of Diseases by Blood Transfusion*, 11 *WORLD J. SURGERY* 30, 31–33 (1987) (discussing diseases transmitted through blood

appears to suggest that AIDS was a foreseeable blood-borne risk even during the early stages of the epidemic. The general common law rule is that the type of injury must be foreseeable, rather than its extent or manner of occurrence.<sup>360</sup> Courts in early cases such as *Estrada* and *Quinones* nevertheless found that AIDS was an unforeseeable risk of negligently ordered or administered blood transfusions.<sup>361</sup> The analysis in this Part shows that the *Estrada* and *Quinones* decisions are consistent with the Reasonable Ignorance of the Relationship doctrine of proximate cause. Although AIDS-defining diseases were foreseeable blood-borne risks even before the AIDS epidemic, the systematic relationship between blood transfusions and AIDS was (1) unknown to the medical profession during the early stages of the epidemic, and (2) not a mere variant of what was known and foreseeable.

The foreseeability issue in *Doughty v. Turner*<sup>362</sup> turns on analogous facts. In *Doughty*, the type of harm suffered by the plaintiff (burning due to splashing of hot molten liquid) was a foreseeable consequence of the defendant's reckless handling of the liquid, yet the defendant escaped liability.<sup>363</sup> The systematic relationship between the defendant's misconduct and the plaintiff's harm (splashing due to *obscure chemical reaction*) was unknown to the defendant, as well as materially

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transfusions, including cytomegalovirus and T-lymphotrophic virus infections); Gary E. Tegtmeier, *Transfusion-Acquired Cytomegalovirus Infection*, in BLOOD SAFETY & SURVEILLANCE 315 (Jeanne V. Linden & Celso Bianco eds., 2001) (discussing the risk of spreading cytomegalovirus through blood transfusions). The Epstein-Barr virus (EBV) can be transmitted by blood transfusion and causes AIDS-defining diseases, including certain types of lymphoma. See generally G. Henle & W. Henle, *The Virus as the Etiologic Agent of Infectious Mononucleosis*, in THE EPSTEIN-BARR VIRUS 297, 297-307 (M. A. Epstein et al. eds., 1979) (discussing foreseeable blood-borne risks in the 1960s and 1970s).

360. Intervening events between the defendant's wrongdoing and the plaintiff's harm, however complex or bizarre, do not deny foreseeability as long as there is no intervening tort or crime, and as long as the ultimate harm is systematically related to the defendant's wrongdoing. See *supra* note 20 and accompanying text; *supra* Part III.

361. Fox v. Estrada, No. 14-97-00821-CV, 1998 WL 831666, at \*1 (Tex. App. Dec. 3, 1998); Quinones v. Long Island Coll. Hosp., 200 A.D.2d 726 (N.Y. App. Div. 1994).

362. Doughty v. Turner Mfg. Co., [1964] 1 Q.B. 518, 518 (C.A. 1963).

363. *Id.* at 518.

different from what was known and foreseeable (splashing due to *mechanical action*).<sup>364</sup>

The analysis of the foreseeability of HIV/AIDS as blood-borne risk focuses on the following issues:

1. A definition of the systematic relationship between medical malpractice and HIV/AIDS that faithfully translates the common law concept into medical science.
2. Whether defendants were reasonably ignorant of the systematic relationship.
3. If defendants were reasonably ignorant, whether the novel and unexpected element in the systematic relationship was a mere variant of what was known and foreseeable.
4. The stage of the AIDS epidemic during which the risk became legally foreseeable.

#### 1. Defining “Systematic Relationship”

The systematic relationship between a medical event and a disease is defined by the *etiology* and *pathogenesis* of the disease. The etiology of a disease is the cause or set of causes of the disease.<sup>365</sup> The pathogenesis is the mechanism by which an etiologic agent produces the disease.<sup>366</sup> For instance, the etiology of lung cancer includes carcinogens such as tobacco smoke.<sup>367</sup> The pathogenesis of lung cancer includes mechanisms such as the interaction of carcinogens with human DNA to cause genetic changes that result in lung cancer.<sup>368</sup> Thus, lung cancer is a foreseeable consequence of tobacco smoke because of medical evidence that tobacco smoke contains

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364. *Id.* (“[I]t would be quite unrealistic to describe this accident as a variant of the perils from splashing.”).

365. SLOANE, *supra* note 25, at 268.

366. Fields, *supra* note 27, at 70; SLOANE, *supra* note 25, at 535 (“[Pathogenesis is] the cellular events and reactions and other pathologic mechanisms occurring in the development of disease.”).

367. *See* Hecht, *supra* note 14, at 1194.

368. *Id.*

an etiologic agent that initiates the pathogenesis of lung cancer.<sup>369</sup>

HIV is the etiologic agent of AIDS.<sup>370</sup> It has unique biological and genetic features that make it an effective agent of the pathogenic mechanisms of AIDS.<sup>371</sup> Transfusion of infected blood transmits the etiologic agent (HIV) that initiates the pathogenesis of AIDS in the body of the recipient of the blood.<sup>372</sup> This establishes a systematic relationship between the risk of HIV/AIDS and medical malpractice such as a negligently administered or ordered blood transfusion. The foreseeability of the specific risk of HIV/AIDS depends on the medical profession's reasonable knowledge of the systematic relationship at the time of alleged malpractice.

## 2. Defendants Were Initially Reasonably Ignorant of the Systematic Relationship

Defendants in early cases such as *Estrada* and *Quinones* were reasonably ignorant of the specific risk of HIV/AIDS because the etiology and pathogenesis of AIDS were unknown to the medical profession at the time.<sup>373</sup> Dr. Luc Montagnier

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369. *Id.*

370. See Francoise Barré-Sinoussi, *HIV As the Cause of AIDS*, 348 LANCET 31, 31 (1996); Letvin, *supra* note 257, at 15 (noting HIV's "etiologic role in AIDS"); Jean L. Marx, *Strong New Candidate for AIDS Agent*, 224 SCIENCE 475, 476-77 (1984) (outlining compelling epidemiological evidence showing a causal relation between HIV and AIDS); Jay A. Nelson et al., *Role of Opportunistic Infections in AIDS*, 4 AIDS 1, 1 (1990) ("The etiologic agent of AIDS is HIV."); Schader & Wainberg, *supra* note 44, at 91 (describing the isolation of HIV, "later confirmed to be the causative agent of AIDS").

371. Weiss, *supra* note 275, at 1273 ("The overwhelming view is that HIV infection is active enough to be directly pathogenic... and that the epidemiological evidence for a causal relation between HIV and AIDS is compelling.")

372. See generally Anthony S. Fauci, *HIV and AIDS: 20 Years of Science*, 9 NATURE MED. 839 (2003) (looking back on the identification of HIV as the etiological agent of aids and how it is spread via blood transfusions).

373. See *Fox v. Estrada*, No. 14-97-00821-CV, 1998 WL 831666, at \*1 (Tex. App. Dec. 3, 1998); *Quinones v. Long Island Coll. Hosp.*, 200 A.D.2d 726 (N.Y. App. Div. 1994); see also MONTAGNIER, *supra* note 327, at 115 (describing AIDS as "an unforeseen epidemic that, indeed, could not have been foreseen within the framework of traditional nosology [the classification of diseases]."); *id.* at 108 (describing AIDS as "an illness [that] has no equal among human diseases."); Walter R. Dowdle, *The Epidemiology of AIDS*, 98 PUB. HEALTH REPS. 308, 308 (1983) ("By now AIDS has become quite well known through

first identified and isolated the human immunodeficiency virus in 1983 at the Pasteur Institute in France.<sup>374</sup> In May 1984, a team led by Dr. Robert Gallo at the National Institutes of Health in the United States confirmed the discovery of the virus and provided virological and epidemiological evidence of the pathogenetic relationship between HIV and AIDS.<sup>375</sup> Dr. Jay Levy of California also independently isolated the virus around the same time.<sup>376</sup> Therefore, the defendants in *Estrada*

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scientific publications and the mass media. But its cause is not known. Its method of transmission is not known. And the ultimate measure of its toll in deaths is not known.”); Robert C. Gallo & Luc Montagnier, *The Discovery of HIV as the Cause of AIDS*, 349 NEW ENG. J. MED. 2283, 2283 (2003) (“[A]t the beginning of the 1980s, we had the essential tools required to search for a retrovirus in this new and menacing disease called AIDS. But why search for a virus, and specifically a retrovirus, in AIDS? The answer was far from obvious in 1982.”); Levine, *supra* note 19, at 424 (“[D]uring the first three to four years of the [AIDS] epidemic, the cause of AIDS was unknown.”); Jean L. Marx, *New Disease Baffles Medical Community*, 217 SCIENCE 618, 618 (1982) (describing AIDS as a “new disease of unknown cause and high virulence”).

374. Fauci, *supra* note 372, at 839 (“In 1983, experimental data indicating an association between a retrovirus and AIDS were published by a research team in France led by Luc Montagnier.”); Gallo & Montagnier, *supra* note 373, at 2284 (“In early 1983, a clear-cut isolate was obtained in Paris . . . from a patient with lymphadenopathy, a syndrome that was considered to be a precursor of AIDS.”); Luc Montagnier, *A History of HIV Discovery*, 298 SCIENCE 1727, 1727–28 (2002).

375. Fauci, *supra* note 372, at 839 (“In 1984, the French group and researchers at the National Institutes of Health, led by Robert C. Gallo, published seminal papers that established, with virological and epidemiological evidence, that the virus now known as HIV was the cause of AIDS.”); Robert C. Gallo et al., *Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS*, 224 SCIENCE 500, 500–01 (1984) (“The increasing evidence of this disease, the types of patients affected, and other epidemiological data suggest the existence of an infectious etiologic agent that can be transmitted . . . [W]e and others have suggested that specific human T-lymphotrophic retroviruses (HTLV) cause AIDS.”); Gallo & Montagnier, *supra* note 373, at 2285 (“[T]he causative relation between HIV and AIDS was accepted by the scientific and medical community in 1984.”); Schader & Wainberg, *supra* note 44, at 91 (“It was [in 1983] that Luc Montagnier and Francoise Barre-Sinoussi isolated a suspect retrovirus which was later confirmed to be the causative agent of AIDS by Robert Gallo in 1984.”).

376. Fauci, *supra* note 372, at 839 (“The virus was also isolated independently by Jay Levy in California from both individuals affected by AIDS and asymptomatic individuals from groups at high risk for AIDS.”); Jay A. Levy et al., *Isolation of Lymphocytopathic Retroviruses from San Francisco Patients with AIDS*, 225 SCIENCE 840, 840 (1984) (describing his discovery of



and *Quinones* properly escaped liability if, in addition to their reasonable ignorance of the risk, the risk was not a mere variant of what was known and foreseeable. The analysis of this issue is considered next.

### 3. Is the Risk of HIV/AIDS a Mere Variant of What Was Foreseeable?

The analysis in this subsection shows that the systematic relationship defining the foreseeability of HIV/AIDS as blood-borne risk is not a mere variant of what was known and foreseeable before the AIDS pandemic.<sup>377</sup> The etiology and pathogenesis of AIDS both differ materially from those of other viral diseases. The etiologic agent (HIV) has a complex genetic structure and novel molecular mechanisms controlling its viral gene expression that distinguish it from other human viruses.<sup>378</sup> The pathogenesis of AIDS is different as well.<sup>379</sup> Professors Narayan and Clements describe the distinctive features of the pathogenetic mechanisms of HIV.

The infection and diseases caused by the human immunodeficiency viruses (HIV) are the antithesis of [the] general concept of pathogenesis of viral disease. The incubation period of months to years that precedes the onset of clinical AIDS, the chronic progressive nature of the disease leading to cachexia and death, the diversity of organ systems affected and the failure of people to recover from the infection emphasize that there is a marked

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HIV, noting that its "biologic properties and prevalence in AIDS patients certainly suggest that [it] could cause AIDS").

377. See Grady, *supra* note 22, at 114 ("The basic purpose of reasonable-foresight proximate cause is to cut off liability for . . . accidents that are not mere variants of those that were ex ante foreseeable.").

378. See Eckstein et al., *supra* note 36, at 1407 ("In addition to the *gag*, *pol* and *env* genes found in all retroviruses, the HIV-1 genome contains six additional genes: *tat*, *rev*, *vif*, *vpr*, *vpu*, and *nef*. These genes confer upon HIV-1 a number of unique abilities, including the capacity to infect non-cycling cells."); Fauci, *supra* note 36, at 617 ("HIV also has at least five additional genes, three of which have known regulatory functions, and the expression of these genes almost certainly has an impact on the pathogenic mechanisms exerted by the virus."); Johnston & Fauci, *supra* note 37, at 888 ("The extraordinary mutability and resulting genetic diversity of HIV, which is substantially more complex than that of other human viruses, also presents a formidable obstacle to immune control."); see also *infra* Part IV.C.3.iii.

379. See Narayan & Clements, *supra* note 37, at 1618.

difference between the mechanisms of pathogenesis of HIV and those of viruses that cause acute disease.<sup>380</sup>

The unique nature of AIDS pathogenesis is directly attributable to features that distinguish the etiologic agent, HIV, from other disease-causing viruses.<sup>381</sup> Three distinctive features of HIV are (1) extreme genetic diversity, (2) a capacity to infect nondividing cells, and (3) a unique genetic structure and molecular mechanisms. These features, discussed below, are material because they play a central role in the unique pathogenesis of AIDS.<sup>382</sup>

#### i. Genetic Diversity

HIV is the “most variable virus known.”<sup>383</sup> Its genetic variability is a powerful weapon against the immune response.<sup>384</sup> It plays a central role in the persistence and

380. See *id.*; see also Mielke, *supra* note 37, at 4 (“HIV is indeed a unique infection; it is able to directly infect specific cells of the human immune system to produce immune abnormalities that lead to the development of opportunistic infections, host compromise, morbidity, and mortality. The retrovirus is able to directly infect cells of the immune system, especially the cells that contain the CD4 surface receptors. The virus contains reverse transcriptase, which is able to reverse the flow of genetic information by converting RNA into proviral DNA that is incorporated into the host cell’s DNA.”).

381. B. Bharati et al., *Incidence of Bacterial and Fungal Co-Infections in Some HIV Infected Indian Population*, 3 INDIAN J. SCI. & TECH. 199, 199 (2010) (“The infection is alarming due to the unique pathogenesis of the virus that decreases the CD4 cells, signaling the emergence of the opportunistic infections, in the host.”); Clements & Zink, *supra* note 33, at 100 (“The unique pathogenesis of lentiviruses is attributable to both their complex genetic structure and the novel molecular mechanisms controlling viral gene expression.”); Nowak & McMichael, *supra* note 38, at 60–62 (describing the unique and difficult-to-verify process of HIV infection and disease progression); Johnston & Fauci, *supra* note 37, at 888 (discussing the “mutability and genetic diversity of HIV” and how that distinguishes the virus’s development).

382. See sources cited *supra* note 381.

383. Nowak & McMichael, *supra* note 38, at 60; see also Bangham & Phillips, *supra* note 39, at 1615; Johnston & Fauci, *supra* note 37, at 888 (explaining how HIV’s genetic diversity is a result of “extraordinary mutability”); Schader & Wainberg, *supra* note 44, at 92 (“Unlike other retroviruses, HIV-1 is extraordinarily mutagenic both within and among patients.”).

384. See Nowak & McMichael, *supra* note 38, at 59–60 (discussing how HIV evades the human immune system through constant rounds of mutation and replication).

pathogenicity of HIV in an infected host by shielding the virus from the immune response and increasing the likelihood that exceptionally virulent and drug-resistant mutants may emerge in the viral population.<sup>385</sup> In the absence of such variability the human immune response might be able to contain HIV indefinitely.<sup>386</sup>

Three distinctive features combine to make HIV the most variable human virus: (1) an error-prone HIV reverse transcriptase enzyme that has no editing mechanism for transcriptional errors, (2) a high replication frequency, and (3) the occurrence of recombination processes between two or more different HIV strains within the same infected individual that enhances genetic variability of HIV.<sup>387</sup>

#### a. Error-Prone Reverse Transcriptase Lends to HIV's High Mutation Rate

HIV infects a host cell by integrating a DNA copy of its genetic information into the genome of the host.<sup>388</sup> This process requires the action of the enzyme reverse transcriptase, which

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385. *Id.* (“[Variability] increases the probability that some genetic change will give rise to an advantageous trait.”); Zhuang et al., *supra* note 280, at 11,273 (“The HIV-1 genome is characterized by its rapid evolution, which permits the virus to escape immune surveillance and to develop drug-resistant variants as well as making it difficult to produce an effective vaccine.”).

386. Bangham & Phillips, *supra* note 39, at 1617 (“[V]iral persistence is enabled, at least in part, by immune escape. If CTL escape could be prevented, CTL responses might contain HIV indefinitely.”).

387. *Id.* at 1615 (attributing difficulty of treatment and prevention of HIV infection to the “high rates of replication, mutation, and recombination of HIV”); Emanuele Fanales-Belasio et al., *HIV Virology and Pathogenetic Mechanisms of Infection: A Brief Overview*, 46 ANNALI DELL’ISTITUTO SUPERIORE DI SANITÀ 5, 9 (2010) (“Variability is the most powerful weapon of HIV, which allows the virus to overcome host immunity and the effects of therapeutic (drugs) and prophylactic (vaccines) interventions. HIV variability is a consequence of at least three peculiar features: 1) the ‘error-prone’ mechanism of action of the virus enzyme reverse transcriptase, that introduces, on average, one substitution per genome per replication round; 2) the very rapid viral replication, that generates a high number of virions per day (estimated around  $10^{10}$ ) in the infected individual and 3) the occurrence of recombination processes between two or more different HIV viruses within the same infected individual.”) (citations omitted).

388. Tang et al., *supra* note 58, at 135 (“The defining feature of a retrovirus is its ability to convert its RNA genome to a DNA intermediate through the virally encoded reverse transcriptase. A subsequent reaction . . . results in the integration of this DNA molecule into host chromosome DNA . . .”).

copies the viral RNA genome into a DNA sequence.<sup>389</sup> The virus mutates during this process because reverse transcriptase is error-prone and has no editing mechanism for transcriptional errors.<sup>390</sup> HIV reverse transcriptase is among the most error prone reverse transcriptase enzymes known.<sup>391</sup> This distinctive feature of HIV contributes significantly to its hyper-mutability, which plays a central role in the pathogenesis of AIDS.<sup>392</sup>

#### b. Genetic Recombination

HIV is a diploid virus: each virus carries two RNA copies, “each full length and potentially able to replicate.”<sup>393</sup> All retroviruses are diploid, but no other virus families, RNA or DNA, share this feature.<sup>394</sup> The two RNA copies in a retroviral particle typically derive from the same parent provirus.<sup>395</sup> However, if an infected cell simultaneously harbors two different proviruses, the genome of the progeny virion may contain one RNA transcript from each of two different parent proviruses.<sup>396</sup> When this genetically diverse virion

389. *Id.*

390. Nowak & McMichael, *supra* note 38, at 59–60 (“The virus mutates readily . . . because reverse transcriptase is rather error prone.”); Roberts et al., *supra* note 43, at 1171 (“[T]he HIV-1 enzyme does not correct errors by exonucleolytic proofreading.”).

391. Conlan et al., *supra* note 44.

392. See Mansky, *supra* note 310, at 1339 (“Reverse transcriptase fidelity clearly plays the major role in determining the rate at which mutations occur during the process of reverse transcription.”); Schader & Wainberg, *supra* note 44, at 92 (“[The] high infidelity of HIV-1 transcriptase, resulting in base additions, deletions, and substitutions, may account for the observed hyper-mutability of the AIDS virus. Today, HIV-1 reverse transcriptase remains the primary scapegoat for drug resistance and viral adaptation.”).

393. Donald S. Burke, *Recombination in HIV: An Important Viral Evolutionary Strategy*, 3 EMERGING INFECTIOUS DISEASES 253, 253 (1997) (“Human immunodeficiency virus (HIV)-1, like all retroviruses, is ‘diploid.’ Each viral particle contains two RNA strands of positive polarity, each full length and potentially able to replicate.”) (citation omitted); *supra* notes 48–49 and accompanying text.

394. Burke, *supra* note 393, at 253 (“No other virus families, RNA or DNA, are diploid.”).

395. *Id.*

396. *Id.* (“Typically both RNA strands in a retroviral particle derive from the same parent provirus. However, if an infected cell simultaneously harbors two different proviruses, one RNA transcript from each provirus can be encapsidated into a single ‘heterozygous’ virion.”). The term “virion” refers to a complete virus outside a host cell. Levy, *supra* note 54, at 188. The term

subsequently infects a new cell, the reverse transcriptase enzyme, in the process of copying the viral RNA genome into a DNA sequence, may switch back and forth between the two RNA templates so that the newly synthesized DNA sequence is recombinant of the two parental genomes.<sup>397</sup> The process of recombination thus enhances genetic variability of HIV within an infected individual by scrambling the genetic content from two different RNA copies to generate a hybrid DNA mosaic.<sup>398</sup> The diploid feature of HIV is a critical factor in its high recombination rate.<sup>399</sup>

All retroviruses generally have high recombination rates,<sup>400</sup> but the recombination rate of HIV is high even relative to other retroviruses, making HIV the most recombinogenic known human virus.<sup>401</sup> By some estimates the HIV

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“provirus” refers to the genetic material of a virus that resides in and is able to replicate in the genome of a host cell. *See, e.g., id.*

397. *Id.* (“When this virion subsequently infects a new cell, the reverse transcriptase may jump back and forth between the two RNA templates so that the newly synthesized retroviral DNA sequence is recombinant between that of the two parents.”) (citations omitted).

398. An & Telesnitsky, *supra* note 49, at 195 (suggesting recombination plays a larger role in HIV diversity than the high mutation rate); Terence D. Rhodes et al., *Genetic Recombination of Human Immunodeficiency Virus Type 1 in One Round of Viral Replication: Effects of Genetic Distance, Target Cells, Accessory Genes, and Lack of High Negative Interference in Crossover Events*, 79 J. VIROLOGY 1666, 1666 (2005) (“Genetic recombination plays an important role in the evolution of human immunodeficiency virus type 1 (HIV-1). Recombination shuffles viral genomes and redistributes the mutations generated from reverse transcription, leading to increased variation within the infected host and, ultimately, the viral populations distributed throughout the world.”) (citations omitted); Simon-Lorier et al., *supra* note 48, at 280 (“This process [recombination] . . . plays a central role in shaping HIV genetic diversity . . .”).

399. An & Telesnitsky, *supra* note 49, at 196 (“Retroviruses are so-called diploid and virions that contain two different RNAs are described as heterozygous. Co-packaging two RNAs in a single virion provides two templates to the reverse transcriptase machinery and is a critical factor in the high frequency of retroviral recombination.”).

400. *See* Delviks-Frankenberry et al., *supra* note 306, at 1668 (“Retroviruses have one of the highest recombination rates among all viruses.”).

401. Jianbo Chen et al., *Comparison of the Genetic Recombination Rates of Human Immunodeficiency Virus Type 1 in Macrophages and T Cells*, 79 J. VIROLOGY 9337, 9337 (2005) (“HIV-1 . . . recombines at a much higher frequency than other retroviruses; in one round of replication with two markers 1 kb apart, the recombination rates of spleen necrosis virus and

recombination frequency can exceed that of other retroviruses by as much as a factor of ten.<sup>402</sup> Recombination contributes significantly to HIV genetic variability<sup>403</sup> and AIDS pathogenesis.<sup>404</sup>

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murine leukemia virus are 4.0 and 4.7%, respectively; in contrast, the recombination rate of HIV-1 is 42.4%.”) (citations omitted); Terrence Rhodes et al., *High Rates of Human Immunodeficiency Virus Type 1 Recombination: Near-Random Segregation of Markers One Kilobase Apart in One Round of Viral Replication*, 77 J. VIROLOGY 11,193, 11,194 (2003) (“We found that HIV-1 recombines at an exceedingly high frequency even when compared with other retroviruses.”); Zhuang et al., *supra* note 280, at 11,281 (“[T]he results presented here support the idea that HIV-1 recombines at an extremely high rate of at least 2.8 crossovers during each cycle of replication, making this the most recombinogenic process observed in any mammalian related system described so far.”).

402. Rhodes et al., *supra* note 401, at 11,193 (“HIV-1 recombination can be 10-fold higher than that of other retroviruses.”).

403. *See id.* at 11,198 (“This observation indicates that recombination is an incredibly powerful tool . . . to . . . generat[e] diversity in the viral population and increas[e] the evolutionary capacity of HIV-1.”).

404. Burke, *supra* note 393, at 257 (“Many of the strains [of HIV] around the world appear to have arisen through recombination, and it is likely that recombination may be an important mechanism by which HIV evades drug or immune pressures.”); Delviks-Frankenberry et al., *supra* note 306, at 1668 (“[R]ecombination can generate a[n HIV] variant to escape the host cell immune response; similarly, recombination can also assort existing drug-resistance mutations to generate a more resistant virus or a variant that is resistant to more than one drug.”); Adewunmi Onafuwa-Nuga & Alice Telesnitsky, *The Remarkable Frequency of Human Immunodeficiency Virus Type 1 Genetic Recombination*, 73 MICROBIOLOGY & MOLECULAR BIOLOGY REV. 451, 472 (2009) (“The vast combinatorial potential of HIV-1 genetic recombination presents one of the greatest challenges to preventing HIV-1 infection and combating HIV disease because it introduces genetic variation that complicates vaccine development and promotes escape from antivirals.”); Rhodes et al., *supra* note 398, at 1666 (“The inherent ability of HIV-1 to recombine poses a constant problem for effective anti-HIV-1 treatment because multidrug-resistant variants can be generated by recombining the genome of singly or weakly resistant viruses. The increased variation caused by recombination also hinders the development of effective vaccines . . . . Therefore, rapid recombination of the HIV-1 genome creates a vast advantage for the evolution of the virus and an enormous difficulty for the host.”); Megan C. Steain et al., *HIV-1 Co-Infection, Superinfection and Recombination*, 1 SEXUAL HEALTH 239, 239 (2004) (“Recombination may result in the emergence of more pathogenic and virulent HIV strains with altered fitness, tropism, and resistance to multiple drugs, and may hamper the development of subtype-based vaccines.”).

### c. Replication Rate

Once integrated into a target cell's chromosomes, the human immune deficiency virus uses the cell's own genetic machinery to replicate itself.<sup>405</sup> Newly created copies of the virus are then released from the cell into the bloodstream of the infected individual, ready to infect other cells in turn and continue the replication cycle.<sup>406</sup> HIV replicates at an exceptionally high frequency within a single infected individual.<sup>407</sup> The high replication rate contributes to AIDS pathogenesis by directly killing CD4<sup>+</sup> T lymphocytes,<sup>408</sup> and by

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405. See SOMPAYRAC, *supra* note 261, at 59–60 (“HTLV-I enters its target cell when its envelope binds to an unknown receptor on the cell's surface, and then fuses with the cell membrane. This ‘injects’ the viral capsid, which encloses two copies of HTLV-I's single-stranded RNA genome, into the cytoplasm of the cell. There the capsid is removed, and a viral enzyme (reverse transcriptase), which is packaged in the capsid, springs into action. This enzyme copies the RNA genome to produce a single-stranded, complementary DNA (cDNA) molecule, destroying the original RNA molecule after it has been copied. The reverse transcriptase protein then makes a complimentary copy of the single cDNA strand to produce a double-stranded cDNA molecule. The net result of all this action is to replace the single-stranded RNA genome with a double-stranded DNA ‘copy’ that contains the viral genetic information.”).

406. *Id.* at 60.

407. See Coffin, *supra* note 281, at 483 (“[T]he unique feature of HIV is the extraordinarily large number of replication cycles that occur during infection of a single individual.”); Nowak & McMichael, *supra* note 38, at 60 (“[A]t least a billion new viral particles are produced in an infected patient each day. [Researchers have] found that, in the absence of immune activity, the viral population would on average double every two days. Such numbers imply that viral particles present in the body 10 years after infection are several thousand generations removed from the original virus. In 10 years, then, the virus can undergo as much genetic change as humans might experience in the course of millions of years.”).

408. David D. Ho et al., *Rapid Turnover of Plasma Virions and CD4 Lymphocytes in HIV-1 Infection*, 373 NATURE 123, 126 (1995) (“[O]ur findings strongly support the view that AIDS is primarily a consequence of continuous, high-level replication of HIV-1, leading to virus- and immune-mediated killing of CD4 lymphocytes.”); Poeschla et al., *Development of HIV Vectors for Anti-HIV Gene Therapy*, 93 PROC. NAT'L ACAD. SCI. 11,395, 11,395 (1996) (“[T]here is every reason to believe that continuous, high-level viral replication is central to disease causation . . . The new estimates reveal a furiously destructive process behind a facade of apparent clinical latency: approximately 10<sup>10</sup> virions produced per day, 140 viral generations per year . . .”).

combining with error-prone reverse transcriptase and viral recombination to enhance the genetic variability of the virus.<sup>409</sup>

## ii. Capacity to Infect Nondividing Cells

In multicellular organisms, tissue grows and discarded older cells are replaced through a biological process known as mitosis.<sup>410</sup> Mitosis is a form of nuclear division by which a cell divides into two daughter cells with the same genetic material.<sup>411</sup> Most retroviruses can enter the nucleus of a cell only while the cell is dividing.<sup>412</sup> HIV, in contrast, possesses genetic features that enable it to infect and replicate efficiently in nondividing cells,<sup>413</sup> including immune cells known as

409. See Coffin, *supra* note 281, at 488 (“[T]he engine that is driving the [immunodeficiency] process is the constant repeated cycles of virus replication.”); Nowak & McMichael, *supra* note 38, at 60 (“HIV’s replication rate further increases the odds that a mutation useful to the virus will arise.”).

410. See MARGIT PAVELKA & JÜRGEN ROTH, FUNCTIONAL ULTRASTRUCTURE: ATLAS OF TISSUE BIOLOGY AND PATHOLOGY 20 (2d ed., 2010) (“For growth of tissue, development of organs, and maintenance of life functions, both production of new cells by cell division and elimination of cells by programmed cell death . . . are necessities. During the cell cycle, regulated by cyclins and cyclin-dependent protein kinases, mitosis serves to equally distribute all parts of the genome among two daughter cells.”).

411. *Id.*

412. See Narayan & Clements, *supra* note 37, at 1620 (“In general, retroviruses have a strong requirement for dividing cells; these cells presumably provide optimal conditions for the synthesis of viral DNA and integration of the proviral DNA. In contrast, lentiviruses replicate efficiently in non-dividing, end-stage cells both in the animal and in cell cultures.”) (citations omitted).

413. See, e.g., Eckstein et al., *supra* note 36, at 1407 (discussing HIV’s “unique abilities, including the capacity to infect noncycling cells”) (citations omitted); Philippe Gallay et al., *HIV-1 Infection of Nondividing Cells Through the Recognition of Integrase by the Importin/Karyopherin Pathway*, 94 PROC. NAT’L ACAD. SCI. 9825, 9825 (1997) (“HIV[-1] can infect nondividing cells because its preintegration complex is recognized by the cell nuclear import machinery and actively transported through the nucleopore . . . . In contrast, oncoretroviruses such as the murine leukemia virus and oncoretroviral vectors cannot traverse an intact nuclear envelope, precluding integration in the absence of mitosis.”) (citations omitted); Narayan & Clements, *supra* note 37, at 1620 (“The effectors [enabling replication in non-dividing cells] are probably encoded by the lentiviral RNAs in the small ORFs unique to these viruses.”); S.C. Piller et al., *Nuclear Import of the Pre-Integration Complex (PIC): The Achilles Heel of HIV?*, 4 CURRENT DRUG TARGETS 409, 409 (2003) (“Unlike other retroviruses, HIV can transport its genetic material, in the form of the large nucleoprotein pre-integration complex (PIC), into the nucleus through the intact nuclear envelope (NE). This enables HIV to infect non-dividing cells



macrophages.<sup>414</sup> Macrophages are white blood cells within tissues that play an important role in the human immune response.<sup>415</sup> Their role is to phagocytize (engulf and then digest) cellular debris and pathogens, and to stimulate lymphocytes and other immune cells to respond to the pathogen.<sup>416</sup>

The ability of HIV to infect macrophages is central to the pathogenesis of AIDS.<sup>417</sup> Macrophages are among the first cells targeted by HIV following initial infection and play an important role throughout the course of HIV infection.<sup>418</sup> HIV-

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such as macrophages and microglial cells.”); Tang et al., *supra* note 58, at 154 (“HIV-1 Vpr also has a role in the nuclear import of HIV-1 preintegration complexes (PICs) into the nucleus of infected cells . . . This makes Vpr an important player in HIV infection of nondividing cells, such as macrophages.”).

414. See Piller et al., *supra* note 413, at 409.

415. See *supra* note 51.

416. See *supra* note 51.

417. Ariberto Fassati, *HIV Infection of Non-Dividing Cells: A Divisive Problem*, 3 RETROVIROLOGY 74, 74 (2006) (describing “how lentiviruses can infect terminally differentiated, non-dividing cells” such as macrophages as “central to HIV-1 transmission and AIDS pathogenesis”); Katherine Kedzierska & Suzanne M. Crowe, *The Role of Monocytes and Macrophages in the Pathogenesis of HIV-1 Infection*, 9 CURRENT MED. CHEMISTRY 1893, 1893–94 (2002) (“Cells of the macrophage lineage play an important role in initial infection with HIV-1 and contribute to the pathogenesis of the disease throughout the course of infection.”); Stevenson, *supra* note 276, at 854 (“[T]here has been a growing suspicion that antigen-presenting cells, including macrophages and DCs, may be central to the strategy used by HIV-1 to resist immune and antiretroviral pressure.”); *supra* note 52 and accompanying text.

418. Kedzierska & Crowe, *supra* note 417, at 1894 (“Cells of macrophage lineage are therefore amongst the first cells infected with HIV-1 following transmission and subsequently contribute to the pathogenesis of HIV-1 infection throughout the course of the disease.”); *id.* (“Resident tissue macrophages . . . are major targets for HIV-1. These cells are susceptible to HIV-1 infection *in vitro* on the day of isolation.”) (citation omitted); see also Carol A. Carter & Lorna S. Ehrlich, *Cell Biology of HIV-1 Infection of Macrophages*, 62 ANNUAL REV. MICROBIOLOGY 425, 426 (2008) (“[T]he HIV-1 infected macrophage is of critical importance in the pathogenesis of HIV because it is a major contributor to early-stage viral transmission, persistence, and virus dissemination throughout the body of the host.”); Jan Mac Orenstein, *The Macrophage in HIV Infection*, 204 IMMUNOBIOLOGY 598, 598 (2001) (“Macrophages play a key role in several critical aspects of HIV disease. They appear to be the first cells infected by HIV and perhaps the very source of HIV production when CD4<sup>+</sup> cells are markedly depleted in the patient.”).

infected macrophages serve as viral targets and reservoirs,<sup>419</sup> support sustained viral production,<sup>420</sup> facilitate pathogenesis of neurological disorders,<sup>421</sup> resist HIV-mediated killing,<sup>422</sup> and contribute to the development of AIDS-defining opportunistic infections.<sup>423</sup>

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419. See Kedzierska & Crowe, *supra* note 417, at 1893 (“Following infection with HIV-1, monocyte/macrophages are resistant to cytopathic effects and persist throughout the course of infection as long-term stable reservoirs for HIV-1 capable of disseminating the virus to tissues.”); Weiss, *supra* note 275, at 1275 (“Infected macrophages could be important reservoirs outside the blood and as carriers of HIV to different organs.”); see also *supra* note 312.

420. Jessica Young et al., *Selective Killing of HIV-1-Positive Macrophages and T Cells by the Rev-Dependent Lentivirus Carrying Anthrolysin O from Bacillus anthracis*, 5 RETROVIROLOGY 36, 36 (2008) (“In particular, cells from the macrophage lineage resist HIV-1-mediated killing and support sustained viral production.”).

421. See Carter & Ehrlich, *supra* note 418, at 426 (“With the ability of this cell type to cross the blood-tissue barrier, an infected macrophage cell is a potent agent for delivery of HIV-1 to all tissues and organs, including the brain.”); Fauci, *supra* note 36, at 621 (reporting evidence of macrophage-induced neuro-pathogenic effects); Ho et al., *supra* note 408, at 282 (“[T]he infected monocyte or macrophage has a central role in the pathogenesis of subacute encephalitis.”); Kedzierska & Crowe, *supra* note 417, at 1899 (“HIV-infected individuals are susceptible to neurological disorders . . . HIV-associated dementia is associated with massive infiltration of blood-derived macrophages to the brain through the disrupted blood-brain barrier, and the formation of multinucleated giant cells and microglial nodules. Both HIV-infected macrophages and microglia are highly activated and produce a number of neurotoxins contributing to disease progression.”); H. A. Smits et al., *Role of Macrophage Activation in the Pathogenesis of Alzheimer’s Disease and Human Immunodeficiency Virus Type 1-Associated Dementia*, 30 EUR. J. CLINICAL INVESTIGATION 526, 531 (2000) (“It is generally assumed that [HIV-associated dementia] is strongly associated with immune activation of glial cells, resulting in alterations of secretory functions. Many of these immune products have been shown to cause alterations in blood-brain barrier integrity and are able to induce adhesion molecules on macrophages and endothelial cells, thereby enhancing monocyte transendothelial migration. Once inside the brain, cytokines, reactive oxygen species and various neurotoxins can be secreted by HIV-infected macrophages. Among others, TNF, arachidonic acid, platelet-activating factor (PAF), NO and Ntox are proposed as neurotoxins and these molecules may activate or directly damage surrounding cells. In addition, HIV-infected macrophages have been shown to release chemokines, which may result in an enhanced infiltration of HIV-infected as well as uninfected macrophages.”) (citations omitted).

422. Young et al., *supra* note 420, at 36.

423. See Kedzierska & Crowe, *supra* note 417, at 1893–94 (“Following HIV-1 infection, effector functions carried out by monocyte/macrophages are also impaired, including phagocytosis, intracellular killing, chemotaxis and cytokine production. Such defects contribute to the pathogenesis of AIDS by

## iii. Unique HIV Genetic Structure and Molecular Mechanisms

The unique and powerful pathogenetic mechanisms of HIV are directly attributable to distinctive aspects of its genetic structure.<sup>424</sup> For instance, the genes that distinguish HIV from viruses in its class—namely the *tat*, *rev*, *vif*, *vpr*, *nef*, and *vpu* genes, the latter found exclusively in HIV-1—play a central role in its high mutation rate and ability to infect and replicate in macrophages.<sup>425</sup> The *tat* and *nef* genes amplify and maintain the replication rate of HIV, a key contributor to genetic diversity.<sup>426</sup> The *rev* gene has been described as “absolutely

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allowing reactivation and development of opportunistic infections . . .”) (citations omitted); Narayan & Clements, *supra* note 37, at 1630 (“Since macrophages constitute the main non-specific cellular defence system of the host, lentivirus replication undoubtedly subverts this arm of the defence system and results in failure of the host to eliminate the virus.”); Orenstein, *supra* note 418, at 598 (“Macrophages play a key role in several critical aspects of HIV disease . . . [O]ppportunistic pathogens can cause an upregulation of HIV production by macrophages, often in the multinucleated form.”); Stevenson, *supra* note 276, at 854 (“Infection of macrophages by HIV-1 occurs primarily through the CCR5 coreceptor and, although there are some exceptions, individuals who lack CCR5 . . . are highly resistant to infection. Therefore, macrophages or mucosal CCR5-positive lymphocytes may be important in establishing infection.”).

424. Clements & Zink, *supra* note 33, at 100 (“The unique pathogenesis of the lentiviruses is attributable to both their complex genetic structure and the novel molecular mechanisms controlling viral gene expression.”).

425. Eckstein et al., *supra* note 36, at 1407 (“In addition to the *gag*, *pol*, and *env* genes found in all retroviruses, the HIV-1 genome contains six additional genes: *tat*, *rev*, *vif*, *vpr*, *vpu*, and *nef*. These genes confer upon HIV-1 a number of unique abilities, including the capacity to infect noncycling cells. Viral protein R (Vpr) in particular is known to play an important role in facilitating infection of nondividing tissue macrophages as well as inducing G2 cell-cycle arrest in dividing T cells.”) (citations omitted); Fauci, *supra* note 36, at 617 (“HIV also has at least five additional genes, three of which have known regulatory functions, and the expression of these genes almost certainly has an impact on the pathogenic mechanisms exerted by the virus.”); Levy, *supra* note 54, at 188 (“Tat is a major protein involved in upregulating HIV replication. Another viral regulatory protein, Rev (regulator of viral protein expression), interacts with a cis-acting RNA loop structure called the Rev responsive element, located in the viral envelope mRNA. This interaction involves cellular proteins and multimers of the Rev protein and permits unspliced mRNA to enter the cytoplasm from the nucleus and give rise to full-length viral proteins needed for progeny production. Thus, Tat and Rev are RNA-binding proteins that interact with cellular factors for optimal activity.”).

426. See Bangham & Phillips, *supra* note 39, at 1616 (“The kinetics of HIV-1 replication are complicated by the regulatory genes, *tat*, *nef*, *vpu*, *vpr*, and *vif*. The Nef protein is particularly important in maintaining the high

essential” for viral replication,<sup>427</sup> in addition to its other contributions to HIV functionality and pathogenicity.<sup>428</sup> The *vpr* gene confers upon HIV the capacity to infect and replicate efficiently in nondividing cells such as macrophages.<sup>429</sup> The *vif*

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replication rate of HIV-1—and therefore its pathogenicity—in vivo. Also, the virus weakens the immune defenses by steadily depleting the CD4<sup>+</sup> T cell population . . . .”); Cameron & Kelly, *supra* note 55, at 26 (“[A] number of HIV proteins interfere with critical cellular processes that facilitate the host immune response. [T]he HIV Nef protein downregulates CD4 receptor and MHC class I molecule expression. Specifically, the HIV tat protein impairs antigen processing by interfering with proteasome function and downregulating MHC class II expression . . . . Nef induce[s] apoptosis of HIV-specific CTLs by increasing the expression of FasL, resulting in apoptosis of Fas-expressing CTLs. This process is referred to as back-killing.”); Fauci, *supra* note 36, at 617 (“The tat gene plays an important role in the amplification of virus replication by encoding a protein that functions as a potent trans-activator of HIV gene expression.”) (citation omitted); Foster & Garcia, *supra* note 55, at 389–90 (“Nef is a pathogenic factor of *Human immunodeficiency virus* (HIV) . . . .”); Freed, *supra* note 55, at 29 (“Although in general the effects of Nef deletion on virus replication kinetics in culture are quite limited, it has been reported that in single-cycle assays, the presence of Nef modestly stimulates virus infectivity.”).

427. Hope & Trono, *supra* note 56 (“Rev is absolutely required for HIV-1 replication: proviruses that lack Rev function are transcriptionally active but do not produce viral late genes and thus do not produce virions.”).

428. See, e.g., Clements & Zink, *supra* note 33, at 100 (“The regulatory genes *tat* and *rev* control viral transcription and RNA transport and translation . . . .”); Freed, *supra* note 55, at 13–14 (“Rev plays a major role in the transport of viral RNAs from the nucleus to the cytoplasm.”); Levy, *supra* note 54, at 188 (“Rev (regulator of viral protein expression), interacts with a cis-acting RNA loop structure called the Rev responsive element, located in the viral envelope mRNA. This interaction involves cellular proteins and multimers of the Rev protein and permits unspliced mRNA to enter the cytoplasm from the nucleus and give rise to full-length viral proteins needed for progeny production . . . . Rev [is an] RNA-binding [protein] that interact[s] with cellular factors for optimal activity.”); Shehu-Xhilaga & Oelrichs, *supra* note 57, at 10 (“[T]he Rev responsive element, within the coding region for gp41, interacts with the Rev protein to assist export of spliced RNA transcripts from the nucleus of the cell.”) (citations omitted).

429. See Eckstein et al., *supra* note 36, at 1407 (“Viral protein R (Vpr) in particular is known to play an important role in facilitating infection of nondividing tissue macrophages as well as inducing G<sub>2</sub> cell cycle arrest in dividing T cells.”) (citations omitted); Mansky, *supra* note 58, at 398 (“Vpr has been found to act intracellularly to influence productive infection and latency, to influence HIV-1 transcription, to inhibit proliferation and activation of cell differentiation in a human muscle cell line, to interact with cellular proteins, to prevent cell proliferation during chronic infection, and to be involved in the nuclear localization of HIV-1 DNA in nondividing cells.”); Tang et al., *supra* note 58, at 154 (“HIV-1 Vpr also has a role in the nuclear import of HIV-1

and *vpu* genes also play important roles in the pathogenicity of HIV.<sup>430</sup>

## VI. SUMMARY

The analysis presented shows that the risk of HIV/AIDS was unforeseeable in the early stages of the epidemic.<sup>431</sup> The etiology and pathogenesis of AIDS were discovered only in 1983 and 1984, respectively.<sup>432</sup> Furthermore, the risk was not a mere variant of what was known and foreseeable. HIV has a complex genetic structure and novel molecular mechanisms controlling its viral gene expression that distinguish it from other human viruses. These distinctive features are material because they confer on HIV unique characteristics that play a central role in the distinctive pathogenesis of AIDS, a pathogenesis that the human immune response can neither contain nor defeat.<sup>433</sup>

This analysis supports the common law evolution of the foreseeability issue in HIV/AIDS blood transfusion cases. Courts in early cases such as *Quinones v. Long Island College*

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preintegration complexes (PICs) into the nucleus of infected cells . . . This makes Vpr an important player in HIV infection of nondividing cells, such as macrophages.”).

430. See Balliet et al., *supra* note 60, 629 (“Although the specific mechanisms of [*nef*] are largely yet undefined, [findings] suggest a critical role in macrophage infection, which is central in the pathogenesis of HIV infection and in neurological and pulmonary sequelae.”); Freed, *supra* note 55, at 29 (“Vif mutation can cause profound defects in virus infectivity . . . Nef plays an important positive role in lentiviral pathogenesis.”); Sakai et al., *supra* note 59, at 5770 (“Vif is required for rapid infection with HIV-1. Since vif viruses infect cells faster than their vif mutant counterparts, Vif function may be required to establish conditions necessary for the typically rapid HIV-1 infection in vitro.”); Shehu-Xhilaga & Oelrichs, *supra* note 57, at 11 (“Viral proteins perform a variety of roles to subvert normal cellular function and facilitate viral replication . . . Vpu promotes degradation of CD4 in the endoplasmic reticulum and Vif is necessary for subsequent efficient infectivity of the newly produced viral particles. Vif counteracts cytidine deaminases (enzymes present especially in macrophages and T cells) that are naturally occurring host defense mechanisms against retroviruses. These proteins include APOBEC3G and APOBEC3F and are degraded by HIV.”) (citations omitted).

431. See generally Robert C. Gallo, *Historical Essay: The Early Years of HIV/AIDS*, 298 SCIENCE 1728 (2002).

432. *Id.* at 1729.

433. See Tersmette, *supra* note 259, at 37–38 (discussing in detail the pathogenesis of HIV infection).

*Hospital*<sup>434</sup> and *Fox v. Estrada*<sup>435</sup> held that HIV/AIDS is not a foreseeable blood-borne risk.<sup>436</sup> Eventually, after scientists had isolated the virus and discovered the pathogenesis of AIDS, courts began to resolve the foreseeability issue in favor of plaintiffs.<sup>437</sup>

## VII. CONCLUSION

This Article analyzes the foreseeability doctrine in negligence cases where a new technology or unexplored scientific principle contributed to a plaintiff's harm. The issue is governed by the Reasonable Ignorance of the Relationship doctrine of proximate cause. The doctrine allows a defendant to escape liability if scientists were *ex ante* reasonably ignorant of the risk that caused the plaintiff's harm.

The main contributions of this Article are the following:

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434. *Quinones v. Long Island Coll. Hosp.*, 607 N.Y.S.2d 103 (N.Y. App. Div. 1994).

435. *Fox v. Estrada*, No. 14-97-00821-CV, 1998 WL 831666, at \*1 (Tex. App. Dec. 3, 1998).

436. *Id.* at \*3 ("The summary judgment proof established that the blood-borne pathogens known to exist in 1982 were treatable, rarely fatal, and did not present the same magnitude of danger to the patient as HIV/AIDS. Blood transfusions had been an accepted life-saving medical practice for many decades, and there was no indication that a killer of the order of HIV/AIDS was lurking in the nation's blood supply. Accordingly, we will not impose an obligation on the medical community in general, and Dr. Estrada in particular, to have anticipated the possibility of so devastating a disease as AIDS."); *Quinones*, 607 N.Y.S.2d at 104 ("Even if it is assumed that negligent medical treatment by the defendant hospital resulted in the decedent's need for a series of blood transfusions in 1980, we are in agreement with the trial court that the risk of receiving blood tainted by the Human Immunodeficiency Virus which causes the Acquired Immune Deficiency Syndrome (AIDS) was not a legally foreseeable risk at the time in question.") (citation omitted).

437. *See, e.g., Snyder v. American Ass'n of Blood Banks*, 676 A.2d 1036, 1048 (N.J. 1996) (finding that the risk that patients may contract AIDS via contaminated blood transfusions is foreseeable, and that the defendant owed a duty to use reasonable precautions to avoid such infections).

1. It presents an analysis of the common law foundations of the Reasonable Ignorance of the Relationship doctrine.
2. It proposes a translation into medical science of the doctrine of foreseeability that preserves its common law meaning.
3. It presents an analysis of the foreseeability of HIV/AIDS as a blood-borne risk. The analysis illustrates the application of the Reasonable Ignorance doctrine to novel issues in medical science.