ANTICIPATING HIV VACCINES: SKETCHING AN AGENDA FOR PUBLIC HEALTH ETHICS AND POLICY IN THE UNITED STATES

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PRÉCIS

Worldwide research and development expenditures on an HIV vaccine are approximately one billion U.S. dollars per year. While vaccines have been highly successful in preventing diseases, the most promising clinical trials to date suggest that a vaccine for HIV will be only moderately efficacious in preventing infection and will require multiple doses. We explore the ethical and policy implications of a moderately effective HIV vaccine. We examine anticipated costs, benefits, risks, and dissemination challenges. We conclude that a twofold approach of (1) using existing treatments to reduce viral loads and prevent transmission and (2) pursuing a cure for HIV may be more cost-effective and beneficial in the long run than developing a vaccine.

I. INTRODUCTION

More than three decades have passed since the initial clinical observation of Acquired Immunodeficiency Syndrome (AIDS) cases in 1981 and since the discovery of the etiologic agent, Human Immunodeficiency Virus (HIV) in 1983.[1] Since these discoveries, public, philanthropic, and commercial entities have invested in research to discover how to prevent, treat, and cure HIV and AIDS. Through this research, great advances have been made, most importantly, the discovery of Combination Antiretroviral Therapy (cART), which has converted AIDS from a nearly universally fatal disease to a chronic condition.[2] Significant research has been made in prevention as well, including: antiretroviral treatments to prevent transmission,[3] pre-exposure and post-exposure prophylaxis,[4] education and prevention strategies,[5] and methods to prevent the maternal-fetal transmission of HIV.[6]

1. Françoise Barré-Sinoussi et al., *Past, Present and Future: 30 Years of HIV Research*, 11 NAT. REVS. MICROBIOLOGY 877, 877 (2013).

2. *Id*. at 879.

3. Myron S. Cohen et al., *Prevention of HIV-1 Infection with Early Antiretroviral Therapy*, 365 NEW ENG. J. MED. 493, 494 (2011).

4. *See* Kenneth H. Mayer, *Antiretroviral Chemoprophylaxis: State of Evidence and the Research Agenda*, 59 CLINICAL INFECTIOUS DISEASES S47, S47 (Supp. 2014); Dawn K. Smith et al., *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States: Recommendations from the U.S. Department of Health And Human Services*, MORBIDITY & MORTALITY WKLY. REP., RECOMMENDATIONS & REPS., Jan 21, 2005, at 1, 3.

5. *See* Helen B. Chin et al., *The Effectiveness of Group-Based Comprehensive Risk-Reduction and Abstinence Education Interventions to Prevent or Reduce the Risk of Adolescent Pregnancy, Human Immunodeficiency Virus, and Sexually Transmitted Infections: Two Systematic Reviews for the Guide to Community Preventive Services*, 42 AM. J. PREV. MED. 272, 274 (2012).

6. *See* Kevin M. De Cock et al., *Prevention of Mother-to-Child HIV Transmission in Resource-Poor Countries: Translating Research Into Policy and Practice*, 283 JAMA 1175 (2000).

None of these advances, however, promise to eradicate the virus from the population. To the extent that we have successfully eradicated other viruses—such as polio and measles—it has been through the development and dissemination of vaccines. In general, such vaccines have been safe, effective, and cost-saving.[7] Consider the vaccine for the Hepatitis B virus (HBV), a sometimes fatal virus that is transmitted in many of the same ways as HIV (through sexual intercourse and intravenous (IV) drug use).[8] Five vaccines now exist.[9] Each is approximately ninety-four percent effective in preventing chronic carriage of all known subtypes or variants of the virus.[10] After vaccinating more than 100 million people in the U.S., no serious side effects have been reported.[11] Only two to four doses are required in infancy to provide immunity throughout the first decade of life.[12] With little public controversy, the vaccine has been mandated for infants in forty-seven states,[13] and since 1990, rates of acute Hepatitis have dropped eight-two percent.[14]

Publicly promoting such a vaccine through coverage by the Affordable Care Act (ACA)[15] and state mandatory vaccination laws arguably meets the five "justificatory conditions" proposed by James Childress and colleagues for justifying a public health policy, even when it clashes with some competing values:

> (1) *Effectiveness*: The policy must be expected to achieve its aim (e.g., significantly reducing rates of HBV-infection was realistic through mandated vaccinations).

7. F. E. Andre et al., *Vaccination Greatly Reduces Disease, Disability, Death and Inequity Worldwide*, 86 BULL. WORLD HEALTH ORG. 140–42 (2008).

8. CTRS. FOR DISEASE CONTROL & PREVENTION, EPIDEMIOLOGY AND PREVENTION OF VACCINE-PREVENTABLE DISEASES 120 (William Atkinson et al. eds., 12th ed. 2012) [hereinafter VACCINE-PREVENTABLE DISEASES].

9. *Hepatitis B*, NAT'L VACCINE INFO. CTR, http://www.nvic.org/Vaccines-and-Diseases/Hepatitis-B.aspx (last visited Mar. 9, 2015); VACCINE-PREVENTABLE DISEASES, *supra* note 8, at 124, xii.

10. VACCINE-PREVENTABLE DISEASES, *supra* note 8, at 134.

11. *Hepatitis B FAQs for the Public*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/hepatitis/B/bFAQ.htm, (last updated Mar. 6, 2015).

12. *See* VACCINE-PREVENTABLE DISEASES, *supra* note 8, at 126; *Hepatitis B FAQs for Health Professionals*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm (last updated Mar. 6, 2015).

13. *State Mandates on Immunization and Vaccine—Preventable Diseases: Hepatitis B*, IMMUNIZATION ACTION COALITION, http://www.immunize.org/laws/hepb.asp (last updated Jan. 15, 2015) (listing Alabama, Montana and South Dakota as the three states who do not have a Hepatitis B childhood vaccination mandate.).

14. *Incidence of Acute Hepatitis B—United States, 1990-2002*, 52 MORBIDITY & MORTALITY WKLY. REP.1245, 1253 (2004).

15. *See The Affordable Care Act and Immunization*, DEP'T OF HEALTH & HUMAN SERVS., http://www.hhs.gov/healthcare/facts/factsheets/2010/09/The-Affordable-Care-Act-and-Immunization.html (last updated Jan. 20, 2012).

> (2) *Proportionality*: The good achieved must balance favorably against the infringement of other values (e.g., reducing chronic HBV-infection rates by eighty-two percent helps to justify some degree of infringement on parental authority or diversion of funding for other health needs).
>
> (3) *Necessity*: The infringement of a value such as autonomy must be necessary to achieve a public health aim such as herd immunity to Hepatitis B (e.g., current high rates of Hepatitis B vaccination arguably would have been difficult to achieve through a voluntary program).
>
> (4) *Least infringement*: The infringement of other values should be minimized (e.g., children are not forcibly vaccinated, rather it is a condition for access to some school systems).
>
> (5) *Public justification*: Policy makers should be transparent and explain the reasons for the policy (e.g., the Centers for Disease Control and Prevention (CDC) has developed an extensive website that provides information about Hepatitis B and the vaccination program).[16]

The National Institute of Allergy and Infectious Diseases (NIAID) states that, "[f]inding a safe, effective, and durable HIV vaccine remains a top priority for NIAID."[17] Several HIV vaccines have advanced to human clinical trials in and have demonstrated some level of success in reducing infection rates.[18] However, as we indicate in this paper, it appears that initial vaccines for HIV will be less effective, will require more doses to achieve immunity, will offer immunity for shorter periods of time, and accordingly, will be more expensive and difficult to administer than the Hepatitis B vaccine (or measles, polio, Human Papillomavirus (HPV), or any other commonly mandated vaccine.)[19] The medical, economic, logistical, and political realities of HIV vaccines are extremely complex. This complexity generates a host of ethical and policy questions.

This paper proceeds by identifying these questions, elucidating why they arise, and explaining their significance. As a general rule, we do not venture to answer these questions. In some instances, this is because further data is needed before anyone can answer the questions; in other instances, it is because the questions pertain to matters of policy that should be resolved through processes of public education, engagement, deliberation, and decision-making. Simply outlining ethical and policy issues surrounding an HIV

16. James F. Childress et al., *Public Health Ethics: Mapping the Terrain*, 30 J. L. MED. & ETHICS 170, 173 (2002).

17. *HIV Vaccine Research*, NAT'L INST. OF ALLERGY & INFECTIOUS DISEASES (last updated Feb. 19, 2014), http://www.niaid.nih.gov/topics/hivaids/research/vaccines/Pages/default.aspx.

18. *See, e.g.*, *An HIV Vaccine: The World's Best Long-Term Hope for Ending AIDS*, FRED HUTCHINSON CANCER RES. CTR., http://www.hvtn.org/en.html (last visited Mar. 25, 2015); Mattia Bonsignori et al., *An Autoreactive Antibody From an SLE/HIV-1 Individual Broadly Neutralizes HIV-1*, 124 J. CLINICAL INVESTIGATION 1835, 1835 (2014).

19. *See infra* Part III.A.

vaccine may sound like a modest goal, but we believe it is crucial at this juncture.

Perhaps no other disease has generated so many passionate stakeholder groups, including:

- Those at highest risk within the U.S., including men who have sex with men (MSM) and IV drug users (IVDU), who have often been marginalized in society;
- Those at highest risk internationally, including heterosexual men and women in many African nations;
- Children who are orphaned by AIDS;
- Government officials who seek to fight HIV/AIDS while wrestling with budget constraints;
- Health care providers who struggle with limits imposed by the scarcity of health resources;
- Pharmaceutical companies that could advance their mission and generate profit with a vaccine discovery, but might also lose revenue from medications used to treat a chronic condition; and,
- Public health experts who have had mixed success in behavior-based prevention efforts.

In such a context, deliberations about HIV vaccines may be highly politicized and contaminated by rhetoric that could unduly influence decision-makers if they are not well informed. This article is intended to provide stakeholders and policymakers with an overview of the complex issues surrounding an HIV vaccine and a basic understanding of why the complexity will resist easy solutions.

While HIV has affected many nations more severely than the U.S. (e.g., in sub-Saharan Africa almost one in twenty adults is infected),[20] we focus our analysis on the U.S. context to examine more effectively, questions surrounding approval from the Food and Drug Administration (FDA), patent law, social dynamics, and other questions that are nation-specific.

In Part II, we provide a description of HIV—or more accurately, the types, groups, and genetic subtypes of retroviruses in the HIV-family, the nature of HIV transmission, and the demographics of the disease burden. In Part III, we examine why it has been so difficult to develop an HIV vaccine, and we explore what kind of efficacy we can reasonably expect from the first generation of HIV vaccines. In Part IV, we try to anticipate the risks of an HIV vaccine, including adverse events, unintended changes in behavior, and social harms. In Part V, we discuss factors that will drive up the costs of an HIV vaccine and discuss some of the ethical issues presented by costs. In Part VI, we try to anticipate controversies surrounding the distribution of an HIV

20. *HIV/AIDS Fact Sheet N°360*, WORLD HEALTH ORG., http://www.who.int/mediacentre/factsheets/fs360/en/ (last updated Nov. 2014).

vaccine. We conclude by applying the five justificatory conditions for public health policies and practices to an HIV vaccine. In the process of doing so, we hope not only to raise awareness of how challenging HIV vaccines are to public policy, but also to identify significant knowledge and process gaps that should be met prior to evaluating an HIV licensing application.

II. THE PROBLEM OF HIV

HIV was first recognized in June of 1981, when the CDC reported five cases of pneumonia caused by *Pneumocystis jirovecii* (at that time referred to as *Pneumocystis carinii*) in MSM living in Los Angeles.[21] These first cases were thought to be a new disease confined to the population of MSM, but it soon expanded to heterosexual men and women and IVDUs throughout much of the world.[22] In 1983, a retrovirus (now known as HIV) was isolated from a patient with this syndrome in France.[23] Within that same year, the FDA approved a commercial test to detect the virus.[24]

HIV manifests as an acute infection with symptoms appearing two to six weeks after laboratory seroconversion.[25] Symptoms include maculopapular rash, fever, myalgia, arthralgia, headache, diarrhea, sore throat, or neurological manifestations.[26] Extremely high levels of the virus are present during acute infection and are likely a significant source of transmission.[27] Antibodies to HIV normally develop within two months,[28] although there have been sporadic reports of delayed seroconversion.[29] For the most part, these antibodies are not able to control or prevent ongoing viral replication.[30]

According to CDC criteria, AIDS is diagnosed when the immune system of a person infected with HIV becomes severely compromised (as measured by the CD4 cell count) and/or the person becomes ill with an opportunistic infection.[31] Without HIV therapy, the individual becomes increasingly

21. *First Report of AIDS*, 50 MORBIDITY & MORTALITY WKLY. REP. 429, 429 (2001).

22. Barré-Sinoussi et al., *supra* note 1, at 877; Michael H. Merson et al., *The History and Challenge of HIV Prevention*, 372 LANCET 475, 475 (2008).

23. Barré-Sinoussi et al., *supra* note 1, at 877.

24. *Id.*

25. Andrew R. Moss & Peter Bacchetti, *Natural History of HIV Infection*, 3 AIDS 55, 55 (1989).

26. *Id.*

27. Penny Lewthwaite & Ed Wilkins, *Natural History of HIV/AIDS*, 37 MED. 333, 333 (2009).

28. *Id.* at 334.

29. Moss & Bacchetti, *supra* note 25, at 55; *see also* S. Skidmore et al., *A Case Study of Delayed HIV-1 Seroconversion Highlights the Need for Combo Assays*, 20 INT'L J. STD & AIDS 205, 205 (2009).

30. Moss & Bacchetti, *supra* note 25, at 55.

31. *About HIV/AIDS*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/hiv/basics/whatishiv.html (last updated Jan. 16, 2015).

susceptible to opportunistic infections,[32] and diseases caused by these pathogens are "AIDS-defining conditions," and include herpes viruses (Kaposi's sarcoma, lymphoma, and cytomegalovirus), *Pneumocystis jerovicii*, invasive fungal infections, and mycobacterial infections such as TB.[33] In the absence of treatment, AIDS develops eight to ten years after initial infection.[34] When the first cases of AIDS presented to clinicians, the only thing they could do was treat the opportunistic infections with marginal success. HIV became the leading cause of death in twenty-five to forty-four year olds by 1993.[35] This trend peaked in 1996 before rapidly declining and, by 2010, HIV was the seventh leading cause of death in that age group.[36] Today, with advances in cART, HIV has been transformed from a once fatal to a now manageable chronic disease.[37] While current cART suppresses the virus, it does not eradicate it, and lifelong treatment is still required,[38] which carries both financial and physical costs. A few cases of HIV eradication (cure) or suppression without requiring cART (functional cure) have been reported,[39] but have generally been in unusual circumstances, such as extremely early treatment,[40] or a bone marrow transplant by a donor genetically incapable of HIV infection,[41] and rebound has been reported in several of these cases.[42]

32. *Id.*

33. *Revised Surveillance Case Definition for HIV infection Among Adults, Adolescents, and Children Aged < 18 Months and for HIV Infection and AIDS Among Children Aged 18 Months to < 13 Years – United States, 2008*, 57 MORBIDITY & MORTALITY WKLY REP 1, 9 (2008) (outlining the AIDS-Defining Conditions in Appendix A).

34. Jair C. Leao et al., *Oral Complications of HIV Disease*, 64 CLINICS 459, 460 (2009).

35. *Update: Mortality Attributable to HIV Infection Among Persons Aged 25-44 Years – United States 1994*, 45 MORBIDITY & MORTALITY WKLY REP. 121, 121 (1996).

36. KAISER FAMILY FOUND., THE HIV/AIDS EPIDEMIC IN THE UNITED STATES 1 (2014) (citing to the CDC's Mortality Slide Show Through 2010); CTRS. FOR DISEASE CONTROL & PREVENTION, MORTALITY SLIDE SERIES 20 (2013), *available at* http://www.cdc.gov/hiv/pdf/statistics_surveillance_HIV_mortality.pdf.

37. Barré-Sinoussi et al., *supra* note 1, at 879.

38. *Id.* at 880.

39. *See generally* Asier Sáez-Cirión et al., *Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission After the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study*, 9 PLOS PATHOGENE 1, 1 (2013).

40. *Id*.; Ari Bitnun et al., *Early Initiation of Combination Antiretroviral Therapy in HIV-1 – Infected Newborns Can Achieve Sustainted Virologic Suppression With Low Frequency of $CD4^+$ T Cells Carrying HIV in Peripheral Blood*, 59 CLINICAL INFECTIOUS DISEASES 1012, 1014 (2014).

41. Gero Hütter et al., *Long-Term Control of HIV by CCR5 Delta32/Delta 32 Stem-Cell Transplantation*, 360 NEW ENG. J. MED. 692, 696-97 (2009).

42. Press Release, Nat'l Inst. Of Allergy & Infectious Disease, "'Mississippi Baby' Now Has Detectable HIV, Researchers Find (Jul. 10, 2014), *available at* http://www.niaid.nih.gov/news/newsreleases/2014/Pages/MississippiBabyHIV.aspx.

A. Viral Mechanisms of HIV

HIV-1 and HIV-2 are members of the *lentivirus* family of *retroviruses*. Cross-species infection from primates to humans probably occurred by blood contamination through hunting. HIV-1 and HIV-2 both cause AIDS, but HIV-2 is both less virulent and less prevalent.[43] HIV-1 causes over ninety-eight percent of AIDS cases worldwide.[44] "HIV-1 can be further subdivided into different groups (M, O, [N, and P]) and subtypes."[45] For example, HIV-1 group M has nine identified genetic subtypes (A-K, excluding E and I).[46] Each genetic subtype is traditionally associated with specific geographical areas. For example, subtype A is associated with West Africa, and subtype B is most prevalent in Europe, the Americas, Japan, Thailand, and Australia.[47] "Globally, subtype C accounts for half of all strains."[48] It is likely that a vaccine will target only certain subtypes, complicating vaccine distribution.

Retroviruses such as HIV have an RNA-genome and require reverse transcription to complete the viral life cycle.[49] This process is inaccurate, and the viral genome is capable of mutating each base pair in its genome up to 100,000 times per day, generating quasi-species of genetically-related viruses soon after infection.[50]

B. Transmission Demographics

HIV is present in blood, semen, and other bodily fluids and is transmitted mainly through sexual intercourse.[51] Globally, the primary modes of transmission are heterosexual contact and mother to child (vertical transmission), but considerable variation exists between and within countries.[52]

43. Lewthwaite & Wilkins, *supra* note 27, at 333; Andrew M.L. Lever, *HIV: The Virus*, 37 MED. 313, 313 (2009).

44. Lever, *supra* note 43, at 313.

45. Lewthwaite & Wilkins, *supra* note 27, at 333; Ana Vallari et al., *Confirmation of Putative HIV-1 Group P in Cameroon*, 85 J. VIROLOGY 1403, 1403 (2011).

46. Abraham J. Kandathil et al., *Molecular Epidemiology of HIV*, 121 INDIAN J. MED. RES. 333, 334 (2005).

47. *Id.* at 337; Lewthwaite & Wilkins, *supra* note 27, at 333.

48. Lewthwaite & Wilkins, *supra* note 27, at 333.

49. Lever, *supra* note 43, at 313.

50. Ricardo Sobhie Diaz et al., *Divergence of HIV-1 Quasispecies in an Epidemiologic Cluster*, 11 AIDS 415, 415 (1997); Alan S. Perelson et al., *HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time*, 271 SCIENCE 1582, 1583 (1996).

51. Lewthwaite & Wilkins, *supra* note 27, at 333.

52. *Id.*

The primary modes of transmission in the U.S. for example, are anal sex and IV-drug use.[53]

We focus on demographic data provided in the CDC's *HIV Surveillance Report, 2012*.[54] Approximately 880,400 (or three in one thousand) individuals are known to be living with HIV throughout the U.S.[55] The CDC estimates that approximately 200,000 additional individuals are infected, but are unaware of their infection.[56] There are approximately 50,000 new diagnoses of HIV and 20,000 deaths from HIV-related illnesses each year.[57] The distribution of HIV varies significantly by race in the U.S. with Black/African American (forty-six percent), White (twenty-eight percent), and Hispanic/Latino (twenty-one percent).[58] Among males, the primary modes of transmission are male-to-male sexual contact (eighty-one percent), followed by heterosexual contact (ten percent), and injection drug use (five percent).[59] Among women, transmission occurs primarily through heterosexual contact (eighty-seven percent) and injection drug use (twelve percent).[60] Children under thirteen comprise half of one percent of all cases, most involving peri-natal transmission (fifty-seven percent).[61]

III. THE DIFFICULTY OF DEVELOPING AN HIV VACCINE

Vaccines have led to the eradication of smallpox and near eradication of polio, and protect humans from measles, rubella, tetanus, mumps, influenza, and Hepatitis B.[62] Wayne Kopf provides a succinct explanation of different ways vaccines work:

> Viral vaccines protect against disease by priming the immune system before pathogen exposure. This generates antibody responses that can prevent infection [as well as] cellular responses that target and eliminate virus-infected cells. Virus-specific neutralizing antibodies bind to proteins on the surface of

53. CTRS. FOR DISEASE CONTROL & PREVENTION, TODAY'S HIV/AIDS EPIDEMIC 3 (2014), *available at* http://www.cdc.gov/nchhstp/newsroom/docs/HIVFactSheets/TodaysEpidemic-508.pdf.

54. *See generally* Ctrs. for Disease Control & Prevention, *Diagnoses of HIV Infection in the United States and Dependent Areas, 2012*, HIV SURVEILLANCE REP., Nov. 2014 [hereinafter SURVEILLANCE REP.].

55. *Id*. at 9.

56. Ctrs for Disease Control & Prevention, *Monitoring Selected National Prevention and Care Objectives Using HIV Surveillance Data—United States and 6 Dependent Areas 2012*, HIV SURVEILLANCE REP., Nov. 2014, at 1, 10 (Supp. Nov. 2014).

57. SURVEILLANCE REP., *supra* note 54, at 19, 40.

58. *Id.* at 18.

59. *Id.*

60. *Id.* at 19.

61. *Id.*

62. Ivan Stratov & Stephen Kent, *Towards an HIV Vaccine*, 32 AUSTRALASIAN SCIENCE 31, 31 (2011).

> viral particles and stop them from infecting host cells. Neutralizing antibodies can also bring about the destruction of virus-infected cells, via cellular effector mechanisms. Where natural virus infection elicits robust neutralizing-antibody responses, vaccines have been developed by using attenuated versions of the live virus (such as for measles, mumps, and rubella); inactivation (for polio); and virus surface protein subunits or virus-like particles (for hepatitis B and human papilloma virus).[63]

Why, after more than three decades, do we not have an effective vaccine against HIV? Most importantly, currently available vaccines exist for pathogens to which many people develop protective immunity (i.e., patients who recover from the illness are protected against re-infection). The vaccine mimics this known protective response. Very few HIV-infected patients are able to control the infection and there are no patients identified who have cleared the infection completely. Those patients who do control the virus appear to do so by generating an effective cytotoxic T cell-response,[64] which is quite different from the antibody-response generated by most licensed vaccines.

Technical barriers exist as well. Because of safety concerns, an effective HIV vaccine would be unlikely to consist of attenuated, actively replicating (live) HIV, due to possible reversion to full virulence. Virus protein subunit vaccines or killed whole virus vaccines, have been problematic due to the extensive variability generated by the sloppiness of the viral polymerase, creating not a single target, but a swarm of related targets.[65] This variability allows "the virus to escape both pharmacological attack and immunological defenses."[66]

Finally, scientists have never before attempted to develop a vaccine against a retrovirus like HIV. Retroviruses, by integrating their genome into ours, are able to hide completely from immune surveillance within quiescent lymphocytes.[67] This means that any vaccine has a small window of opportunity in which to prevent infection and would have to be extremely effective, repelling all attempts by HIV to attach to and infect host cells. HIV produces viral proteins that actively interfere with the anti-HIV immune response in both infected and uninfected cells.[68] For all these reasons, an effective HIV vaccine will likely require uniquely different strategies from currently licensed vaccines, which will likely increase cost and complicate distribution methods.

63. Wayne C. Koff, *Accelerating HIV Vaccine Development*, 464 NATURE 161, 161 (2010).

64. Stratov & Kent, *supra* note 62, at 32.

65. Dennis R. Burton et al., *A Blueprint for HIV Vaccine Discovery*, 12 CELL HOST & MICROBE 396, 396-97 (2012).

66. Lever, *supra* note 43, at 316; *see also* Travis C. Porco & Sally M. Blower, *Designing HIV Vaccination Policies: Subtypes and Cross-Immunity*, 28 INTERFACES 167, 167-68 (1998).

67. Lever, *supra* note 43, at 315.

68. *Id.*

Multiple vaccine strategies have been tried since the discovery that HIV causes AIDS. The first Phase I HIV vaccine trial took place in 1987.[69] According to the International AIDS Vaccine Initiative's database, two hundred and twelve Phase I trials, nineteen Phase I/II trials, and thirty-four Phase II trials have taken place as of January 2015.[70] These studies have provided both promising results and serious setbacks, most notably the early stopping of a Merck STEP vaccine study in 2003, after the realization that the vaccine increased the risk of HIV acquisition in some participants.[71] Only three Phase III studies of HIV vaccines have been done, involving two AIDSVAX types (B/B in Canada, the Netherlands, and Puerto Rico; and B/E in Thailand)[72] and a combination study of AIDSVAX B/E with ALVAC, also known as RV144.[73] The most promising of these trials was RV144, a six-year trial conducted in Thailand with the sponsorship of the U.S. Army HIV Research Program and NIAID.[74] The trial involved 16,400 people.[75] While the vaccine had an initial efficacy of approximately seventy percent, this declined to about thirty percent within three and a half years.[76] Although U.S. public health officials have never approved a vaccine with such low efficacy, the RV144 trial is the first vaccine to demonstrate any significant efficacy against HIV, and has renewed hopes for a marketable vaccine.[77]

A. Anticipated Effectiveness of a Vaccine

In evaluating the efficacy of a vaccine, several endpoints are used: (1) susceptibility to establishment of infection upon exposure, (2) progression of

69. José Esparza, *An HIV Vaccine: How and When*, 79 BULL. WORLD HEALTH ORG. 1133, 1135 (2001).

70. *See IAVIReport: Clinical Trials Database*, INT'L AIDS VACCINE INITIATIVE, http://www.iavireport.org/Trials-Database/Pages/default.aspx (last updated February 10, 2015) [hereinafter *Clinical Trials Database*]. Summaries of all of the trials references in this paragraph can be accessed in their Clinical Trials Database.

71. *See Questions & Answers: HVTN 502 & HVTN 503 HIV Vaccine Clinical Trials*, NAT'L INST. OF ALLERGIES & INFECTIOUS DISEASES, http://www.niaid.nih.gov/news/qa/pages/step_qa.aspx (last updated Feb. 6, 2008); *The STEP Study*, NAT'L AIDS MANUAL, http://www.aidsmap.com/The-STEP-study/page/1065651/ (last visited Mar. 9, 2015).

72. *Clinical Trials Database*, *supra* note 70.

73. *Id.*

74. *See RV 144 Trial*, U.S. MILITARY HIV RES. PROG., http://www.hivresearch.org/research.php?ServiceID=13, (last visited March 9, 2015); *see also Phase III Trial-Thailand*, U.S. MILITARY HIV RES. PROG. (2010), http://www.hivresearch.org/media/pnc/9/media.439.pdf.

75. Supachai Rerks-Ngarm et al., *Vaccination With ALVAC and AIDSVAX To Prevent HIV-1 Infection in Thailand*, 361 NEW ENGL. J. OF MED. 2209, 2210 (2009).

76. Kyeen M. Andersson et al., *The Potential Impact of an HIV Vaccine with Rapidly Waning Protection on the Epidemic in Southern Africa: Examining the RV144 Trial Results*, 29 VACCINE 6107, 6108 (2011).

77. *Clinical Trials Database*, *supra* note 70, at Special Report Thai Trial Results.

the disease among those who are already infected, and (3) infectiousness or the risk of transmission to others.

Most currently available vaccines are highly efficacious in reducing susceptibility to viral infection. For example, both vaccines currently licensed to prevent HPV—Gardasil and Cervarix—are nearly one hundred percent efficacious in preventing diseases caused by exposure to high-risk strains of HPV (HPV sixteen and eighteen),[78] which together account for seventy percent of all cervical cancers as well as many cancers of the vagina and vulva.[79] The HBV vaccine is ninety-four percent effective in preventing susceptibility to chronic carriage of the HBV.[80]

In contrast to HPV and HBV vaccines, early HIV vaccines are likely to be low to moderate in reducing susceptibility, but may slow disease progression and lower infectiousness.[81] Whereas efficacy in reducing susceptibility is the primary aim of vaccine development, control of the HIV epidemic could be achieved if a vaccine reduced the rate of transmission to less than one per infected individual.[82]

In contrast to efficacy, which is determined under experimental conditions, effectiveness is the ability of a vaccine to produce outcomes of interest in the "real world" and is affected by factors such as patient compliance, cost, behavioral changes, and supply.[83] However, when evaluating new drugs and biologics for safety and effectiveness, the FDA typically equates effectiveness with efficacy in clinical trials conducted under conditions that are often times more controlled than most patient care settings.[84]

As we proceed to evaluate the risks and benefits of an HIV vaccine, we propose a hypothetical scenario. No HIV vaccine to date has exceeded an initial efficacy of seventy percent or sustained an efficacy above forty percent.[85] We will optimistically, and somewhat arbitrarily, assume for the

78. Barbara Romanowski, *Long Term Protection Against Cervical Infection with the Human Papillomavirus: Review of Currently Available Vaccines*, 7 HUMAN VACCINES 161, 161-62 (2011).

79. *Id*. at 164-65.

80. Hilton Whittle et al., *Observational Study of Vaccine Efficacy 14 Years After Trial of Hepatitis B Vaccination in Gambian Children*, 325 BMJ 1, 2 (2002).

81. *Public Health Considerations for the Use of a First Generation HIV Vaccine*, 17 AIDS W1, W2 (2003).

82. *Id.* at W3.

83. *See* INS'T OF MED., GUIDELINES FOR CLINICAL PRACTICE: FROM DEVELOPMENT TO USE 61, 66-68 (Marilyn J. Field & Kathleen N. Lohr eds.,1992); *see generally* Colin Depp & Barry D. Lebowitz, *Clinical Trials: Bridging the Gap Between Efficacy and Effectiveness*, 19 INT'L REV. PSYCHIATRY 531 (2007).

84. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 1 n. 2 (1998).

85. *See* Elisa F. Long & Douglas K. Owens, *The Cost-Effectiveness of a Modestly Effective HIV Vaccine in the United States*, 29 VACCINE 6113, 6113 (2010) (where vaccine efficacy was

sake of argument that a vaccine is sixty percent efficacious in preventing HIV upon exposure. However, it has a significantly lower rate of effectiveness because it requires recipients to obtain four shots over a six-month period as well as an annual booster shot.[86]

B. Anticipating the Risks of an HIV Vaccine

Proactive management of the risks of an HIV vaccine will be a necessary component of any successful HIV vaccine approval process and subsequent campaign.

1. What adverse events might an HIV vaccine cause?

HIV vaccine clinical trials have reported only mild to moderate vaccine reactions. Adverse events observed during HIV vaccine trials have been similar to other vaccines: pain and swelling localized at the injection site, fevers of mild to moderate severity, chills, diarrhea, aches and pains, nausea, headache, dizziness, and fatigue.[87] Standard strategies for managing safety risks from vaccines include providing information on risks, adverse event reporting, long-term monitoring programs, and mechanisms of legal redress for injury.[88] However, existing vaccine safety surveillance programs, such as the Vaccine Adverse Event Reporting System (VAERS), may be insufficient for adequately monitoring HIV vaccine safety, given the characteristics of likely recipient populations and the relative homogeneity of trial subjects. As VAERS relies on self-reporting and reporting by medical professionals,[89] the

highest at approximately seventy percent in the first year, but rapidly declined over time, showing a thirty-one percent vaccine efficacy overall).

86. *See* Kristen Jill Kresge, *Special Report: Thai Trial Results, Results from RV144 Send Scientists in Search of Clues*, IAVI REPORT, http://www.iavireport.org/Special-Features/Pages/SpecialReportThaiTrialResults.aspx (last visited Mar. 8, 2015) (discussing the RV 144 HIV vaccine trial that used a prime-boost regimen consisting of six shots—four primers and two boosters—given over the course of six months, which one sponsor of the trial stated was "not exactly a deployable regimen").

87. Andrew T. Catanzaro et al., *Phase 1 Safety and Immunogenicity Evaluation of a Multiclade HIV-1 Candidate Vaccine Delivered by a Replication-Defective Recombinant Adenovirus Vector*, 194 J. INFECTIOUS DISEASES 1638, 1640, 1643 (2006); Elizabeth. L. Cooney et al., *Safety of and Immunological Response to a Recombinant Vaccinia Virus Vaccine Expressing HIV Envelope Glycoprotein*, 337 LANCET 567, 569 (1991); Frances H. Priddy et al., *Safety and Immunogenicity of a Replication- Incompetent Adenovirus Type 5 HIV-1 Clade B gag/pol/nef Vaccine in Healthy Adults*, 46 CLINICAL INFECTIOUS DISEASES 1769, 1772 (2008).

88. *See generally Vaccine Adverse Event Reporting System*, U.S. DEP'T HEALTH & HUMAN SERVS., https://vaers.hhs.gov/index (last visited Mar. 26, 2015).

89. Weigong Zhou et al., *Surveillance for Safety After Immunization: Vaccine Adverse Event Reporting System (VAERS) – United States, 1991-2001*, in CTR. FOR DISEASE CONTROL & PREVENTION, SURVEILLANCE FOR SAFETY AFTER IMMUNIZATION: VACCINE ADVERSE EVENT

adverse events experienced in high-risk communities with limited health care access may go unreported. Moreover, it is unclear whether our standard processes for compensating those injured by vaccination will work with an HIV vaccine. Injuries attributed to most of the vaccines administered in the U.S., including the HPV and HBV vaccines, are compensated through the National Vaccine Injury Compensation Program (VICP).[90] The VICP allows individuals claiming an injury caused by a covered vaccine to petition the U.S. Federal Claims Court for compensation, including coverage of the medical expenses incurred as a result of the injury.[91] However, the VICP only covers vaccines that are routinely administered to children.[92] Thus, an HIV vaccine would be added to the list of VICP covered vaccines only if it is recommended for routine administration to children. Moreover, a new mechanism for legal redress of HIV vaccine injuries will likely need to be developed.

Additional concerns regarding vaccine safety could be addressed via FDA Risk Evaluation and Mitigation Strategies (REMS). A product of the Food and Drug Administration Amendments Act of 2007 (FDAAA),[93] REMS are required risk management plans that extend beyond typical labeling requirements to ensure the benefits of a particular treatment outweigh its risks.[94] The FDA is not required to order REMS for a particular biologic, but rather considers several factors in making that determination: the size of the targeted population, seriousness of the disease, expected benefit and duration of the treatment, and the seriousness of potential side effects.[95] Given the deadly and widespread nature of HIV, it seems the FDA could very well consider requiring REMS for an HIV vaccine. REMS must include a timetable for submissions of REMS-assessments and may also include a medication guide, a communication plan, elements to assure safe use, and an implementation system.[96] Medication guides are written in non-technical

REPORTING SYSTEM (VAERS) 2 (2003), http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5201a1.htm.

90. *See* U.S. DEP'T HEALTH & HUMAN SERVS., WHAT YOU NEED TO KNOW ABOUT THE NATIONAL VACCINE INJURY COMPENSATION PROGRAM (VICP) 1, 1-2 (2011). The VICP was created through the National Childhood Vaccine Injury Act of 1986. *Id*. at 1. *See also* 42 U.S.C. § 300AA-1 (2012).

91. Katherine M. Cook & Geoffrey Evans, *The National Vaccine Injury Compensation Program*, 127 PEDIATRICS S74, S75 (2011).

92. *Id.* at S75.

93. *See generally* Food and Drug Administration Safety and Innovation Act, Pub. L. No. 110–85, 121 Stat. 823 (2007).

94. FOOD & DRUG ADMIN., A BRIEF OVERVIEW OF RISK EVALUATION AND MITIGATION STRATEGIES (REMS) 1-2, *available at* http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf (last accessed Mar. 22, 2015) [hereinafter RISK EVALUATION & MITIGATION].

95. *Id.* at 6.

96. *Id.* at 7.

language and presented in an easily accessible format providing information such as possible side effects, overdose precautions and instructions, and a brief description of the product.[97] Communication plans attempt to increase understanding of a drug's or biologic's risks through letters to health care providers, circulating information contained in the REMS to various professional societies, and encouraging methods to alleviate risks.[98] Finally, Elements to Assure Safe Use (ETASU) establish the requirements that health care professionals must meet before administering, prescribing, or continuing a particular treatment.[99] The related implementation system dictates the steps a drug or biologic sponsor will take to ensure that ETASU are executed and followed.[100] Examples of ETASU include possessing specific training or certifications, or subjecting patients to monitoring.[101] As a product of some or all of these parts, REMS can help identify and address concerns with vaccine safety.

2. How will an HIV vaccine affect risky sexual behavior?

As HIV prevention technologies diminish perceptions of risk, risk-taking behavior may increase, a phenomenon referred to as "risk compensation."[102] If individuals perceive a significant protective effect of an HIV vaccine, they may be more willing to engage in risky behaviors. Absent a fully protective vaccine and optimal uptake, increases in risky behavior, such as IVDU and unprotected sex, may increase the incidence of HIV transmission. For example, a decrease in the use of condoms, which provide between eighty and ninety percent protection against HIV when regularly used, may increase the overall incidence of HIV.[103] Risk compensation thus has the potential to offset the population-level benefit of an HIV vaccine. In addition to diminishing the net benefit of an HIV vaccine, risk compensation may increase the incidence of other sexually transmitted infections, unwanted pregnancy, and IV use.

Mathematical modeling suggests the extent to which risk compensation may offset the benefits of a vaccination program. However, mathematical modeling has been very limited.

97. *Id.* at 8.

98. *Id.* at 10.

99. RISK EVALUATION & MITIGATION, *supra* note 94, at 12.

100. *Id.* at 16.

101. *Id.* at 13.

102. Lisa A. Eaton & Seth C. Kalichman, *Risk Compensation in HIV Prevention: Implications for Vaccines, Microbicides, and Other Biomedical HIV Prevention Technologies*, 4 CURRENT HIV/AIDS REP. 165, 170 (2007).

103. Markus J. Steiner & Willard Cates Jr., *Condoms and Sexually-Transmitted Infections*, 354 NEW ENG. J. MED. 2642, 2642 (2006).

Andersson et al. used prevalence data for South Africa to model the relationship between vaccine efficacy and risk compensation.[104] Published in 2007, the study concluded that a twenty-five percent decrease in condom use following a vaccination program, with a forty percent effective vaccine, would decrease HIV prevalence from twenty percent to fifteen percent (as compared to a decrease from twenty percent to thirteen percent without a decrease in condom use).[105] The study assumed that the vaccine would have one hundred percent take (elicit some immunological response in all recipients), provide ten years of protection, and would be administered to seventy-five percent of the population over seventeen years of age.[106] However, given a twenty percent effective vaccine and a fifty percent decrease in condom use, a vaccination program would increase the prevalence of HIV.[107] As the model used the much higher prevalence rates found in South Africa (approximately eleven and a half percent for men; twenty percent for women),[108] these findings do not provide an indication of how risk compensation might impact the benefits of a vaccination program in the U.S., which has very low prevalence rates.

Long et al.'s discussion of the potential benefits and costs of an HIV vaccine considered how an increase in sexual partners would impact the benefits of vaccination.[109] The authors concluded that if vaccinated individuals had twenty-five percent more sexual partners than unvaccinated individuals, a vaccine of at least sixty-five percent efficacy would provide a net benefit due to population mixing (HIV-infected individuals would be more likely to have sex with a vaccinated individual).[110] The authors did not account for other changes in risk behavior.

Blower et al.'s study of HIV eradication in San Francisco, which found that a modest increase in risk behavior of ten percent would offset any decrease in incidence offered by a fifty percent effective vaccine, offers the most insight into risk compensation following a vaccination program in the U.S.[111]

104. Kyeen M. Andersson et al., *Predicting the Impact of a Partially Effective HIV Vaccine and Subsequent Risk Behavior Change on the Heterosexual HIV Epidemic in Low- and Middle-Income Countries: A South African Example*, 46 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES, 78, 79 (2007).

105. *Id.* at 81.

106. *Id.* at 79-80.

107. *Id.* at 81.

108. *Id.* at 79.

109. Long & Owens, *supra* note 85, at 6116.

110. *Id.* at 6116-17.

111. S. M. Blower & A.R. McLean, *Prophylactic Vaccines, Risk Behavior Change, and the Probability of Eradicating HIV in San Francisco*, 265 SCIENCE 1451, 1453 (1994); Peter A. Newman et al., *HIV Risk and Prevention in a Post-Vaccine Context*, 22 VACCINE 1954, 1954 (2004).

Subsequent work by Rajaraman et al. emphasizes the role of the transmission network in modulating the effectiveness of a vaccine intervention.[112] In sexually transmitted diseases such as HIV, transmission requires risky behavior by both the infected patient and the uninfected partner—a two-sided behavior. This contrasts with diseases, such as influenza, that are primarily transmitted through the risky behavior of individuals. An individual's risky behavior, including travel and contact with crowds, increases the risk of transmission to multiple others—a one-sided behavior.[113] For one-sided behaviors, high vaccination coverage mitigates increased risky behavior. For two-sided interactions, vaccination must be combined with programs to decrease risky behavior, as modeling of this behavior reveals that unintended outcomes occur at high levels of vaccination. Additionally, this modeling reveals that interventions that target highly connected individuals (as is common among HIV transmission networks) can sometimes be worse than random interventions.[114]

Studies of anticipated behavioral changes have predicted a modest increase in risky behavior following vaccination with an HIV vaccine.[115] In interviews conducted with 1,164 high-risk individuals in Los Angeles County, Newman et al. found modest anticipated increases in high-risk behaviors.[116] After receiving a hypothetical HIV vaccine of fifty percent efficacy, six percent of respondents said they would use condoms less for vaginal sex, seven percent said they would use condoms less for anal sex, and approximately seven and a half percent anticipated an increase in sexual partners.[117] However, anticipated risk compensation increased dramatically when subjects were presented with a high-efficacy HIV vaccine.[118] Similarly, twenty-two percent of respondents in a South African study believed that they would use condoms less frequently after receiving a thirty percent effective vaccine.[119] The conclusions supported by these studies are limited by the reliance on individual reporting of

112. Rajmohan Rajaraman et al., *Network Effects of Risk Behavior Change Following Prophylactic Interventions*. 8 PLOS ONE, Aug. 2013, at 1, 12.

113. *Id.* at 2.

114. *Id.* at 6.

115. Richard A. Crosby & David R. Holtgrave, *Will Sexual Risk Behaviour Increase After Being Vaccinated for AIDS?*, 17 INT'L J. STD & AIDS 180, 182 (2006); Peter A. Newman et al., *Preventive HIV Vaccine Acceptability and Behavioral Risk Compensation among a Random Sample of High- Risk Adults in Los Angeles (LA VOICES)*, 44 HEALTH SERVS RES. 2167, 2175 (2009) [hereinafter *Preventive HIV Vaccine*]; Kyeen M. Andersson, et al., *Anticipated Changes in Sexual Risk Behaviour Following Vaccination with a Low-Efficacy HIV Vaccine: Survey Results from a South African Township*, 23 INT'L J. STD & AIDS 636, 738 (2012) [hereinafter *Anticipated Changes*].

116. *Preventive HIV Vaccine*, *supra* note 115, at 2171, 2175.

117. *Id.* at 2174.

118. *Id.*

119. *Anticipated Changes*, *supra* note 115, at 737-38.

anticipated changes in behavior, which may overestimate or underestimate actual changes in behavior.

In contrast, studies of the behavioral changes of HIV vaccine trial participants suggest that risk compensation will not increase significantly in response to a vaccine. A recent study of participants in a South African vaccine efficacy trial did not find evidence of risk compensation.[120] The majority of trial participants maintained baseline risk behaviors during the course of the study. At six months, approximately thirty percent of men and thirty-six percent of women stated that they had changed from having unprotected sex to having protected sex.[121] These findings are consistent with the observation that many participants in pre-exposure prophylaxis (PrEP) trials engaged in safer sexual practices after enrollment.[122]

The decrease in risky sexual behaviors following enrollment in preventative trials may be attributed to the provision of risk counseling services.[123] Preventative trials are designed to reduce potential harms and generally include a mechanism to minimize risk compensation. In addition to risk counseling, education regarding the efficacy of vaccines is crucial to minimizing risk compensation. The public is likely to overestimate the efficacy profile of an approved and marketed HIV vaccine. Interviews with high-risk individuals revealed that participants generally presumed that an approved vaccine would be one hundred percent efficacious.[124] Moreover, an individual who has an all-or-nothing understanding of efficacy may increase risky behavior after HIV exposure, considering failure to contract the disease as evidence of a completely protective effect.[125]

The extent to which informational initiatives may combat the problem of risk compensation is unclear. Participants who have reported engaging in risky sexual behavior during an HIV vaccine trial accurately recounted the trial's directions to practice safe sex,[126] suggesting that risk compensation is not solely attributable to information deficits.

120. G. E. Gray et al., *Does Participation in an HIV Vaccine Efficacy Trial Affect Risk Behaviour in South Africa?*, 31 VACCINE 2089, 2092 (2013).

121. *Id*. at 2093.

122. Robert M. Grant et al., *Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men*, 363 NEW ENG. J. MED. 2587, 2598 (2010); Jared M. Baeten et al., *Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women*, 367 NEW. ENG. J. MED. 399, 408-09 (2012).

123. Gray et al., *supra* note 120, at 2094.

124. *Preventive HIV Vaccine*, *supra* note 115, at 1960.

125. *Id.*

126. Margaret A. Chesney et al., *Risk Behavior for HIV Infection in Participants in Preventive HIV Vaccine Rrials: A Cautionary Note*, 16 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES & HUMAN RETROVIROLOGY, 226, 227-28 (1997).

Lessons may be learned from PrEP, a drug intervention that provides forty-four percent additional protection against HIV infection.[127] The CDC released guidance for PrEP in May 2014, recognizing that HIV preventative programs should be implemented in conjunction with other preventative services. According to the CDC, these include "educating patients about their medications; helping them anticipate and manage side effects; helping them establish dosing routines that mesh with their work and social schedules; providing reminder systems and tools; addressing financial, substance abuse, or mental health needs that may impede adherence; and facilitating social support."[128] The report acknowledges that current findings regarding that antiretroviral medication adherence may be only partially applicable to adherence enhancement among PrEP-users.[129]

It is worth noting that despite good evidence for efficacy in multiple trials, there has been low uptake of PrEP thus far,[130] indicating that there is still considerable confusion both among providers and patients about who should be prescribed PrEP, for how long, and how costs should be covered. However, physicians that work with the MSM community have said that a preventive measure that is available with more intermittent dosing might see more interest and uptake.[131] Similar features might be present in a moderate-efficacy, high-cost HIV vaccine.

3. What social harms might an HIV vaccine cause for recipients?

The social response to HIV/AIDS has historically been defined by social stigma and the threat of discrimination.[132] An HIV vaccine may exacerbate existing stigmas and present new opportunities for discrimination, especially if the vaccine is disseminated to narrow populations already at risk of stigma and discrimination (such as the MSM community and racial minorities.)[133] For

127. Douglas Krakower & Kenneth H. Mayer, *Promising Prevention Approaches: Tenofovir Gel and Prophylactic Use of Antiretroviral Medications,* 8 CURRENT HIV/AIDS REPS. 241, 242 (2011).

128. DAWN K. SMITH ET AL., PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2014 CLINICAL PRACTICE GUIDELINE 1, 44 (2014).

129. *Id*.

130. Stacy Lu, *Preventing HIV, One Pill at a Time*, MONITOR ON PSYCHOLOGY, Jan. 2015, at 40, 41.

131. Mark Mascolini, *Who's Prepared to Make PrEP work?*, 17 RES. INITIATIVE TREATMENT ACTION 1, 16 (2012).

132. *See* WORLD HEALTH ORG., GLOBAL HIV/AIDS RESPONSE: EPIDEMIC UPDATE AND HEALTH SECTOR PROGRESS TOWARDS UNIVERSAL ACCESS PROGRESS REPORT 2011 at 1, 4, 76, 101 (2011), *available at* http://whqlibdoc.who.int/publications/2011/9789241502986_eng.pdf?ua=1.

133. *See generally* Peter Newman et al., *What Can HIV Vaccine Trials Teach Us About Future HIV Vaccine Dissemination?*, 26 VACCINE 2528, 2532-34 (2008) [hereinafter *Future Vaccine Dissemination*].

early recipients, the motivator for uptake may be perceived as engagement in high-risk behavior,[134] potentially alienating the recipient from his or her community. Dissemination strategies must accordingly account for inadvertent privacy invasions through inference.[135] For instance, mobile HIV vaccination sites may permit the inference that those entering or leaving are interested in receiving the vaccine because they engage in high-risk behaviors.[136] Similarly, overutilization of needle exchange and HIV testing clinics as sources of vaccine dissemination may function to discourage uptake by associating recipients with high-risk behavior.

In inducing an antibody-response, an HIV vaccine also induces seropositivity and thus, HIV vaccine recipients will test seropositive for HIV.[137] Although false positives may be distinguished from actual viral seropositivity depending on the nature of the vaccine and the assay used, vaccine-induced seropositivity complicates the interpretation of HIV testing results, increasing the likelihood that an individual may be considered HIV positive.[138] False seropositives mistaken for actual HIV infection may have implications for travel, immigration, and insurance discrimination.[139]

C. Anticipated Costs

At least two factors generate concern that the costs of an HIV vaccine could be too high to make global distribution feasible. First, Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that research and development (R&D) of new drugs and therapeutics typically takes ten to fifteen years, costs an average of $1.2 billion, and only twenty percent of marketed drugs "return revenues that match or exceed R&D costs."[140] The total investment in R&D costs worldwide for an HIV vaccine from 2009-2013 has been estimated at $4.27 billion (U.S.D.), which is sixty-eight percent of all investment in HIV/AIDS-R&D.[141] In contrast, investment in prevention

134. *Id.* at 2532.

135. *Id.* at 2534.

136. Malika Roman Isler et al., *Acceptability of a Mobile Health Unit for Rural HIV Clinical Trial Enrollment and Participation*, 16 AIDS & BEHAVIOR 1895, 1897-98 (2012).

137. Cristine J. Cooper et al., *Vaccine-Induced HIV Seropositivity/Reactivity in Noninfected HIV Vaccine Recipients*, 304 JAMA 275, 275, 279 (2010).

138. *Id*. at 280, 282.

139. *Future Vaccine Dissemination*, *supra* note 133, at 2532.

140. PHARMACEUTICAL RES. & MANUFACTURERS OF AM., 2013 INDUSTRY PROFILE: BIOPHARMACEUTICAL RESEARCH INDUSTRY ii (2013) [hereinafter BIOPHARMACEUTICAL RESEARCH], *available at* http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf.

141. HIV VACCINES & MICROBICIDES RESOURCE TRACKING WORKING GRP., HIV PREVENTION RESEARCH & DEVELOPMENT INVESTMENT IN 2013: IN A CHANGING GLOBAL DEVELOPMENT, ECONOMIC AND HUMAN RIGHTS LANDSCAPE 3 (July 2014), *available at* http://hivresourcetracking.org/sites/default/files/RTWG2014.pdf.

treatment (ninety-six percent efficacious in preventing transmission) has been $0.24 billion (U.S.D.), or two percent of investment totals in the same time period.[142]

A second potential financial barrier is the goal of generating significant income from sales to recoup R&D costs and generate a profit for investors, which might be both significant and protected by patent law. Simply defined, a patent is an exclusive property right granted to an entity for a particular invention so long as the invention is new or involving an inventive step; it is a right to exclude others from producing, using, or selling the patented invention.[143] Patent law also grants patent holders with the authority to determine price setting within certain limits.[144] Since patent holders are generally able to control price setting, subject to constraints on monopolization, the financial barriers to access can vary considerably.[145] It is also important to note that any one vaccine contains several distinct parts or processes (e.g., antigen, adjuvant, and the delivery device), most of which are individually patentable.[146] This feature of vaccination can make avoiding infringement difficult, as manufacturers must consider not only the vaccine itself, but the very basics of its composition.[147]

One potential way of overcoming the obstacles to vaccine access in the U.S. is through compulsory licensing via antitrust laws and lawsuits for patent misuse.[148] U.S. antitrust laws permit actions against a patent holder if the alleging party can demonstrate that a particular patent has been wrongfully broadened in a way that negatively affects either competition or the integrity of the patent system.[149] If antitrust laws are breached, that patent can be deemed unenforceable or under certain circumstances the patent holder may be compelled to grant a third party a license to engage in the manufacture of the patented product.[150] Another potential way to increase access in the U.S. is through the process of price negotiation. Since major health maintenance organizations (HMO) and pharmacy benefit managers cover sixty-seven percent of U.S. patients, this represents a particularly attractive mechanism for

142. *Id.*

143. Christopher Garrison, Intellectual Property Rights and Vaccines in Developing Countries 8 (April 13, 2004) (Background Paper for World Health Organization Workshop).

144. Jerome H. Reichman, Compulsory Licensing of Patented Inventions: Comparing United States Law and Practice With Options Under the TRIPS Agreement 2-3 (June 13-16, 2006) (Paper Presented at the Association of American Law Schools midyear conference).

145. *Id.*

146. Hillary Greene, *Patent Pooling Behind the Veil of Uncertainty: Antitrust, Competition Policy, and the Vaccine Industry*, 90 B.U. L. REV. 1398, 1400 (2010).

147. *Id.*

148. *See generally* Reichman, *supra* note 144.

149. *Id.* at 3.

150. *See id.*

driving down costs.[151] Patent-pooling, a form of voluntary licensing, is another option licensors have to help increase manufacturing efficiency and reduce the costs of producing vaccinations.[152] Patent-pooling is the process of joint licensors creating a pool of their respective patents so that one license can convey the entirety of the pool to a potential licensee.[153] However, overusing voluntary licensing can have a negative impact on competition, as royalty payments typically do not lower prices to the same extent as general market competition. Lastly, the most common remedy for antitrust violations in the U.S. is the invocation of the government-use provision, 28 U.S.C. § 1498. This provision grants the government or its contractors the authority to use a patented product or process without license so long as the patent holder is paid "reasonable and entire compensation."[154] Determining an appropriate price would likely require consideration of the patented vaccine's status under the Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act), a major piece of legislation governing the approval and marketing of generic drugs.[155]

A vaccine like the one proposed in this piece may also qualify for FDA-granted market exclusivity for up to seven years if certain statutory requirements are met.[156] By granting exclusivity, the FDA promotes innovation by rewarding manufacturers who expend the resources necessary to deliver new, effective products with exclusivity over the market, and thus, increase revenue. Moreover, this statutory exclusivity can exist without a concurrently running patent.[157] This is another potential avenue available to help drive R&D while avoiding some of the hindrances of intellectual property and patent law.

From an international standpoint, there are additional mechanisms within the Agreement on Trade Related Aspects of Intellectual Property (TRIPS) that serve to increase global access to important vaccines on a global level.[158]

151. John H. Barton & Ezekiel J. Emanuel, *The Patents-Based Pharmaceutical Development Process: Rationale, Problems, and Potential Reforms*, 294 JAMA 2075, 2078 (2005).

152. Greene, *supra* note 146, at 1424.

153. *Id*. at 1415.

154. Reichman, *supra* note 144, at 5.

155. Robin J. Strongin, *Hatch-Waxman, Generics, and Patents: Balancing Prescription Drug Innovation, Competition, and Affordability*, NAT'L HEALTH POLICY FORUM, June 21, 2001, 1 at 8-9, *available at* http://www.nhpf.org/library/background-papers/BP_HatchWaxman_6-02.pdf (highlighting the provisions of Hatch-Waxman which covered drug price competition and the Abbreviated New Drug Application (ANDA) process for generics and patent term restoration).

156. *See generally* 21 C.F.R. § 314.108 (2014).

157. *Frequently Asked Questions About Drugs*, FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082690.htm (last visited Mar. 6, 2015).

158. *See generally* UNAIDS, WHO, & UNDP, POLICY BRIEF: USING TRIPS FLEXIBILITIES TO IMPROVE ACCESS TO HIV TREATMENT (2015), *available at* http://www.who.int/phi/phi_trips_policybrief_en.pdf.

TRIPS is the most comprehensive multilateral agreement on intellectual property. In addition to voluntary licensing and compulsory licensing mentioned above, TRIPS also includes two other measures: tiered pricing and bulk purchasing.[159] Tiered pricing is the practice of setting prices based on the developmental status of the purchasing country.[160] This approach, however, can be negatively affected by scheduled divergence, an event that hinders access because manufacturers cannot keep up with a vaccine demand that differs considerably between nations, especially when manufacturers rely on sales within developed countries to cover the majority of their costs.[161] Lastly, TRIPS also provides for bulk purchasing and advanced purchasing commitments.[162] The bulk purchasing mechanism operates on the general principle that a large volume of goods can be bought at a cheaper price per unit,[163] a principle especially appropriate for vaccines, considering their widespread demand. Similarly, advanced purchase commitments (i.e., bulk purchasing done prior to development or widespread manufacturing) provide added incentives for developers and manufacturers to generate vaccines by assuring a willing purchaser.[164] While patents may burden access to an approved HIV vaccine, there are existing mechanisms for overcoming these impediments.

Even if the barriers of R&D costs and patent law are overcome and a reasonable price per dose is established, an HIV vaccine may still be cost prohibitive. Again for the sake of argument, we will stipulate a hypothetical cost per dose for each vaccine of $250 based on the analysis of Elisa Long and Douglas Owens.[165] Based on our hypothesized dosing schedule of four doses in year one and an annual booster, the total cost is $1,000 in year one and the ten-year cost is $3,250 per person. If recipients do not follow up with the annual boosters, vaccine efficacy will decline rapidly.[166]

Such costs may be prohibitive to widespread dissemination, particularly at a global level, where poverty is more prevalent and transmission patterns are not limited to easily identifiable high-risk groups. In fact, if an HIV vaccine is only moderately effective and some of its effectiveness is offset by behavioral risk adjustments, then the costs of an HIV vaccine do not supplant, but rather are added to the costs of other preventive measures and treatment.

159. Garrison, *supra* note 143, at 3.

160. Barton & Emanuel, *supra* note 151, at 2078.

161. Garrison, *supra* note 143, at 23.

162. *Id.* at 3; *see also* Ernst R. Berndt & John A. Hurvitz, *Vaccine Advance-Purchase Agreements For Low-Income Countries: Practical Issues*, 24 HEALTH AFF. 653, 653 (2005).

163. Garrison, *supra* note 143, at 23.

164. Berndt & Hurvitz, *supra* note 162, at 654.

165. Long & Owens, *supra* note 85, at 6117.

166. *Id.* at 6115.

D. Anticipated Distribution Controversies

Distribution of an HIV vaccine will be affected by economic factors, logistics, the efficacy of the vaccine, and social reactions within different nations and communities.

1. Should vaccine distribution target high-risk populations?

For reasons of cost-effectiveness, a low to moderate efficacy HIV vaccine (less than eighty percent efficacy) will likely be recommended only for high-risk populations.[167] A low to moderate efficacy vaccine will also carry the same problems as the Bacille Calmette-Guérin (BCG) vaccination to prevent TB. For example, although it may be modestly effective, use of the BCG vaccine complicates health care services by interfering with the most commonly used testing modalities for asymptomatic (latent) TB.[168] Similarly, a modestly effective HIV vaccine may be problematic, as it would result in positive HIV tests (i.e., ELISA and Western blot) for patients at highest risk for acquiring HIV. This would require the use of a more expensive test (the HIV viral load) for screening this population.

It is unclear whether high-risk populations will spontaneously seek vaccination if the benefits are only modest. For example, even with good efficacy, when patients comply with a daily regime of PrEP, uptake has been very slow within the MSM community.[169] It is likely that widespread vaccination within high-risk populations will require targeted vaccine campaigns, which may include social marketing, educational outreach programs, strategically located delivery centers, and financial incentivizing—all of which add to the costs of a vaccine campaign.[170]

While these strategies do not directly encroach upon the autonomy of the individual target recipient, they may compound social pressure and stigma. Social marketing, which exploits the desire for social acceptance, may

167. Jose Esparza et al., *Estimation of "Needs" and "Probable Uptake" for HIV/AIDS Preventive Vaccines Based on Possible Policies and Likely Acceptance (A WHO/UNAIDS/IAVI Study)*, 21 VACCINE 2032, 2034 (2003).

168. The standard method for testing TB is the Mantoux tuberculin skin test (TST), which injects tuberculin purified protein derivative (PPD) into the inner surface of the forearm. CTRS. FOR DISEASE CONTROL & PREVENTION, TB ELIMINATION: TUBERCULIN SKIN TEST 1 (2011), *available at* http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.pdf. Although responses are inconsistent, studies have shown that prior BCG vaccination increases the risk of receiving a false-positive result under a TST. *Id.*; Kathleen Rowland et al., *How Should We Manage a Patient With a Positive PPD and Prior BCG Vaccination*, 55 J. FAMILY PRACTICE 718, 719 (2006).

169. Mascolini, *supra* note 131.

170. Jeroen Luyten et al., *Vaccination Policy and Ethical Challenges Posed by Herd Immunity, Suboptimal Uptake and Subgroup Targeting*, 4 PUB. HEALTH ETHICS 280, 282, 284 (2011).

exaggerate perceptions of homogeneous characteristics (for example, the belief that all members of the MSM community practice unsafe sex) and exacerbate social anxieties among members of the target population.[171] Educational outreach programs and local delivery centers may inadvertently facilitate perceptions that HIV is isolated to socially deviant communities. Financial incentives, when offered only to those in high-risk populations, may encourage perceptions of social dependency. Efforts to target vaccine uptake must balance public health goals with respect for target populations.

The risk of alienating at-risk populations may be managed by including members of at-risk populations in the development of targeting campaigns. To minimize the risk of stigma and discrimination, targeting policies should also focus as much as possible on relevant individual factors, such as identifying populations with high prevalence of HIV in their sexual network, and individuals who present with recurrent sexually transmitted diseases (STD).[172] A focus on individually relevant factors rather than group generalizations will decrease opportunities for stigma. For example, targeting men who have unsafe sex with men, rather than the entire MSM community, recognizes the diversity of the MSM community.[173] However, the tailoring of targeted vaccine policy to individual characteristics requires greater scrutiny, poses a risk of invading individual privacy, and would require physicians to take more complete sexual histories to identify individuals at risk.[174]

The success of targeted vaccination efforts will be limited by inequalities in health care access, as dissemination programs will need to rely on the existing health care infrastructure.[175] Thus, eradication of HIV will likely depend not only on the successful development of preventive technologies, but also investment in expanding the health care infrastructure to disadvantaged communities. For example, although African American and Latino communities have historically exhibited suboptimal uptake of vaccines and HIV treatment, poor uptake likely reflects access issues.[176]

The Belmont Report, which provides ethical principles to guide research funded by the U.S. government, additionally raises justice-based concerns about targeting at-risk populations in the U.S. for distribution of a vaccine, if the clinical trials leading to the development and approval of a vaccine

171. Alison Thompson, *Human Papilloma Virus, Vaccination and Social Justice: An Analysis of a Canadian School-Based Vaccine Program*, 6 PUB. HEALTH ETHICS 11, 16 (2013).

172. *See, e.g.*, Luyten et al., *supra* note 170, at 285.

173. *Id.*

174. *Id.* at 286.

175. Esparza et al., *supra* note 167, at 2037.

176. *Future Vaccine Dissemination*, *supra* note 133, at 2529.

recruited participants from developing nations.[177] For example, individuals who assume the risks of clinical trials should belong to the same group of individuals who are likely to benefit from the trials.[178] That is, the context of HIV vaccine research may require that we have a plan for affordable distribution of the vaccine within resource-poor nations concomitant with U.S. distribution. However, this will pose a significant challenge to the market if the vaccine is approved only for use in high-risk populations because this would radically restrict the size of the U.S. market, which commonly shoulders the primary burden in the recovery of R&D costs.[179]

2. Might the state mandate an HIV vaccine?

The question remains whether an approved HIV vaccine should be mandated. States have traditionally been charged with making determinations regarding mandatory vaccination via school attendance requirements as well as deciding which exemptions should be recognized.[180] A state derives its authority to mandate vaccinations from the police power, a product of the Tenth Amendment to the U.S. Constitution, which grants states those powers "not delegated to the United States."[181] In *Jacobson v. Massachusetts*, the Supreme Court of the United States held that a Massachusetts law requiring citizens to undergo vaccination for smallpox was a valid exercise of the police power.[182] The Court held that the law bore a substantial relationship to the protection of public health and it was reasonable for the state legislature to invest the Board of Health with the power to determine which diseases threaten the community's safety.[183] States also have traditionally relied on the *parens patriae* (Latin for "parent of the country") doctrine, the traditional authority for the state to protect its citizens.[184]

Since the states' police power has been widely accepted for decades, primarily on the basis of public health, general vaccination requirements are

177. NAT'L COMM'N FOR PROT. HUMAN SUBJECTS BIOMEDICAL & BEHAVIORAL RES., THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH 9-10 (1978).

178. Harold Varmus & David Satcher, Editorial, *Ethical Complexities of Conducting Research in Developing Countries*, 337 NEW ENG. J. MED. 1003, 1004-05 (Oct. 1997).

179. *Immunization, Vaccines and Biologicals: HIV/AIDS*, WORLD HEALTH ORG., http://www.who.int/immunization/topics/hiv/en/WHO.INT (last updated Jun. 18, 2008).

180. James G. Hodge, Jr. & Lawrence O. Gostin, *School Vaccination Requirements: Historical, Social, and Legal Perspectives*, 90 KY. L.J. 831, 851 (2001-2002).

181. U.S. CONST. amend. X.

182. *Jacobson v. Mass.*, 197 U.S. 11, 35 (1905).

183. BARRY R. FURROW ET AL., HEALTH LAW: CASES, MATERIALS AND PROBLEMS 76 (7th ed. 2013).

184. Allen Craig et al., *New Adolescent Vaccines: Legal and Legislative Issues*, 35 J.L. MED. & ETHICS 106, 108 (2007).

usually legitimate, subject to a few constitutional limits that vaccination laws must conform to in order to withstand constitutional scrutiny. First, the legislative measure must serve a public health necessity, which means the public health powers can only be invoked to combat an avoidable harm.[185] Second, the measure must be reasonable, namely it must bear a "real or substantial relation" to the protection of the public health.[186] Third, the measure must be proportional, meaning the measure's burden cannot be excessive or outweigh its anticipated benefit.[187] Finally, the public health measure itself cannot cause harm to its subjects.[188] So long as vaccination mandates conform to the above limitations, they will likely defeat constitutional challenges.

States will need to keep in mind that just because an HIV vaccine is FDA-approved does not mean that it will necessarily pass these four tests for the use of police powers. HIV vaccines with low, moderate, and high efficacy need to be treated differently. While a highly efficacious HIV vaccine could accomplish a public health benefit if mandated, a low or moderately efficacious HIV vaccine could very well have the opposite effect.[189] Based on the fact that mandate decisions fall to the state, decisions of whether or not to mandate HIV vaccination will be geographical in nature and deeply influenced by a state's rate of HIV infection.

3. Social Controversy

While the justification for mandating vaccination may be strongest in regard to diseases that spread by casual contact, there are other vaccinations commonly mandated even though their associated diseases are not likely to be spread via casual contact. For example, tetanus and Hepatitis B are unlikely to be contracted from casual contact, since tetanus is most commonly acquired through contamination of a cut or wound, and HBV is largely sexually-transmitted.[190] The highly infectious nature of HBV as a blood borne pathogen[191] and the public health need to ensure the safety of the blood supply have likely also contributed to its inclusion as a mandatory vaccine.

185. Kristin Cook, Note, *Ethical and Legal Issues Accompanying Legislation Requiring HPV Vaccination of Girls*, 18 HEALTH MATRIX 211, 221 (2008).

186. *Id.*

187. *Id.* at 222.

188. *Id.*

189. *See* Esparza et al., *supra* note 167, at 2034, and accompanying text.

190. Gillian Haber et al., *The HPV Vaccine Mandate Controversy*, 20 J. PEDIATRIC & ADOLESCENT GYNECOLOGY 325, 326 (2007).

191. *See Hepatitis B Fact Sheet N°204*, WORLD HEALTH ORG., http://www.who.int/mediacentre/factsheets/fs204/en/ (last updated Mar. 2014).

Currently, HBV vaccination is mandatory in all states with the exceptions of Alabama, South Dakota, and Montana.[192] It is interesting to contrast the history and status of the HBV vaccine to the HPV vaccine, which similarly aims to prevent the spread of a sexually transmitted virus.

Over the past decade there has been notable protest regarding compulsory HPV vaccination of school-aged children.[193] The controversy surrounding HPV vaccination is focused on both social and scientific grounds. From a scientific position, critics of mandatory vaccination feel that since the long-term effectiveness of HPV vaccines is not known, it is inappropriate to mandate vaccination in light of uncertainties concerning risk to the public.[194] On the social side, critics of mandatory HPV vaccination focus on the fact that HPV is not casually contracted, although it is highly infectious, with a prevalence rate as high as fifty percent in sexually active female adolescents and young adults.[195] These critics maintain that providing vaccinations for HPV may undermine abstinence-based teachings and that vaccines will offer a false sense of security that could lead to a decline in safe sex practices.[196] Vamos, McDermott, and Daley write:

> Childhood immunizations, such as measles, chicken pox, and polio, are mandatory for school-aged youth and are required because of their highly contagious nature, especially in settings where people congregate in large numbers. Therefore, the question is whether there is justification for mandating parents to vaccinate their children against a sexually transmitted virus, one that can only be transmitted through sexual behavior that some people view as being irresponsible.[197]

Any effort to widely distribute an HIV vaccine may face similar challenges within certain sectors of society, which view sexual behavior not merely in terms of introducing "risk factors," but also in terms of morality, and frequently, a traditional sexual morality that condemns sex outside of heterosexual marriage.

Allowing exceptions to mandatory vaccination has been a means of addressing social outcry. Forty-eight states (excluding Mississippi and West Virginia) recognize religious exemptions.[198] The level of evidence needed to

192. *See supra* note 13 and accompanying text.

193. *See* Haber et al., s*upra* note 190.

194. Cheryl A. Vamos et al., *The HPV Vaccine: Framing the Arguments For and Against Mandatory Vaccination of All Middle School Girls*, 78 J. SCH. HEALTH 302, 305 (2008).

195. Jessica A. Kahn et al., *Mediators of the Association Between Age of First Sexual Intercourse and Subsequent Human Papillomavirus Infection*, 109 PEDIATRICS 1, 1 (2002).

196. Haber et al., *supra* note 190, at 327.

197. Vamos et al., *supra* note 194, at 304 (citation omitted).

198. Kevin M. Malone & Alan R. Hinman, *Vaccination Mandates: The Public Health Initiative and Individual Rights*, *in* LAW IN PUB. HEALTH PRACTICE 262, 273 (Richard A. Goodman ed., 2nd ed. 2007).

invoke a religious exemption varies by state. A few states require that the patient be a member of an organized, recognized, or established religion, while others grant exemptions only if the beliefs are "genuinely and sincerely held," while still others require only a completed form stating opposition.[199] Philosophical exemptions are more malleable than their religious counterparts and are also more commonly invoked. Laws governing these exemptions typically require little evidence to support objection, many times only requiring a written statement.[200] However, many states treat philosophical exemptions as an all or nothing affair, requiring one to forego all vaccinations instead of expressing objections to only specific vaccines.[201] Twenty states recognize some form of philosophical exemptions.[202]

Exceptions have not, however, always satisfied those who object to mandating vaccination. Following FDA approval of Gardasil and Cervarix and the recommendation of the national Advisory Committee on Immunization Practices (ACIP), state legislatures began drafting HPV vaccination laws.[203] At least forty-two states have introduced HPV vaccination legislation to either require vaccination or provide funding to educate the public and twenty-five of these states have enacted such legislation with nearly all legislative measures focusing on grant-funding to educate the public.[204] The road to specifically mandate HPV vaccinations has proven to be more difficult. Only Virginia and the District of Columbia currently have laws mandating HPV vaccination for schooling.[205]

The 2007 events in Texas provide an illustrative example of challenges to mandatory vaccine laws covering STDs. In 2007, Texas Governor Rick Perry, believing immediate action was necessary, bypassed the state legislature and

199. Alicia Novak, *The Religious and Philosophical Exemptions to State Compelled Vaccination: Constitutional and Other Challenges*, 7 U. PA. J. CONST. L. 1101, 1107-1108 (2005).

200. *Id.* at 1109.

201. *Id.*

202. Arizona, Arkansas, California, Colorado, Idaho, Louisiana, Maine, Michigan, Minnesota, Missouri, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Texas, Utah, Vermont, Washington, and Wisconsin recognize philosophical exemptions. *States With Religious and Philosophical Exemptions From School Immunization Requirements*, NAT'L CONF. OF STATE LEGISLATURES, http://www.ncsl.org/research/health/school-immunization-exemption-state-laws.aspx (last updated March 3, 2015).

203. *See* KAISER FAMILY FOUND., THE HPV VACCINE: ACCESS AND USE IN THE U.S. 13 (Feb. 2015), *available at* http://files.kff.org/attachment/fact-sheet-the-hpv-vaccine-access-and-use-in-the-u-s. The FDA approved Gardasil in 2006 and Cervarix in 2009. *Id*. at 2; *see also HPV Vaccine Polices*, NAT'L CONF. OF STATE LEGISLATURES, http://www.ncsl.org/research/health/hpv-vaccine-state-legislation-and-statutes.aspx (last visited March 6, 2015) [hereinafter *HPV Vaccine Policies*].

204. *HPV Vaccine Policies*, *supra* note 203.

205. *Id.*

issued an executive order mandating HPV vaccination for girls entering the sixth grade.[206] Almost as quickly as its issuance, the newly signed law generated substantial public backlash.[207] Even though the Texas law, like the Virginia and District of Columbia laws that are currently in force, allowed exemptions on medical, religious, and philosophical grounds, concerned parents still expressed disdain over the perceived erosion of their decision-making authority and the hassle of having to formally request exemption.[208] Another common challenge confronting HPV vaccine mandates is the parental fear that vaccinating their children against a STD conveys an implied message that sexual activity before marriage is permissible.[209]

Some opponents also argue that mandatory HPV vaccination laws violate the Equal Protection Clause of the Fourteenth Amendment as such laws (including both Virginia's and the District of Columbia's formulations) require only girls to be vaccinated despite the FDA's approval for Gardasil usage among males.[210] Following this extensive public backlash, the Texas legislature passed a bill nullifying Governor Perry's executive order, and Governor Perry subsequently withheld his veto.[211] Overall, the arguments advanced by Perry's critics are the ones most commonly used to attack similar vaccination requirements and should be anticipated if an HIV vaccine is mandated.

Interestingly, mandating vaccination for STDs has also proven controversial among some groups that support vaccination. For example, the Catholic Medical Association of the U.S. supports widespread HPV vaccination and identifies no ethical issues with the vaccine itself, but strongly opposes mandatory vaccination.[212] We expect that if an HIV vaccine is not recommended for children, and if no attempts are made to mandate the vaccine, the backlash from religious groups will be significantly less than if the HIV vaccine was mandated for school-aged children. However, as a predominant STD, HIV vaccination is likely to be more effective if given prior to sexual debut.

206. Cook, *supra* note 185, at 214.

207. *Id.* at 216-17.

208. *Id.* at 217.

209. Carrie A. Roll, *The Human Papillomavirus: Should It Be Mandatory or Voluntary?*, 10 J. HEALTH CARE L. & POL'Y 421, 440 (2007).

210. Christina O. Hud, *The Virginia Gardasil Law: A Constitutional Analysis of Mandated Protection for Schoolchildren Against the Human Papillomavirus*, 17 WASH. & LEE. J. CIV. RTS. & SOC. JUST. 224, 259, 263 (2010).

211. *HPV Vaccines Policies*, *supra* note 203.

212. CATHOLIC MED. ASS'N, CATHOLIC MED. ASS'N POSITION PAPER ON HPV IMMUNIZATION 2-3 (2007), *available at* http://www.cathmed.org/assets/files/Position%20Paper%20on%20HPV%20Immunization.pdf.

Admittedly, mandatory HBV vaccination generated comparably little controversy and almost no literature, despite the fact that HBV is primarily sexually-transmitted.[213] This may be due in part to the timing of the rollout of the HBV vaccine. The current vaccine has been used since 1986, a time in which there was considerable concern for the safety of the blood supply from a variety of blood borne pathogens, including HBV, HIV, and non-A/non-B Hepatitis (subsequently identified as Hepatitis C).[214] We suspect that the increased controversy over HPV is due to backlash against vaccination from a younger population, which never experienced the original devastation caused by vaccine-preventable diseases, as well as increased influence from political factions within the U.S. that seek to minimize government intervention into the lives of citizens. In the current climate, mandating an HIV vaccine would likely receive a reaction more comparable to the HPV vaccine than to the HBV vaccine. Additionally, the potential backlash concerning mandatory HIV vaccination will likely be magnified based on its potential moderate efficacy profile as compared to the efficacy profiles of the HPV and HBV vaccines.

IV. CONCLUSION

To summarize, based on the most promising clinical trials to date, we anticipate the first vaccine approved to prevent HIV infection will be only modestly effective. The type of HIV vaccine that can be expected will not fully eradicate the disease and, therefore, will not replace the need for ongoing and improved prevention and treatment efforts. Additionally, a broad vaccination campaign will be costly given that immunization may require multiple doses in the first year and annual booster doses. To avoid risk compensation, the vaccine campaign will require a significant educational component, though it is not clear that risk compensation is due to informational deficits. Social resistance to any effort at mandating an HIV vaccine is likely to be strong. While we have focused on the U.S. context, many of the overarching concerns—efficacy being limited to specific strains, costs, the burden of administering multiple doses, risk compensation, and social resistance—pertain to international settings to an even greater extent than the U.S.

213. *See Testimony on Hepatitis B Vaccine Before the H. Comm. on Gov't Reform, Subcomm. on Criminal Justice, Drug Policy, and Human Resources*, 106th Cong. 1-9 (1999), *available at* http://www.hhs.gov/asl/testify/t990518b.html. (testimony from Harold S. Margolis, M.D.Chief, Hepatitis Branch, Division of Viral & Rickettsial Diseases, U.S. Department of Health & Human Services).

214. INST. OF MED., HIV AND THE BLOOD SUPPLY: AN ANALYSIS OF CRISIS DECISIONMAKING, at v (Lauren B. Leveton et al., eds. 1995).

A. Suggestions for Justificatory Conditions

We started this paper by presenting the ways that HBV vaccines arguably satisfy a set of widely recognized justificatory conditions for public health policies. In contrast to HBV vaccines, the HIV vaccines we anticipate in the near future do not satisfy the conditions nearly so well. However, in most cases, we lack the knowledge and clear processes to draw appropriate conclusions. In what follows, we present the justificatory conditions and offer suggestions on what would need to occur before a determination is made regarding whether any particular HIV vaccine should be licensed and approved for marketing.

1. *Effectiveness*: The policy must be expected to achieve its aim.

HIV vaccines pose a challenge to this requirement: What level of real-world effectiveness is sufficient? How long must it be sustained? Just as the FDA has issued *Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines*,[215] it would be helpful if the FDA issued proactive guidance on the bounds of effectiveness that would be considered acceptable for licensing an HIV vaccine. Further research is also needed to provide reliable data on real-world effectiveness as opposed to efficacy within a controlled trial.

2. *Proportionality*: The good achieved must balance favorably against the infringement of other values.

Determinations of proportionality require that the benefits of a vaccine be weighed against at least two competing considerations: cost and risk compensation. Between 2009 and 2013, worldwide R&D expenditures on an HIV vaccine were approximately $4.27 billion.[216] Is an HIV vaccine likely to be cost-effective after considering anticipated real-world effectiveness rates, costs of implementing the program with boosters, and ongoing needs for education and treatment? And will the effectiveness rates be high enough to reduce the disease burden even after taking into account risk compensation? To answer this question, we urgently need updated mathematical models of the potential for risk compensation in the context of a vaccination campaign in the U.S. Proportionality determinations may vary significantly depending on the population in which the vaccine is approved for use. However, such a determination might rest largely upon answers to other questions posed (pertaining to effectiveness, cost, and risk compensation).

215. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CLINICAL DATA NEEDED TO SUPPORT THE LICENSURE OF PANDEMIC INFLUENZA VACCINES 1 (2014), *available at* http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm.

216. *See* BIOPHARMACEUTICAL RESEARCH, *supra* note 140, at 32.

3. *Necessity*: The infringement of values must be necessary to achieve the intended public health goal.

One could argue that an HIV vaccine would likely pass this test because there is no way to develop an HIV vaccine that will not incur costs or run the risk of some risk compensation. However, one could also argue that it is not necessary to approve a vaccine with lower than standard rates of efficacy. That is, if the ultimate goal is to reduce the burden of HIV on the population using limited funds, one could argue that it makes more sense to focus funding on other prevention measures, treatment, and R&D aimed not only at vaccines, but also on treatments or cures.

4. *Least infringement*: The infringement of other values should be minimized.

One obvious strategy for least infringement might be to initially approve an HIV vaccine only for high-risk populations and to approve the vaccine for a limited period of time, to conduct post-marketing research that might include cost-effectiveness and the impact on risk compensation.

5. *Public justification*: Policy makers should be transparent and explain the reasons for the policy.

More generally, we would interpret this to require inclusion of stakeholders in deliberations, such as through public comment opportunities or the creation of review boards that reflect diversity. To satisfy this justificatory condition, two modifications of FDA processes might be appropriate. First, the FDA's approval process requires an overall determination that the anticipated benefits outweigh risks.[217] The scope of this risk-benefit analysis is not clearly articulated. Can it include the risk of diverting public funding from research on cures and the provision of treatments? Can it include risks of behavioral change? Clarifying the scope of the risk-benefit analysis prospectively and transparently will assist in the evaluation of an HIV licensing application. Second, the composition of FDA's review committees might benefit from expansion to include diverse epidemiologists, policy experts, economists, ethicists, and representatives of populations most at risk for HIV infection. Within the FDA, the Center for Biologics Evaluation and Research (CBER) reviews applications for the approval of vaccines.[218] A former director of CBER, Norman Taylor, states "[m]ost of our staff started in a laboratory or in

217. *About FDA: How FDA Evaluates Regulated Products: Drugs*, FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/Transparency/Basics/ucm269834.htm (last visited March 3, 2015).

218. *Vaccine Product Approval Process*, FOOD & DRUG ADMIN., http://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicslicenseapplicationsblaprocess/ucm133096.htm (last updated June 18, 2009).

a clinical setting, a hospital or some other clinical setting, so we have . . . the ability and the knowledge base to evaluate these products."[219] However, it is unclear whether standard CBER laboratory and clinical backgrounds and data analysis are adequate to make the required determination of efficacy when efficacy is well below previously approved thresholds and diminishes rapidly in the absence of boosters (or perhaps even with boosters). It is even less clear that CBER staff have the expertise to conduct the kind of broad risk-benefit analysis described above. The FDA does have a standing Vaccines and Related Biological Products Advisory Committee (VRBPAC), which can provide a secondary review of applications. However, it is unclear whether the composition of the advisory committee reflects the broad array of expertise and stakeholder representation that the review of an HIV vaccine might require.

Like most citizens of the world, we hope that science will one day produce an HIV vaccine that is similar to many other vaccines, with rates of efficacy approaching one hundred percent. In the meantime, health policy makers will do well to anticipate the opportunities and challenges that a moderately effective HIV vaccine will present.

219. *FDA Basic Video: Norman Baylor Discusses Vaccines*, FOOD & DRUG ADMIN. (April 11, 2014), http://www.fda.gov/AboutFDA/Transparency/Basics/ucm195661.htm.