of a pragmatic open-label randomised trial. *Lancet*. 2016;387:53–60.
131. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med*. 2015;373:2237–2246.
135. Tanser F, Bärnighausen T, Grapsa E, et al. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science*. 2013;339:966–971.
145. Population Action International and the African Institute for Development Policy. Population, climate change, and sustainable development in Africa; June 2012. http://populationaction.org/wp-content/uploads/2012/06/PAI-AFIDEP.pdf. Accessed February 28, 2014.
151. Baird S, Garfein R, McIntosh C, et al. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. *Lancet*. 2012;379:1320–1329.
152. Pronyk PM, Hargreaves JR, Kim JC, et al. Effect of a structural intervention for the prevention of intimate-partner violence and HIV in rural South Africa: a cluster randomised trial. *Lancet*. 2006;368:1973–1983.
155. de Waal A, Whiteside A. New variant famine: AIDS and food crisis in southern Africa. *Lancet*. 2003;362:1234–1237.
173. Kim JC, Watts CH, Heargraves JR, et al. Understanding the impact of a microfinance-based intervention on women's empowerment and the reduction of intimate partner violence in South Africa. *Am J Public Health*. 2007;97:1794–1802.
221. Piot P, Abdool Karim SS, Hecht R, et al. Defeating AIDS–advancing global health. *Lancet*. 2015;386:171–218.

References

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. 2012;380:2095–2128.
2. UNAIDS. Fact sheet - world AIDS day; 2017. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. Accessed January 23, 2018.
3. UNAIDS. AIDSinfo; 2017. http://aidsinfo.unaids.org/. Accessed January 8, 2018.
4. UNAIDS. *Right to Health*. Geneva, Switzerland: UNAIDS; 2017.
5. Kharsany ABM, Karim QA. HIV infection and AIDS in Sub-Saharan Africa: current status, challenges and opportunities. *Open AIDS J*. 2016;10:34–48.
6. UN Women. Facts and figures: HIV and AIDS; 2016. http://www.unwomen.org/en/what-we-do/hiv-and-aids/facts-and-figures. Accessed January 23, 2018.
7. WHO. Fact sheet on adolescent health; 2015. http://www.wpro.who.int/mediacentre/factsheets/docs/fs_201202_adolescent_health/en/. Accessed January 23, 2018.
8. UNICEF. *For Every Child, End AIDS – Seventh Stocktaking Report*. New York: UNAIDS; 2016.
9. UNAIDS. Core epidemiology slides; 2017. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_2017_core-epidemiology-slides_en.pdf. Accessed January 23, 2018.
10. UNAIDS. Ending AIDS: progress towards the 90-90-90 targets; 2017. http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf. Accessed January 23, 2018.
11. UNAIDS announces nearly 21 million people living with HIV now on treatment [press release]. Geneva, Switzerland: UNAIDS; 2017.
12. Ghys P, Walker N, Ward H, et al. Improved methods and tools for HIV/AIDS estimates and projections. *Sex Transm Infect*. 2006;82(supplIII).
13. Macro International. Demographic and health surveys. http://www.orcmacro.com/Survey/Demographic/dhs.aspx. Accessed September 20, 2008.
14. GBD 2015 HIV Collaborators. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the global burden of disease study 2015. *Lancet HIV*. 2016;3:e361–e387.
15. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. *HIV/AIDS Surveillance in Europe 2011*. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2012.
16. UNAIDS. *UNAIDS World AIDS Day Report 2012*. Geneva, Switzerland: UNAIDS; 2012.
17. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. *HIV/AIDS Surveillance in Europe 2017 (2016 Data)*. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2017.
18. Euro HIV, Nardone A, Alix J. HIV infection in Europe. Bull Épidémiol Hebdomadaire Institut Veille Sanitaire. 2007:46-47.
19. Brown AE, Kirwan PD, Chau C, et al. *Towards Elimination of HIV Transmission, AIDS and HIV-Related Deaths in the UK – 2017 Report*. London: Public Health England; 2017.
20. Beyrer C, Wirtz AL, O'Hara G, et al. The expanding epidemic of HIV-1 in the Russian Federation. *PLoS Med*. 2017;14:e1002462.
21. UNAIDS. *Global Report 2012: UNAIDS Report on the Global AIDS Epidemic*. Geneva, Switzerland: UNAIDS; 2012.
22. Institute for Health Metrics and Evaluation. GBD compare; 2017. https://vizhub.healthdata.org/gbd-compare/. Accessed January 23, 2018.
23. UNAIDS. *The GAP Report 2014 - Children and Pregnant Women Living With HIV*. Geneva, Switzerland: UNAIDS; 2014.
24. UNAIDS. *2015 Progress Report on the Global Plan Towards the Elimination of New HIV Infections Among Children and Keeping Their Mothers Alive*. Geneva, Switzerland: UNAIDS; 2015.
25. Hallett TB, Aberle-Grasse J, Bello G, et al. Declines in HIV prevalence can be associated with changing sexual behaviour in Uganda, urban Kenya, Zimbabwe, and urban Haiti. *Sex Transm Infect*. 2006;82(suppl 1):i1–i8.
26. Kirungi WL, Musinguzi J, Madraa E, et al. Trends in antenatal HIV prevalence in urban Uganda associated with uptake of preventive sexual behavior. *Sex Transm Infect*. 2006;82:36–41.
27. Fabiani M, Nattabi B, Pioretti C, et al. HIV prevalence and factors associated with infection in the conflict-affected region of northern Uganda. *Confl Health*. 2007;1:1–8.
28. Uganda Ministry of Health. *Uganda Population-Based HIV Impact Assessment UPHIA 2016–2017 - Summary Sheet: Preliminary Findings*. Kampala: Uganda Ministry of Health; 2017.
29. Nkambule R, Nuwagaba-Biribonwoha H, Mnisi Z, et al. Substantial progress in confronting the HIV epidemic in Swaziland: first evidence of national impact. Paper presented at 9th International AIDS Society Conference on HIV Science 2017; Paris.
30. Karim SA. Is the UNAIDS target sufficient for HIV control in Botswana? *Lancet HIV*. 2016;3:e195–e196.
31. Shisana O, Rehle T, Simbayi L, et al. *South African National HIV Prevalence, Incidence and Behaviour Survey, 2012*. Cape Town, South Africa: HSRC Press; 2014.
32. Pettifor AE, Rees HV, Kleinschmidt I, et al. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS*. 2005;19:1525–1534.
33. Gregson S, Nymukapa A, Garnett G, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet*. 2002;359:1896–1903.
34. de Oliveira T, Kharsany AB, Graf T, et al. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. *Lancet HIV*. 2017;4:e41–e50.
35. Morris M, Kretzschmar M. Concurrent partnerships and the spread of HIV. *AIDS*. 1997;11:641–648.
36. Lagarde E, Carael M, Auvert B. Concurrency and HIV prevalence. *AIDS*. 2002;16:679–680.
37. Carael M, Glynn R, Lagarde E. Sexual networks and HIV in four African populations: the use of a standardised behavioural survey with biological markers. In: Morris M, ed. *Network Epidemiology: A Handbook for Network Survey Design and Data Collection*. Oxford: Oxford University Press; 2004:58–84.
38. Helleringer S, Kohler HP, Kalilani-Phiri L. The association of HIV serodiscordance and partnership concurrency in likoma island (Malawi), Malawi. *AIDS*. 2009;23:1285–1287.
39. Lurie MN, Williams BG, Zuma D, et al. Who infects whom? HIV-1 concordance and discordance among migrant and nonmigrant couples in South Africa. *AIDS*. 2003;17:2245–2252.
40. Coffee M, Lurie MN, Garnett GP. Modelling the impact of migration on the HIV epidemic in South Africa. *AIDS*. 2007;21:343–350.
41. Van der Loeff MF, Awasana AA, Sarge-Njie R, et al. Sixteen years of HIV surveillance in a west African research clinic reveals divergent epidemic trends of HIV-1 and HIV-2. *Int J Epidemiol*. 2006;35:1322–1328.
42. Fryer HR, Van Tienen C, Van Der Loeff MS, et al. Predicting the extinction of HIV-2 in rural Guinea-Bissau. *AIDS*. 2015;29:2479–2486.
43. Jenkins C, Robalino DA. *HIV/AIDS in the Middle East and North Africa: The Costs of Inaction*. Washington, DC: World Bank; 2003.
44. Pendse R, Gupta S, Yu D, et al. HIV/AIDS in the South-East Asia region: progress and challenges. *J Virus Erad*. 2016;2(suppl 4):1–6.
45. Sarkate P, Paranjpe S, Ingole N, et al. Monitoring HIV epidemic in pregnant women: are the current measures enough? *J Sex Transm Dis*. 2015;2015:194831.
46. Mathers BM, Degenhardt L, Phillips B, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet*. 2008;372:1733–1745.
47. World Health Organization. *HIV/AIDS in the South East Asia Region*. New Delhi: World Health Organization Regional Office for South East Asia; 2007.
48. Kermode M, Nuken A, Medhi GK, et al. High burden of hepatitis C & HIV co-infection among people who inject drugs in Manipur, Northeast India. *Indian J Med Res*. 2016;143:348–356.
49. National Health and Family Planning Commission of the People's Republic of China. *2015 China AIDS Response Progress Report*. 2015.
50. Hornby L, Zhang A. Increase in number of HIV cases in China raises concerns. *Financial Times*. 2016.
51. Dong Z, Xu J, Zhang H, et al. HIV incidence and risk factors in Chinese young men who have sex with men—a prospective cohort study. *PLoS ONE*. 2014;9:e97527.
52. UNAIDS. *UNAIDS Data 2017*. Geneva, Switzerland: UNAIDS; 2017.
53. Ministry of Health. *National HIV Sentinel Surveillance Report*. Hanoi, Vietnam: Ministry of Health; 2007.
54. The World Bank. The global AIDS epidemic among people who inject drugs; 2013. http://www.worldbank.org/content/dam/Worldbank/document/GlobalHIVEpidemicsAmongPeopleWhoInjectDrugs.pdf.
55. Zhang L, Yap L, Xun Z, et al. Needle and syringe programs in Yunnan, China yield health and financial return. *BMC Public Health*. 2011;11:250.
56. UNAIDS. *UNAIDS Report on the Global AIDS Epidemic 2012*. Geneva, Switzerland: UNAIDS; 2012.
57. UNAIDS. *Do No Harm - Health, Human Rights and People Who Use Drugs*. Geneva, Switzerland: UNAIDS; 2016.
58. Idele P, Gillespie A, Porth T, et al. Epidemiology of HIV and AIDS among adolescents: current status, inequities, and data gaps. *J Acquir Immune Defic Syndr*. 2014;66(suppl 2):S144–S153.
59. García PJ, Bayer A, Cárcamo CP. The changing face of HIV in Latin America and the Caribbean. *Curr HIV/AIDS Rep*. 2014;11:146–157.
60. UNAIDS Brazil. Estatísticas; 2016. https://unaids.org.br/estatisticas/. Accessed January 16, 2018.
61. Grinsztejn B, Jalil EM, Monteiro L, et al. Unveiling of HIV dynamics among transgender women: a respondent-driven sampling study in Rio de Janeiro, Brazil. *Lancet HIV*. 2017;4:e169–e176.
62. United Nations General Assembly Special Session. HIV/AIDS report to UNAIDS. http://data.unaids.org/pub/Report/2008/brazil_2008_country_progress_report_en.pdf. Accessed September 26, 2008.
63. Guimarães ML, Marques BCL, Bertoni N, et al. Assessing the HIV-1 epidemic in Brazilian drug users: A molecular epidemiology approach. *PLoS ONE*. 2015;10:e0141372.
64. UNAIDS. Honduras – overview; 2017. http://www.unaids.org/en/regionscountries/countries/honduras. Accessed January 16, 2018.
65. Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-transmission per coital act in monogamous heterosexual HIV-1 discordant couples in Rakai, Uganda. *Lancet*. 2001;357:1149–1153.
66. Powers KA, Poole C, Pettifor AE, et al. Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. *Lancet Infect Dis*. 2008;8:553–563.
67. Pilcher CD, Tien HC, Eron JJ Jr, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. *J Infect Dis*. 2004;189:1785–1792.
68. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med*. 2000;342:921–929.
69. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.
70. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375:830–839.
71. de Vicenzi I, Carael M. Transmission sexuelle du VIH: risques et pratiques hétérosexuelles. In: Berrebi A, ed. *Le Sida Au Féminin*. Paris: Editions Doin; 2001.
72. Morrison CS, Chen PL, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition: an individual participant data meta-analysis. *PLoS Med*. 2015;12:e1001778.
73. Auvert B, Taljaard D, Lagarde E, et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. *PLoS Med*. 2005;2:e298.
74. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet*. 2007;369:643–656.
75. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in young men in Rakai, Uganda: a randomized trial. *Lancet*. 2007;369:657–666.
76. Auvert B, Buvé A, Lagarde E. Male circumcision and HIV infection in four cities in sub-saharan Africa. *AIDS*. 2001;15:S31–S40.
77. Turner AN, Morrison CS, Padian NS, et al. Men's circumcision status and women's risk of HIV acquisition in Zimbabwe and Uganda. *AIDS*. 2007;21:1779–1789.
78. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis*. 2001;28:579–597.
79. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other STDs to sexual transmission of HIV infection. *Sex Transm Infect*. 1999;75:3–17.
80. Laga M, Nzila N, Goeman J. The interrelationship of sexually transmitted diseases and HIV infection: implications for the control of both epidemics in Africa. *AIDS*. 1991;5:S55–S64.
81. Grosskurt H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet*. 1995;346:530–536.
82. Wawer MJ, Sewankambo NK, Serwadda D, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomized control trial. *Lancet*. 1999;353:525–535.
83. Gray RH, Wabwire-Mangen F, Kigozi G, et al. Randomized trial of presumptive sexually transmitted

disease therapy during pregnancy in Rakai, Uganda. *Am J Obstet Gynecol*. 2001;185:1209–1217.

84. Weiss H. Epidemiology of herpes simplex virus type 2 infection in the developing world. *Herpes*. 2004;11: 24A–35A.
85. Freeman EE, Weiss HA, Glynn JR, et al. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS*. 2006;20:73–83.
86. Brown JM, Wald A, Hubbard A, et al. Incident and prevalent herpes simplex virus type 2 infection increases risk of HIV acquisition among women in Uganda and Zimbabwe. *AIDS*. 2007;21:1515–1523.
87. Watson-Jones D, Weiss HA, Rusizoka M, et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. *N Engl J Med*. 2008;358: 1560–1571.
88. Celum C, Wald A, Hughes J, et al. Effect of acyclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371:2109–2119.
89. Freeman EE, Orroth KK, White RG, et al. Proportion of new HIV infections attributable to herpes simplex 2 increases over time: simulations of the changing role of sexually transmitted infections in sub-Saharan African HIV epidemics. *Sex Transm Infect*. 2007;83:i17–i24.
90. Ghys P, Fransen K, Diallo MO, et al. The association between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Côte d'Ivoire. *AIDS*. 1997;11:F85–F93.
91. Cohen MS, Hoffman IF, Royce R, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet*. 1997;349:1863–1873.
92. Francis SC, Looker C, Vandepitte J, et al. Bacterial vaginosis among women at high risk for HIV in Uganda: high rate of recurrent diagnosis despite treatment. *Sex Transm Infect*. 2016;92:142–148.
93. World Health Organization. *WHO Validates Countries' Elimination of Mother-to-Child Transmission of HIV and Syphilis [Press Release]*. Geneva, Switzerland: World Health Organization; 2016.
94. World Health Organization. *WHO Validates Elimination of Mother-to-Child Transmission of HIV and Syphilis in Cuba [Press Release]*. Geneva, Switzerland: World Health Organization; 2015.
95. UNAIDS. *On the Fast-Track to an AIDS-Free Generation*. Geneva, Switzerland: UNAIDS; 2016.
96. Van de Perre P, Simonon A, Msellati P, et al. Postnatal transmission of human immunodeficiency virus type 1 from mother to infant: a prospective cohort study in Kigali, Rwanda. *N Engl J Med*. 1991;325:593–598.
97. Coovadia HM, Rollins NC, Bland RM, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet*. 2007;369:1107–1116.
98. UNAIDS. *Children and HIV - Fact Sheet*. Geneva, Switzerland: UNAIDS; 2016.
99. DeBeck K, Cheng T, Montaner JS, et al. HIV and the criminalisation of drug use among people who inject drugs: a systematic review. *Lancet HIV*. 2017;4: e357–e374.
100. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Health*. 2017;5:e1192–e1207.
101. World Health Organization. HIV/AIDS: injecting drug use. http://www.who.int/hiv/topics/idu/about/en/. Accessed April 20, 2014.
102. Mesquita F, Jacka D, Ricard D, et al. Accelerating harm reduction interventions to confront the HIV epidemic in the western Pacific and Asia: the role of WHO (WPRO). *Harm Reduct J*. 2008;5:26.
103. Mathers BM, Degenhardt L, Ali H, et al. 2009 reference group to the UN on HIV and injecting drug use. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. *Lancet*. 2010;375:1014–1028.
104. Tagny CT, Mbanya D, Tapko JB, et al. Blood safety in sub-Saharan Africa: a multi-factorial problem. *Transfusion*. 2008;48:1256–1261.
105. Baggaley RF, Boily MC, White RG, et al. Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis. *AIDS*. 2006;20:805–812.
106. Piot P, Bartos M, Larson H, et al. Coming to terms with complexity: a call to action for HIV prevention. *Lancet*. 2008;372:845–859.
107. Carael M, Buvé A, Awusabo-Asare K. The making of HIV epidemics: what are the driving forces? In: Laga M, ed. *AIDS in Africa*. 2nd ed. London: Rapid Science Publishers; 1997:23–32.
108. Donovan B, Ross MW. Preventing HIV: determinants of sexual behavior. *Lancet*. 2000;355:1897–1901.
109. Caraël M. Sexual behaviour. In: Cleland J, Ferry B, eds. *Sexual Behaviour and AIDS in the Developing World*. London: Taylor and Francis; 1995.
110. White R, Cleland J, Caraël M. A multi-country analysis of associations between premarital sex and extramarital sex. *AIDS*. 2000;14:2323–2331.
111. Wellings K, Collumbien M, Slaymaker E, et al. Sexual behaviour in context: a global perspective. *Lancet*. 2006;368:1706–1728.
112. Anderson RM, May RM. Transmission dynamics of HIV infection. *Nature*. 1987;26:137–142.
113. Morris M, ed. *Network Epidemiology: A Handbook for Survey Design and Data Collection*. London: Oxford University Press; 2004.
114. Yorke JA, Heathcote HW, Nold A. Dynamics and control of the transmission of gonorrhoea. *Sex Transm Dis*. 1978;5:31–37.
115. Bertrand JT, O'Reilly K, Denison J, et al. Systematic review of the effectiveness of mass communication programs to change HIV/AIDS-related behaviors in developing countries. *Health Educ Res*. 2006;21:567–597.
116. Kirby D, Obasi A, Laris BA. The effectiveness of sex education and HIV education interventions in schools in developing countries. *World Health Organ Tech Rep Ser*. 2006;938:103–150.
117. Foss AM, Hossain M, Vickerman PT, et al. A systematic review of published evidence on intervention impact on condom use in sub-Saharan Africa and Asia. *Sex Transm Dis*. 2007;83:510–516.
118. Brazilian Health Ministry. *Resposta: Experience of the Brazilian AIDS Program*. Brasilia: Ministry of Health; 2006.
119. Gregson S, Garnett GP, Nyamukapa C, et al. HIV decline associated with behavior change in eastern Zimbabwe. *Science*. 2006;311:664–666.
120. Cleland J, Ali MM. Sexual abstinence, contraception, and condom use by African women: a secondary analysis of survey data. *Lancet*. 2006;368:1788–1793.
121. Ali MM, Cleland J. Sexual and reproductive behavior among single women aged 15-24 in eight Latin-American countries: a comparative analysis. *Soc Sci Med*. 2005;60:1175–1185.
122. Allen S, Meinzen-Derr J, Katuzman M, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. *AIDS*. 2003;17:733–740.
123. Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them better work. *Lancet*. 2008;372:669–684.
124. Gray RH, Li X, Kigozi G, et al. The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. *AIDS*. 2007;21:845–850.
125. National Institute of Allergy and Infectious Diseases. NIAID-sponsored adult male circumcision trials in Kenya and Uganda. http://www3.niaid.nih.gov/news/QA/AMC12_QA.htm. Accessed October 30, 2008.
126. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329:1168–1174.
127. van der Straten A, Van Damme L, Haberer JE, et al. Unravelling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS*. 2012;26:F13–F19.
128. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med*. 2016;375:2121–2132.
129. Thigpen M, Kebaabetswe P, Paxton L, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012;367:423–434.
130. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016;387:53–60.
131. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med*. 2015;373:2237–2246.
132. Iwuji C, Orne-Gliemann J, Balestre E, et al The impact of universal test and treat on HIV incidence in a rural South African population: ANRS 12249 TasP trial, 2012-2016. Paper presented at 21st International AIDS Conference (AIDS 2016); July 18-22, 2016; Durban, South Africa.
133. Hayes R, Floyd S, Schaap A, et al. A universal testing and treatment intervention to improve HIV control: One-year results from intervention communities in Zambia in the HPTN 071 (PopART) cluster-randomised trial. *PLoS Med*. 2017;14:e1002292.
134. Bavinton B, Grinsztejn B, Phanuphak N, et al HIV treatment prevents HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil Paper presented at 9th IAS Conference on HIV Science (IAS 2017); July 23-26, 2017; Paris.
135. Tanser F, Bärnighausen T, Grapsa E, et al. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science*. 2013;339:966–971.
136. National Institute of Allergy and Infectious Diseases. Experimental HIV vaccine regimen is well-tolerated, elicits immune responses [press release]. July 24, 2017.
137. Bekker LG, Gray GE. Hope for HIV control in southern Africa: the continued quest for a vaccine. *PLoS Med*. 2017;14:e1002241.
138. Oster AM, France AM, Panneer N, et al Analysis of US HIV sequence data indicates that recent and rapid HIV transmission is focused among young Hispanic/Latino men who have sex with men. Paper presented at 9th IAS Conference on HIV Science (IAS 2017); Jul 23-26, 2017, 2017; Paris.
139. Blankenship KM, Bray SJ, Merson MH. Structural interventions in public health. *AIDS*. 2000;14:11–21.
140. Gupta GR, Parkhurst JO, Ogden JA, et al. Structural approaches to HIV prevention. *Lancet*. 2008;372: 764–775.
141. International Labour Organization. *Global Employment Trends for Youth 2004*. Geneva: ILO; 2005.
142. United Nations Population Fund. *State of the World Population 2007. Unleashing the Potential of Urban Growth*. New York: United Nations Population Fund; 2007.
143. United Nations Population Fund. *Status Report on Adolescents and Young People in Sub-Saharan Africa*. Johannesburg, South Africa: United Nations Population Fund; 2012.
144. UN-HABITAT. *The Challenge of Slums: UN-HABITAT's New Global Report on Human Settlements*. Nairobi: UN-HABITAT; 2004.
145. Population Action International and the African Institute for Development Policy. Population, climate change, and sustainable development in Africa; June 2012. http://populationaction.org/wp-content/uploads/2012/06/PAI-AFIDEP.pdf. Accessed February 28, 2014.
146. Moreno EL, Warah R. The state of the world's cities report 2006/7. http://www.un.org/Pubs/chronicle/2006/issue2/0206p24.htm.
147. Zuma K, Lurie MN, Williams BG, et al. Risk factors of sexually transmitted infections among migrant and non-migrant sexual partnerships from rural South Africa. *Epidemiol Infect*. 2005;133:421–428.
148. Li X, Zhang L, Stanton B, et al. HIV/AIDS-related sexual risk behaviors among rural residents in China: potential role of rural-to-urban migration. *AIDS Educ Prev*. 2007;19:396–407.
149. Chantavanich S. *Mobility and HIV/AIDS in the Greater Mekong Subregion*. Bangkok: Asian Development Bank; 2000.
150. Piot P, Greener R, Russell S. Squaring the circle: AIDS, poverty, and human development. *PLoS Med*. 2007;4:1571–1575.
151. Baird S, Garfein R, McIntosh C, et al. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. *Lancet*. 2012;379:1320–1329.
152. Pronyk PM, Hargreaves JR, Kim JC, et al. Effect of a structural intervention for the prevention of intimate-partner violence and HIV in rural South Africa: a cluster randomised trial. *Lancet*. 2006;368:1973–1983.
153. Pettifor A, MacPhail C, Hughes JP, et al. The effect of a conditional cash transfer on HIV incidence in young women in rural South Africa (HPTN 068): a phase 3, randomised controlled trial. *Lancet Glob Health*. 2016;4:e978–e988.
154. Kilburn K, Pettifor A, Edwards J, et al. The effect of a conditional cash transfer for HIV prevention on the experience of partner violence for young women: evidence from a randomized experiment in South Africa HPTN 068. *J Int AIDS Soc*. 2017;20(S5):38–39.
155. de Waal A, Whiteside A. New variant famine: AIDS and food crisis in southern Africa. *Lancet*. 2003;362:1234–1237.
156. Accorsi S, Fabiani M, Nattabi BM, et al. The disease profile of poverty: morbidity and mortality in northern Uganda in the context of war, population displacement and HIV/AIDS. *Trans R Soc Trop Med Hyg*. 2005;99:226–233.
157. Dunkle KL, Jewkes RK, Brown HC, et al. Transactional sex among women in Soweto, South Africa: prevalence, risk factors and association with HIV infection. *Soc Sci Med*. 2004;59:1581–1592.
158. UNAIDS. *The Gap Report 2014*. Geneva, Switzerland: UNAIDS; 2014.

159. UNAIDS. *Prevention Gap Report*. Geneva, Switzerland: UNAIDS; 2016.
160. UNAIDS. *Get on the Fast-Track: The Lifecycle Approach to HIV*. Geneva, Switzerland: UNAIDS; 2016.
161. Glynn JR, Carael M, Auvert B, et al. Why do young women have a much higher prevalence of HIV than young men? A study in Kisumu, Kenya, and Ndola, Zambia. *AIDS*. 2001;15:51–60.
162. Carael M, Glynn J. HIV infection in young adults in Africa: context, risks, and opportunities for prevention. In: Carael M, Glynn J, eds. *HIV, Resurgent Infections and Population Change in Africa*. New York: Springer; 2007:123–154.
163. Luke N. Confronting the "sugar daddy" stereotype: age and economic asymmetries and risky sexual behavior in urban Kenya. *Int Fam Plan Perspect*. 2005;31:6–14.
164. Hallman K. *Socioeconomic Disadvantage and Unsafe Sexual Behaviors Among Young Women and Men in South Africa*. Washington, DC: Population Council; 2004.
165. Langeni T. Contextual factors associated with treatment-seeking and high-risk sexual behaviour in Botswana among men with symptoms of sexually transmitted infections. *Afr J AIDS Res*. 2007;6:261–269.
166. Gregson S, Nymukapa A, Garnett G, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet*. 2002;359: 1896–1903.
167. Shisana O, Rehle T, Simbayi LC, et al. *South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey*. Cape Town, South Africa: Human Sciences Research Council; 2005. http://www.hsrc.ac.za/media/2005/11/z20051130_1.html.
168. World Health Organization. *WHO Multi-Country Study on Women's Health and Domestic Violence Against Women. Summary Report of the Initial Findings on Prevalence, Health Outcomes and Women's Responses*. Geneva, Switzerland: World Health Organization; 2005.
169. Garcia-Moreno C, Heise L, Jansen H, et al. Violence against women. *Science*. 2005;310:1282–1283.
170. Go VF, Sethulakshmi CJ, Bentley ME, et al. When HIV-prevention messages and gender norms clash: the impact of domestic violence on women's HIV risk in slums of Chennai, India. *AIDS Behav*. 2003;7:263–272.
171. Maman S, Mbwambo JK, Hogan NM, et al. HIV-positive women report more lifetime partner violence: findings from a voluntary counseling and testing clinic in Dar es Salaam, Tanzania. *Am J Public Health*. 2003;92:1331–1337.
172. Fonck K, Leye E, Kidula N, et al. Increased risk of HIV in women experiencing physical partner violence in Nairobi, Kenya. *AIDS Behav*. 2005;9:335–339.
173. Kim JC, Watts CH, Heargraves JR, et al. Understanding the impact of a microfinance-based intervention on women's empowerment and the reduction of intimate partner violence in South Africa. *Am J Public Health*. 2007;97:1794–1802.
174. Jewkes R, Nduna M, Jama PN. *Stepping Stones, South African Adaptation*. 2nd ed. Pretoria, South Africa: Medical Research Council; 2002.
175. Jewkes R, Nduna M, Levin J, et al. A cluster randomized controlled trial to determine the effectiveness of stepping stones in preventing HIV infections and promoting safer sexual behavior amongst youth in the rural Eastern Cape, South Africa: trial design, methods, and baseline findings. *Trop Med Int Health*. 2006;11:3–16.
176. Castro A, Farmer P. Understanding and addressing AIDS-related stigma: from anthropological theory to clinical practice in Haiti. *Am J Public Health*. 2005;95:53–59.
177. Wolfe WR, Weiser SD, Leiter K, et al. The impact of universal access to antiretroviral therapy on HIV stigma in Botswana. *Am J Public Health*. 2008;98:1865–1871.
178. Liu H, Li X, Stanton B, et al. Risk factors for sexually transmitted disease among rural-to-urban migrants in China: implications for HIV/sexually transmitted disease prevention. *AIDS Patient Care STDS*. 2005;19:49–57.
179. UNAIDS. *Comparative Analysis: Research Studies From India and Uganda. HIV and AIDS-Related Discrimination, Stigmatization, and Denial*. Geneva, Switzerland: UNAIDS; 2000.
180. Piot P Why AIDS Is Exceptional. Speech at the London School of Economics. London, February 8, 2005.
181. Brown L, Macintyre K, Trujillo L. Interventions to reduce HIV/AIDS stigma: what have we learned? *AIDS Educ Prev*. 2003;15:49–69.
182. Global HIV Prevention Working Group. Bringing HIV Prevention to scale: an urgent global priority; 2007. http://data.unaids.org/pub/report/2007/pwg-hiv_prevention_report_final_en.pdf.
183. UNAIDS. Kenya launches self-test kits and PrEP; 2017. http://www.unaids.org/en/resources/presscentre/featurestories/2017/may/20170505_kenya. Accessed January 25, 2018.
184. The World Bank. Antiretroviral therapy coverage for PMTCT (% of pregnant women living with HIV); 2018. https://data.worldbank.org/indicator/SH.HIV.PMTC.ZS?view=chart. Accessed January 25, 2018.
185. World Health Organization. Global health sector strategy on HIV/AIDS; 2011-2015. http://whqlibdoc.who.int/publications/2011/9789241501651_eng.pdf.
186. World Health Organization. *Guidance on Couples HIV Testing and Counselling Including Antiretroviral Therapy for Treatment and Prevention in Serodiscordant Couples*. Geneva, Switzerland: UNAIDS; 2012.
187. Johnson CC, Kennedy C, Fonner V, et al. Examining the effects of HIV self-testing compared to standard HIV testing services: a systematic review and meta-analysis. *J Int AIDS Soc*. 2017;20:21594.
188. Figueroa C, Johnson C, Verster A, et al. Attitudes and acceptability on HIV self-testing among key populations: a literature review. *AIDS Behav*. 2015;19:1949–1965.
189. Indravudh PP, Sibanda EL, d'Elbee M, et al. 'I will choose when to test, where I want to test': investigating young people's preferences for HIV self-testing in Malawi and Zimbabwe. *AIDS*. 2017;31(suppl 3):S203–s212.
190. Chanda MM, Ortblad KF, Mwale M, et al. HIV self-testing among female sex workers in Zambia: A cluster randomized controlled trial. *PLoS Med*. 2017;14:e1002442.
191. Dalal S, Johnson C, Fonner V, et al. Improving HIV test uptake and case finding with assisted partner notification services. *AIDS*. 2017;31:1867–1876.
192. World Health Organization. *Guidelines on HIV Self-Testing and Partner Notification: Supplement to Consolidated Guidelines on HIV Testing Services*. Geneva, Switzerland: World Health Organization; 2016.
193. US Department of Health & Human Services. What is the HIV care continuum? 2016. https://www.hiv.gov/federal-response/policies-issues/hiv-aids-care-continuum. Accessed January 19, 2018.
194. Micek MA, Gimbel-Sherr K, Baptista AJ, et al. Loss to follow-up of adults in public HIV care systems in central Mozambique: identifying obstacles to treatment. *J Acquir Immune Defic Syndr*. 2009;52:397–405.
195. Kober K, Van Damme W. Scaling up access to antiretroviral treatment in southern Africa: who will do the job? *Lancet*. 2004;364:103–107.
196. Yu D, Souteyrand Y, Banda MA, et al. Investment in HIV/AIDS programs: does it help strengthen health systems in developing countries? *Global Health*. 2008;4:8.
197. Kaiser Family Foundation/UNAIDS. *Donor Government Funding for HIV in Low- and Middle-Income Countries in 2016*. Menlo Park, CA: 2017.
198. World Health Organization. Global HIV/AIDS response: epidemic update and health sector progress towards universal access. Progress report 2011. http://www.who.int/hiv/pub/progress_report2011/en/.
199. Blacker J. The impact of AIDS on adult mortality: evidence from national and regional statistics. *AIDS*. 2004;18:S19–S26.
200. World Health Organization. Tuberculosis and HIV; 2018. http://www.who.int/hiv/topics/tb/about_tb/en/. Accessed January 9, 2018.
201. Lucas SB, Hounnou A, Peacock C, et al. The mortality and pathology of HIV infection in a west African city. *AIDS*. 1993;7:1569–1579.
202. Le Coeur S, Halembokaka G, Khlat M, et al. Impact of AIDS on adult mortality: a morgue-based study in Pointe-Noire, Republic of Congo. *AIDS*. 2005;19: 1683–1687.
203. Tollman SM, Kahn K, Sartorius B, et al. Implications of mortality transition for primary health care in rural South Africa: a population based surveillance study. *Lancet*. 2008;372:893–901.
204. Tawfik L, Kinoti SN. *The Impact of HIV/AIDS on the Health Workforce in Developing Countries. The World Health Report*. Geneva, Switzerland: World Health Organization; 2006.
205. Shisana O. HIV/AIDS prevalence among South African health workers. *S Afr Med J*. 2004;94:846–850.
206. Chen L, Evans T, Anand S, et al. Human resources for health: overcoming the crisis. *Lancet*. 2004;364:1984–1990.
207. Gupta A, Juneja S, Vitoria M, et al. Projected uptake of new antiretroviral (ARV) medicines in adults in low- and middle-income countries: a forecast analysis 2015-2025. *PLoS ONE*. 2016;11:e0164619.
208. Demographic and socioeconomic impact of AIDS: taking stock of the empirical evidence. *AIDS*. 2004;18:S1–S7.
209. International Labour Organization (ILO) and German Agency for Technical Cooperation (GTZ). HIV/AIDS, work and development in Tanzania; 2004. http://www.ilo.org/aids/Publications/WCMS_116298/lang–en/index.htm.
210. Sidibé M, Piot P, Dybul M. AIDS is not over. *Lancet*. 2012;380:2058–2060.
211. Walker N, Ghys P Proportion of child mortality attributable to HIV. Presented at Meeting on the Empirical Evidence for the Demographic and Socio-Economic Impact of AIDS. Durban, South Africa, March 26-28, 2003.
212. Zaba B, Whitworth J, Marston M, et al. HIV and mortality of mothers and children: evidence from cohort studies in Uganda, Tanzania, and Malawi. *Epidemiology*. 2005;16:275–280.
213. AVERT. Children, HIV and AIDS; 2017. https://www.avert.org/professionals/hiv-social-issues/key-affected-populations/children#footnoteref18_9qsrq16. Accessed January 19, 2018.
214. UNICEF, UNAIDS, USAID. *Children on the Brink, 2004: A Joint Report on Orphan Estimates and a Framework for Action*. Washington, DC: UNICEF, UNAIDS, USAID; 2005.
214a. UN General Assembly, Transforming our world: the 2030 Agenda for Sustainable Development, 21 October 2015, A/RES/70/1. https://www.refworld.org/docid/57b6e3e44.html. Accessed November 22, 2018.
215. The Global Fund. Financials. https://www.theglobalfund.org/en/financials. Accessed January 19, 2018.
216. US President's Emergency Plan for AIDS Relief (PEPFAR). *PEPFAR Funding: Fiscal Year 2004-2017 PEPFAR Funding*. Washington, DC: PEPFAR; 2016.
217. Jahn A, Floyd S, Crampin AC, et al. Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. *Lancet*. 2008;371:1603–1611.
218. UNAIDS. HIV/AIDS, human resources and sustainable development. Presented at the World Summit on Sustainable Development, Johannesburg. Geneva, Switzerland: UNAIDS; 2002.
219. World Health Organization, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report, 2008. http://www.who.int/hiv/pub/towards_universal_access_report_2008.pdf. Accessed February 2014.
220. UNAIDS. Update: review of global commission on HIV and the law identifies progress and challenges; 2017. http://www.unaids.org/en/resources/presscentre/featurestories/2017/july/20170714_hiv-and-law. Accessed December 12, 2017.
221. Piot P, Abdool Karim SS, Hecht R, et al. Defeating AIDS–advancing global health. *Lancet*. 2015;386: 171–218.

119 Epidemiology and Prevention of AIDS and HIV Infection, Including Preexposure Prophylaxis and HIV Vaccine Development

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Acquired immunodeficiency syndrome (AIDS) is the most severe manifestation of a clinical spectrum of illness caused by infection with human immunodeficiency virus (HIV). The syndrome is defined by the development of serious opportunistic infections, neoplasms, or other life-threatening manifestations resulting from progressive HIV-induced immunosuppression. AIDS was first recognized in mid-1981, when unusual clusters of *Pneumocystis jirovecii* pneumonia and Kaposi sarcoma were reported in young, previously healthy homosexual men in New York City, Los Angeles, and San Francisco.[1,2] The subsequent documentation of cases among persons with hemophilia, blood transfusion recipients, and persons who inject drugs (PWIDs) and their sex partners suggested that a transmissible agent was the primary cause of the immunologic defects characteristic of AIDS. In 1983, 2 years after the first reports of AIDS, a cytopathic retrovirus was isolated from persons with AIDS and associated conditions such as chronic lymphadenopathy.[3,4] By 1985 serologic tests to detect evidence of infection with HIV had been developed and licensed.

Blood obtained in 1959 from an adult Bantu man living in what is now the Democratic Republic of Congo represents the oldest known case of HIV-1 infection in the world.[5] HIV sequences from that sample and others from the same region in Africa suggest that humans acquired a common ancestor of the HIV-1 M group by cross-species transmission under natural circumstances in approximately 1933 (1919–45).[6] HIV infection has become pandemic, affecting every region of the world, and is a major cause of morbidity and mortality, particularly among young adults. HIV is spread primarily through heterosexual contact, with women now accounting for more than half of new HIV infections in adults.[7] Transmission through transfusion of blood and blood products has been virtually eliminated in countries that have systematically instituted HIV antibody screening of donated blood and plasma and heat treatment of clotting factors. In developed countries sharp declines in the incidence and mortality of AIDS have been noted after the use of active antiretroviral therapy (ART) became widespread in 1996.[8] As a result, the number of persons living with HIV infection continues to rise, and evidence suggests that new infections in the United States remain stable, except among men who have sex with men (MSM) and, in particular, black young MSM, in whom rates have increased.[9] In the United States the HIV epidemic increasingly affects women, minorities, persons living in the Southeast, and the poor.[10,11] The control and prevention of HIV infection, whether on a global or an individual scale, must be grounded in an understanding of the changing epidemiology of HIV.

HIV AND AIDS SURVEILLANCE IN THE UNITED STATES

The Centers for Disease Control and Prevention (CDC) collects, analyzes, and disseminates surveillance data on HIV infection and AIDS. All 50 states, the District of Columbia, and all US territories require the reporting of AIDS cases to local health authorities by name, and they in turn use a uniform surveillance case definition and case report form to report cases to the CDC.[12]

The initial AIDS surveillance case definition, which was established soon after the first reports of unexplained illnesses associated with cellular immunodeficiency in homosexual or bisexual men, formally listed the opportunistic infections and neoplasms indicative of underlying immunosuppression.[13] In the absence of previously described causes of immunosuppression, a diagnosis of one of these conditions was defined as AIDS. The definition did not include the less severe manifestations of HIV infection and was designed to be highly specific and provide a standard means to monitor trends of severe immunodeficiency caused by what was then an unknown agent.

The AIDS surveillance case definition was modified in 1985, 1987, 1993, 2008, and again in 2014.[14–17] Each revision to the AIDS surveillance case in the United States has been done in response to diagnostic and therapeutic advances and to improve standardization and compatibility of surveillance data regarding persons at all stages of HIV disease.

In 1993 the AIDS surveillance definition was expanded to include evidence of severe immunosuppression (<200 $CD4^+$ T lymphocytes/μL or a $CD4^+$ T-lymphocyte percentage of total lymphocytes of <14) and a series of clinical conditions that, in the presence of HIV infection, were considered AIDS defining (Table 119.1).

Evaluation studies have shown that AIDS surveillance has provided complete and timely information on diagnosed cases of AIDS in the United States. A national multicenter study published in 1992 used computerized medical records in six areas to determine that 92% of persons with AIDS-defining conditions were reported to local health departments.[18] Of these previously reported cases, 67% were reported to local health departments within 2 months of the date of diagnosis. Studies of state and local death certificate information and national vital statistics found that the completeness of reporting persons with AIDS ranged from 80% to 96% and that 70% to 90% of HIV-related deaths were reported to AIDS surveillance groups.[19–21] Therefore the reporting of AIDS in the United States has been among the most complete of all reportable diseases and conditions.[22,23] However, advances in HIV treatment have slowed the progression of HIV disease for infected persons and contributed to a decline in AIDS incidence; as a result, many persons infected with HIV may never develop AIDS. Therefore data from the AIDS reporting system, although still important, have become less informative about current trends in HIV transmission. This led public health authorities, in 1999, to recommend that all states and territories include surveillance for HIV infection and not just for AIDS.[24] In addition, a revised surveillance case definition for HIV infection that incorporated the reporting criteria for HIV infection and AIDS into a single case definition was recommended by the Council of State and Territorial Epidemiologists at its 1998 annual meeting and published by the CDC in 1999.[25]

TABLE 119.1 AIDS-Defining Conditions

Bacterial infections, multiple or recurrent[a]
Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive[b]
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1-month duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex, chronic ulcer(s) (>1-month duration); bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1-month duration)
Kaposi sarcoma
Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia[a]
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium-intracellulare complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary[b] or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii pneumonia
Pneumonia, recurrent[b]
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome of HIV infection

[a]Children younger than 13 years.
[b]Added in the 1993 expansion of the AIDS surveillance case definition for adolescents and adults.

TABLE 119.2 Surveillance Case Definition for HIV Infection in Persons Age ≥6 Years: United States, 2014

STAGE	LABORATORY EVIDENCE[a]	CLINICAL EVIDENCE
Stage 0	Negative or indeterminate HIV test within 180 days of the first confirmed positive test *or* Detection of HIV antigen or nucleic acids before an antibody test is positive	None required (acute retroviral syndrome is possible)
Stage 1	Laboratory confirmation of HIV infection *and* $CD4^+$ T-lymphocyte count ≥500 cells/μL *or* $CD4^+$ T-lymphocyte percentage ≥26	None required (but no AIDS-defining condition)
Stage 2	Laboratory confirmation of HIV infection *and* $CD4^+$ T-lymphocyte count of 200–499 cells/μL *or* $CD4^+$ T-lymphocyte percentage of 14–25	None required (but no AIDS-defining condition)
Stage 3 (AIDS)	Laboratory confirmation of HIV infection *and* $CD4^+$ T-lymphocyte count of <200 cells/μL *or* $CD4^+$ T-lymphocyte percentage of <14[b]	*or* documentation of an AIDS-defining condition (with laboratory confirmation of HIV infection)[b]
Stage unknown[c]	Laboratory confirmation of HIV infection *and* no information on $CD4^+$ T-lymphocyte count or percentage	*and* no information on presence of AIDS-defining conditions

[a]The $CD4^+$ T-lymphocyte percentage is the percentage of total lymphocytes. If the $CD4^+$ T-lymphocyte count and percentage do not correspond to the same HIV infection stage, select the more severe stage.
[b]Documentation of an AIDS-defining condition supersedes a $CD4^+$ T-lymphocyte count of ≥200 cells/μL and a $CD4^+$ T-lymphocyte percentage of total lymphocytes of ≥14. Definitive diagnostic methods for these conditions are available in Appendix C of the 1993 revised HIV classification system and the expanded AIDS case definition. (Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*.1992;41[RR-17]:1–19)
[c]Although cases with no information on the $CD4^+$ T-lymphocyte count or percentage or on the presence of AIDS-defining conditions can be classified as stage unknown, every effort should be made to report $CD4^+$ T-lymphocyte counts or percentages and the presence of AIDS-defining conditions at the time of diagnosis. Additional $CD4^+$ T-lymphocyte counts or percentages and any identified AIDS-defining conditions can be reported as recommended. (Council of State and Territorial Epidemiologists. Laboratory Reporting of Clinical Test Results Indicative of HIV Infection: New Standards for a New Era of Surveillance and Prevention [Position Statement 04-ID-07]. 2004. http://www.cste.org/ps/2004pdf/04-ID-07-final.pdf.)
From Schneider E, Whitmore S, Glynn KM, et al; Centers for Disease Control and Prevention. Revised surveillance case definitions for HIV infection among adults, adolescents, and children age <18 months and for HIV infection and AIDS among children aged 18 months to <13 years–United States, 2008. MMWR Recomm Rep. *2008;57(RR-10):1–12.*

In the 2008 revision of the surveillance case definition for adults and adolescents, the CDC required laboratory-confirmed evidence of HIV infection to meet the surveillance case definition. Diagnostic confirmation of an AIDS-defining condition alone without laboratory-confirmed evidence of HIV infection is no longer sufficient to classify an adult or adolescent as HIV infected for surveillance purposes. The incorporation of laboratory confirmation of HIV infection into the surveillance case definition was also consistent with the 2007 recommendations of the World Health Organization (WHO).[26]

The 2014 revision consolidated the case definition to apply to persons of all ages, revised the laboratory and diagnostic criteria to eliminate the confirmatory Western immunoblot from the testing algorithm, and accounted for the detection and discrimination of HIV-1 and HIV-2 infections (also see Chapter 120).[27] This revised algorithm reduces the rate of false-positive tests and the number of tests needed to diagnose HIV infection. For laboratory confirmation of HIV infection, the revised surveillance case definition accepts a positive combined HIV-1/2 antigen/antibody test, followed by positive nucleic acid testing. With the laboratory confirmation of HIV infection and the $CD4^+$ T-lymphocyte count, cases are classified into one of five HIV infection stages: 0, 1, 2, 3, or unknown (Table 119.2). Stage 0 is established by either a negative or indeterminate result that is followed by a positive result on subsequent testing within 180 days or the detection of HIV p24 antigen or nucleic acids before an antibody test is positive. If the criteria for stage 0 are met, the stage is defined as 0 regardless of $CD4^+$ T-lymphocyte cell counts, percentages, or the presence of opportunistic illness diagnoses. In stage 1 the person has no AIDS-defining conditions and either a $CD4^+$ T-lymphocyte cell count of ≥500 cells/μL or a percentage of ≥26. In stage 2 there are no AIDS-defining conditions, and the $CD4^+$ T-lymphocyte cell count is between 200 and 499 cells/μL or a percentage between 14 and 25. Stage 3 corresponds to AIDS; the patient has a $CD4^+$ T-lymphocyte cell count of less than 200 cells/μL (or a percentage <14) or documentation of an AIDS-defining condition. Finally, when the $CD4^+$ T-lymphocyte cell count is not available or there is no information of an AIDS-defining condition, the patient is classified as HIV infected, stage unknown. One must stress that the revised case definition is intended for public health surveillance and not for clinical diagnosis.

HIV INFECTION AND AIDS IN ADULTS

Incidence and Prevalence of AIDS and HIV in the United States (Also See Chapter 118 for Global Data)

The CDC estimates that 1,122,990 persons age ≥13 years were living with diagnosed or undiagnosed HIV infection in the United States at the end of 2015, for an overall HIV prevalence of 418.7 per 100,000 population.[28] As more people came to know their HIV status, the percentage of persons living with undiagnosed HIV decreased from 16.9% in 2010 to 14.5% in 2015 and thus, at year-end 2016, 991,447 persons were living in the United States with diagnosed HIV infection for a prevalence of 306.6 per 100,000 population.[29] The majority of those

living with HIV were nonwhite (65%), and 67% were MSM. The HIV prevalence rates for blacks (1435.4/100,000) and Hispanics (587.6/100,000) were, respectively, 7.3 and 2.9 times the rate for whites (196.7/100,000).[29]

In 2008 the CDC published the first national HIV incidence estimates, using novel laboratory assays that differentiate recent versus long-standing HIV infection.[30] This analysis showed that an estimated 56,300 new HIV infections (95% confidence interval [CI], 48,200 to 64,500) occurred in 2006, for an overall incidence rate of 22.8 cases per 100,000 population.[11] The revised number of new infections was substantially higher than the previous estimate of 40,000 annual new infections in the United States.[31] Since then, HIV incidence has declined from 41,800 in 2010 to 38,500 in 2015, with the rate decreasing from 16.3 in 2010 to 14.4 in 2014.[28] Seventy-three percent of new infections occurred among men, 42.1% among blacks, and 65.1% among MSM. The highest rates are for blacks/African Americans at 49.5 per 100,000 population. From 2010–15 there was an increase in new infections among persons age 25 to 34 years with no significant change in persons ≥55 years and a decrease in all other age groups. HIV diagnoses are not evenly distributed across states and regions. Southern states now account for more than half (52%) of all HIV diagnosis. The rate of HIV diagnosis among adults and adolescents in 2017 in the United States and six dependent areas was 11.8 per 100,000 population and varied from a high of 46.3 in the District of Columbia to 0.0 in American Samoa and the Republic of Palau (Fig. 119.1).

Serologic Monitoring of the HIV Epidemic

In 2003 the CDC implemented the National HIV Behavioral Surveillance System (NHBS) to estimate and monitor HIV behaviors, prevalence, and trends among persons at risk of HIV infection. This survey is conducted in rotating annual cycles, with each one of three risk groups (MSM, PWIDs, and high-risk heterosexuals) surveyed each year. In general, the patterns of HIV transmission observed in these studies in the United States are similar to those observed through AIDS case surveillance—higher rates of HIV infection are found among men than women, among blacks and Hispanics than whites, and among persons 20 to 45 years of age than those in other age groups. In addition, the National Health and Nutrition Examination Survey (NHANES), a program started in the 1960s to assess the health and nutritional status of noninstitutionalized adults and children in the United States, has been used to estimate HIV prevalence. NHANES data suggests that the prevalence of HIV infection among adults age 18 to 59 years residing in households in the United States was 0.39% for the period 2007–12.[32]

Homosexual and bisexual men remain a major population with an increased prevalence of HIV infection. In the 2014 NHBS survey among MSM, the overall HIV prevalence was 22%, but it was 36% among black MSM, 17% among Hispanic MSM, and 15% among white MSM.[9]

In contrast to the epidemic among homosexual and bisexual men, the epidemic among PWIDs has been more concentrated geographically within the United States. Among PWIDs the initial HIV seroprevalence studies demonstrated very high rates of HIV infection in the Northeast and along the Atlantic Coast and low rates on the West Coast and in cities in other areas.[33,34] Surveys conducted in drug treatment centers in 1997 showed a median HIV seroprevalence rate of 14.8% (range, 0%–37.7%) among PWIDs entering drug treatment programs.[35] Similar findings have been noted in subsequent studies; HIV seroprevalence among PWIDs admitted to drug treatment centers in Baltimore (25%) and Newark (24%) was high, whereas it was low in San Francisco (7%), Seattle (5%), Denver (2%), and Detroit (1%).[36,37] However, among most large metropolitan areas, the HIV prevalence rates among PWIDs

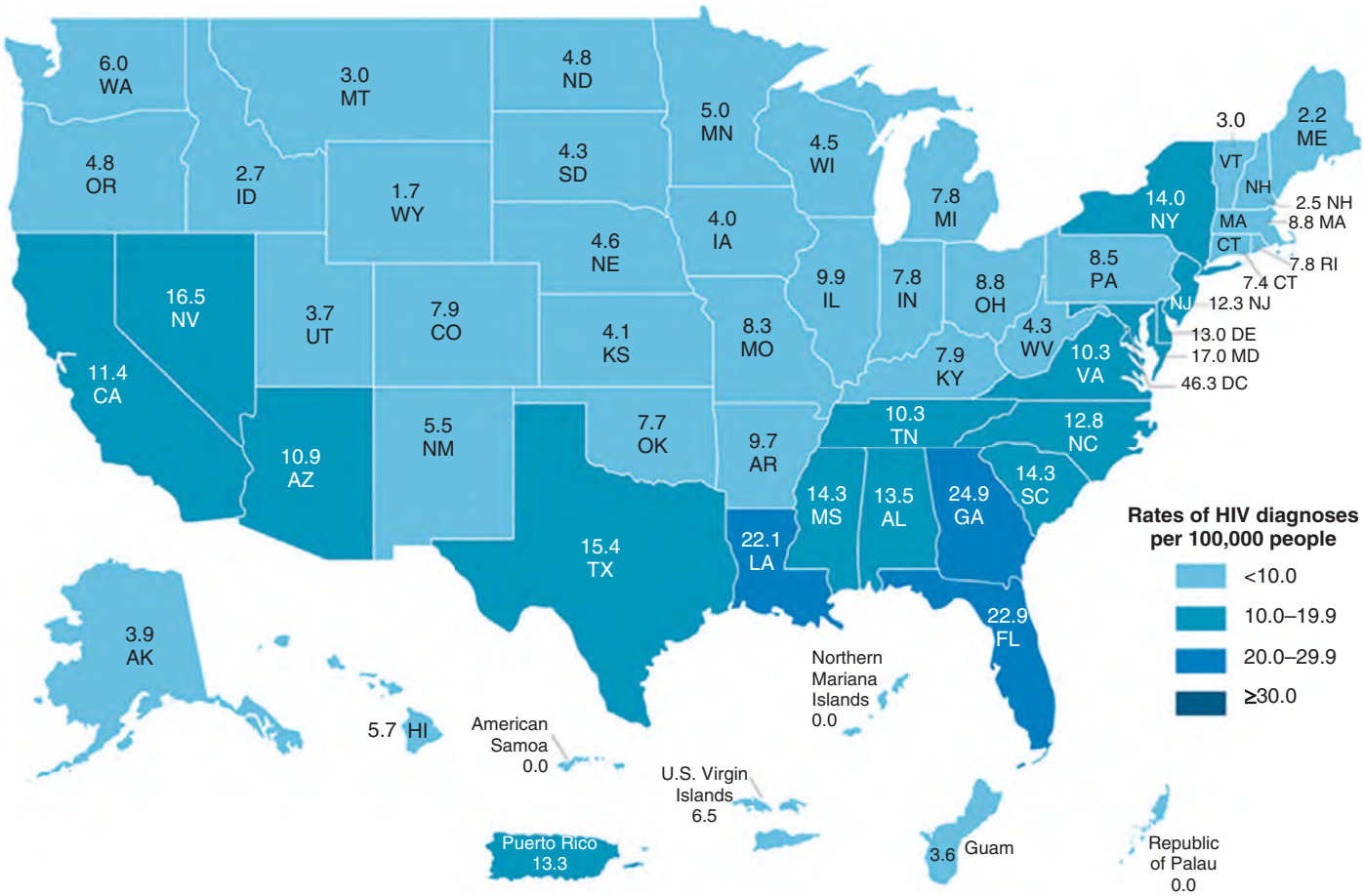

FIG. 119.1 Rates of HIV diagnoses in the United States, 2017. *(From the Centers for Disease Control and Prevention.* HIV in the United States by Region. https://www.cdc.gov/hiv/statistics/overview/geographicdistribution.html. *Accessed January 23, 2019.)*

continues to be less than 10%, and approximately 40% have a prevalence of less than 5%.[38,39] The number of new HIV infections attributed to injection drug use (IDU) in the United States had decreased in recent years, but as a result of the opioid epidemic, outbreaks of HIV infection among PWIDs are now occurring in the United States, with the CDC recently identifying 220 counties in 26 states as potentially vulnerable to HIV outbreaks among PWIDs.[40]

HIV infection acquired through heterosexual contact is the primary route of infection among women, particularly those who are members of minority groups.[41,42] Despite this, the number of reported cases of HIV/AIDS attributable to high-risk heterosexual contact has declined for both men and women. Despite this decline, more than 7000 women were diagnosed with HIV in 2016, and women represent 19% of new HIV diagnoses in the United States.[29]

The data from a cohort study conducted among drug users in Baltimore, a high-incidence and high-prevalence city, suggest that the incidence of HIV has doubled among drug-using men who also engage in homosexual sex and among women who have had a recent sexually transmitted infection, suggesting that sexual behavior is a major determinant of risk even among drug users.[43]

Surveys conducted in clinical settings indicate that the HIV infection rate is higher than it is in a more representative sample of the general population.[44–47] For this reason, since 2006 the CDC has recommended opt-out HIV screening as part of routine clinical care in all health care settings.[48] In many areas tuberculosis (TB) patients have high rates of HIV infection, and HIV screening should be provided to all those diagnosed with TB.[47] Among patients with syphilis the overall HIV seroprevalence was 15.7%; among men the seroprevalence was 27.5% and among women 12.4%.[49] However, among MSM and those with syphilis the seroprevalence ranged from 64.3% to 90%.

HIV prevalence rates among adolescents attending adolescent medicine clinics in three metropolitan areas (Baltimore, Houston, and New York City) that collected data each year from 1993–97 showed an overall HIV prevalence rate of 0.4% (range, 0.2%–0.5%).[50] The rates were the same for male and female patients (0.4%) and were approximately the same among patients 13 to 19 years of age (0.4%) and those 20 to 24 years of age (0.5%). However, the rates were higher among black patients (0.6%) than among Hispanic and white patients (0.1%).

Studies of HIV seroprevalence in entrants to correctional facilities have indicated a wide range of rates, with the highest in areas with a moderate-to-high incidence of AIDS.[51] From 1991–92 the median HIV seroprevalence was 2.9% (range, 0%–15%) in 35 correctional facilities in 17 metropolitan areas.[52] The rates ranged from 1% to 12.5% for men and 0% to 24% for women, which is a reflection of the high rates of drug use in these persons. Among entrants to the New York State prison system between 1987 and 1997, 12% of men and 18% of women were infected with HIV.[53] Between 1992 and 1998 data from nearly 500,000 HIV tests performed in correctional facilities in the United States demonstrated an overall HIV seroprevalence of 3.4%, 56% of which were among persons newly identified as HIV infected.[54] More recent data suggests that nationally the HIV prevalence among incarcerated persons has decreased, and it is now 1.5%. However, in state prisons in Florida, Maryland, and New York the prevalence exceeds 3%.[55]

As previously stated, although surveillance for HIV infection has traditionally focused on the incidence of AIDS and the prevalence of HIV, new diagnostic technologies that allow the estimation of incident HIV infection have become available, including the use of the sensitive–less sensitive enzyme immunoassay (EIA) test (or the serologic testing algorithm for recent HIV seroconversion [STAHRS]) and the measurement of HIV RNA by polymerase chain reaction (PCR) in pooled blood specimens that test negative for HIV (see Chapter 120).[30,56] Having an HIV surveillance system that focuses on incident rather than prevalent infections undoubtedly allows better monitoring of the HIV epidemic.[57] AIDSVu (http://aidsvu.org) is an interactive online mapping tool that allows users to visualize and explore HIV surveillance data at the state, county, and ZIP code levels.

Exposure Categories

Since the first cases of AIDS were reported in 1981 in the United States, cases in MSM have consistently represented the largest number of AIDS cases reported. The cases of AIDS among recipients of blood or blood components and among persons with hemophilia increased dramatically during the mid-1980s, but since 1987 the numbers have declined; after the implementation of HIV antibody testing in March 1985, no more than 5 cases of transfusion-associated HIV infection per year were reported to the CDC during the subsequent years, compared with 714 cases in 1984.[58] Since the initiation of HIV antibody screening of donated blood and plasma, heat treatment of clotting factors, P24 antigen testing, and, since 1999, nucleic acid amplification testing (NAAT) of donor samples, the window period for potential HIV transmission by blood transfusion has decreased to 12 days, and the estimated risk for HIV transmission by blood products is now 1 in 1.4 to 1 in 1.8 million units.[59]

Heterosexual contact cases consist of persons who report exposure to a person with or at increased risk for HIV infection (e.g., a person who uses injects drugs [PWID]) or those born in countries where heterosexual transmission is the major route of HIV infection (e.g., areas of sub-Saharan Africa and some Caribbean countries). In 1992, for the first time the number of cases diagnosed among women infected through heterosexual contact exceeded the number infected through IDU and represented 68% of cases among women reported in 2002.[28] Blacks and Hispanics account for greater than 75% of all persons reported with AIDS attributed to heterosexual contact.[60] For AIDS cases reported in 2006, 17% of men and 73% of women reported having acquired HIV through high-risk heterosexual contact. In the past persons with sex partners of unknown HIV infection or risk status were classified in the undetermined category, but since September 2000 the procedures for investigating cases reported without risk have changed from ascertaining risk for all reported cases to estimating risk distributions from statistical models and population-based samples. Selected follow-up and investigation of heterosexual contact cases have identified other sources of exposure to HIV infection for some persons, especially men.[61,62] Nonetheless, it is unlikely that such misclassification bias has significantly influenced national trends.[63]

Of the 30,870 cases of HIV infection among adults and adolescent males reported in 2017, 4% occurred in MSM who are also PWIDs. Except for this group, persons with more than one reported mode of exposure to HIV are counted only once in a hierarchy of exposure categories.[29]

The cases in persons with no reported exposure to HIV through any of the recognized routes are classified as "no risk reported or identified." This category includes cases that are being followed up by local health department officials; cases in persons whose exposure history is incomplete because they died, declined to be interviewed, or were lost to follow-up; and cases in persons who were interviewed or for whom other follow-up information was available and no mode of exposure was identified. Previous studies indicate that when follow-up information is obtained, an established exposure mode can be identified for greater than 90% of these persons, and they are subsequently reclassified into the appropriate exposure category.[64] Although the surveillance and investigation of cases with an undetermined risk can assist in detecting unusual modes of transmission (e.g., transplantation), such instances remain rare.[65]

AIDS Trends

The 1993 change in the AIDS case definition[16] dramatically altered trends in the incidence of AIDS because of a large increase in reported AIDS cases. In 1993, the first year that the new case definition was used, 103,500 AIDS cases were reported to the CDC among persons 13 years or older, compared with 49,016 cases in 1992. In 1994, 1995, and 1996 the number of AIDS cases reported annually decreased, in contrast to the artificial peak in the number of cases reported in 1993. Since the implementation of the revised case definition, more than half of all cases have been reported based on a $CD4^+$ T-lymphocyte count of less than 200 cells/μL. However, in 1995 and 1996 the occurrence of AIDS-defining opportunistic illnesses and death among persons with AIDS decreased 7% and 25%, respectively, for the first time in the epidemic.[16,66] Declines in the incidence of AIDS continued from 1998–99, but these declines began to level off, and there was essentially no change from 1999–2001. From 2002–06 the estimated number of newly diagnosed

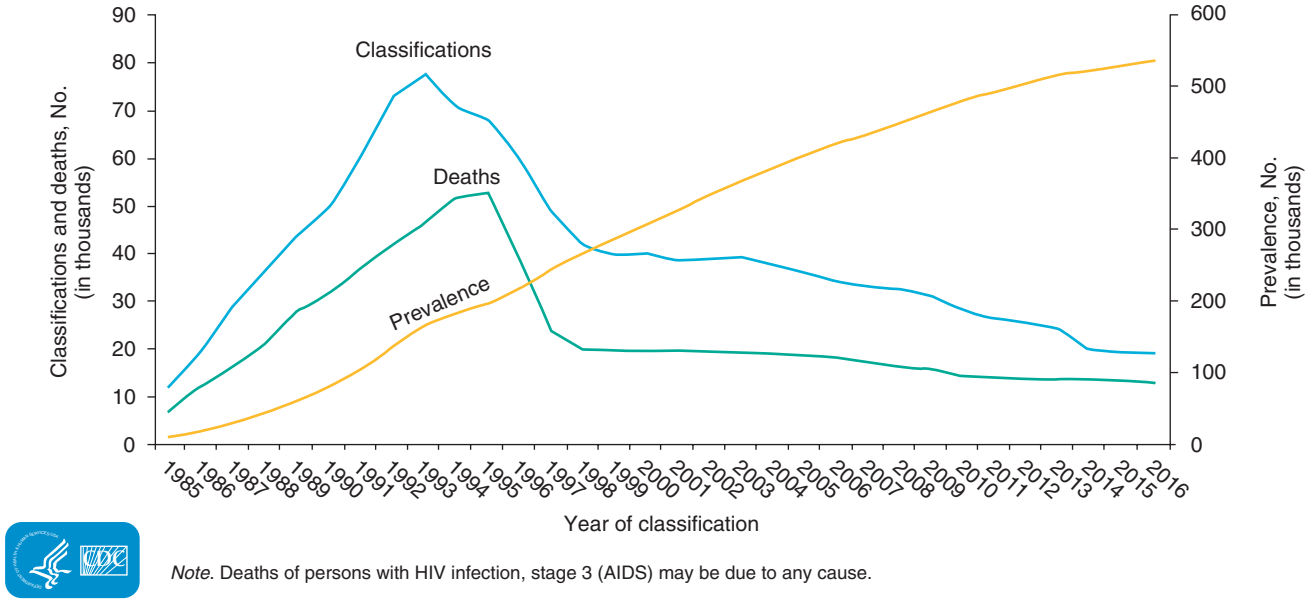

FIG. 119.2 Stage 3 (AIDS) classifications, deaths, and persons living with diagnosed HIV infection ever classified as stage 3 (AIDS) 1985–2016: United States and six dependent areas. *(From the Centers for Disease Control and Prevention; National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Division of HIV/AIDS Prevention.* Trends in HIV Infection Stage 3 (AIDS). https://npin.cdc.gov/publication/trends-hiv-infection-stage-3-aids. *Accessed January 23, 2019.)*

AIDS cases remained stable, with 37,852 cases reported in 2006, for a rate of 12.3 per 100,000 population in the United States. From 2007–10 the estimated number of annual AIDS diagnoses continued to remain stable, but the rate continued to decline, for an estimated rate of AIDS diagnoses in 2010 of 10.8 per 100,000 population.[67] After the introduction of highly active ART, the number of deaths and new AIDS cases began to decline. Between 1995 and 1998 AIDS deaths declined by 63% (from 51,760–18,823) and continued to decline from 16,947 in 2002 to 14,061 in 2006, a 17% decrease; but since then, rates have stabilized, with approximately 15,000 deaths per year. In 2016 there were 15,428 deaths, for a rate of 4.8 per 100,000[29] (Fig. 119.2). Surveillance now monitors HIV infection and classifies as stage 3 what used to be called AIDS. In 2017 the rate of HIV infections classified as stage 3 (AIDS) was 5.4 per 100,000.[29]

Demographic Characteristics of HIV Infection

Men accounted for 81% of HIV infections diagnosed in 2017, and HIV rates were much higher for men (23.1/100,000) than women (5.2/100,000).[29] From 2012–17 the HIV infection rate was highest for persons age 25 to 29 years (32.9), followed by persons age 20 to 24 years (28.7). The only age group for which the rate of HIV infection increased during that timeframe is that between the ages of 25 and 29 years. Since 1991 the percentage of AIDS cases reported among persons 50 years or older has also steadily increased, and in 2017 they represented 17% of all HIV diagnosis.[29] The CDC estimated that 6.4% of incident HIV infections occurred among persons 55 years or older between 2010 and 2016.[28]

In 2017 26.2% of the persons diagnosed with HIV infection were white, 43.5% were black non-Hispanic (39% of reported cases among men and 60% among women), and 24.7% were Hispanic (Table 119.3). In 2017 the rate of HIV diagnoses was 41.10 per 100,000 for blacks and 16.1 per 100,000 for Hispanics, compared with 5.1 per 100,000 for whites.[29] Rates among American Indian/Native Alaskans have slightly increased since 2012; however, only 212 cases were reported in 2017 in these populations.[29]

Hispanics with AIDS represent different countries of origin and cultures.[68] The rate of AIDS is the highest for Hispanics in the Northeast and Puerto Rico. IDU is the predominant exposure mode in Puerto Rican–born men and women with AIDS who are residing in either Puerto Rico or the US mainland. The AIDS rate among Hispanics is the lowest in the West. Hispanics with AIDS in this area are primarily from Mexico or Central and South America and are less likely to report a history of IDU.

TABLE 119.3 Characteristics of Persons Reported With Acquired Immunodeficiency Syndrome and Rates by Year of Report: United States, 1997 and 2010

	1997		2010	
	NO. (*n* = 60,634)	RATE[a]	NO. (*n* = 33,015)	RATE[a]
Sex[b]				
Male	47,312 (78%)	44.0	24,749 (71%)	20.0
Female	13,322 (22%)	11.5	8242 (29%)	6.4
Race/Ethnicity				
White non-Hispanic	20,197	10.4	8875	4.4
Black	27,075	83.7	16,118	43.0
Hispanic	12,466	37.7	6636	13.7
Asian/Pacific Islander	448	4.5	44	9.7
American Indian/ Native Alaskan	206	10.4	170	7.2

[a]Per 100,000 population, extrapolating from the official 1980 census count and 2009 postcensus estimates. http://222.census.gov/ipc/www/idb/.
[b]Rates by sex are only for adult/adolescent cases of acquired immunodeficiency syndrome.
From Centers for Disease Control and Prevention. HIV/AIDS surveillance report. MMWR Morb Mortal Wkly Rep. *1997;9:1–43; and Centers for Disease Control and Prevention. HIV/AIDS surveillance report.* MMWR Morb Mortal Wkly Rep. *2006;18:1–55.*

Geographic Distribution of HIV Infection

The first cases of AIDS reported in the United States were clustered among homosexual and bisexual men and PWIDs in the major metropolitan areas of the East and West Coasts.[69] Since then, AIDS cases

have been reported from all 50 states, the District of Columbia, Puerto Rico, the Virgin Islands, and Guam. However, HIV and AIDS cases are distributed unevenly across the United States.[28] In 2017 HIV rates were highest in the South (16.12/100,000 population), followed by the Northeast (10.6/100,000 population), and lowest in the Midwest (7.4/100,000 population)

The geographic distribution of HIV/AIDS has changed over time. The southern region of the United States accounted for 52% of HIV diagnoses in 2017.[29] Between 1999 and 2003 there was a 13.8% increase in the incidence of AIDS in the southern region of the United States, more than any other region of the country.[70] In most of the United States the majority of people diagnosed with HIV live in metropolitan areas, but in the South 23% of new HIV diagnoses are among people living in suburban and rural areas. In 2017 the six cities with the highest rates of HIV diagnoses per 100,000 population were all in the South: Miami-Fort Lauderdale-West Palm Beach, FL (35.8); Orlando-Kissimmee-Sanford, FL (28.6); Atlanta-Sandy Springs-Roswell, GA (27.3); New Orleans–Metairie, LA (27.0) and Baltimore, MD (26.8); and Baton Rouge, LA (26.9).[29]

Clinical Manifestations of HIV Infection

Spectrum and Progression of HIV Infection

The spectrum of HIV infection ranges from an asymptomatic state to severe immunodeficiency and associated serious secondary infections, neoplasms, and other conditions.[71] Initial or primary infection with HIV can be followed by an acute mononucleosis-like illness. The features of this acute illness associated with seroconversion include fever, lymphadenopathy, sweats, myalgia, arthralgia, rash, malaise, lethargy, sore throat, anorexia, nausea, vomiting, diarrhea, headache, photophobia, and mucocutaneous ulcers.[72,73] Less common manifestations have also been reported, including a variety of neurologic conditions (e.g., aseptic meningitis, myelopathy, radiculopathy, peripheral neuropathy, and Guillain-Barré syndrome),[74] *Candida* esophagitis,[75] and mucocutaneous ulceration (see Chapter 122).

Estimates of the frequency of symptoms among those with primary HIV infection range from 40% to 90%. The signs and symptoms of acute HIV infection are usually manifested days to weeks after exposure.[76–78] In a comprehensive review of primary HIV infection, the interval between exposure and symptomatic illness was reported to range on average from 2 to 4 weeks, with the duration of illness lasting from 1 to 2 weeks.[75] However, the diagnosis of acute HIV infection is frequently missed as the symptoms associated with acute HIV-1 infection are nonspecific. In a group of 23 persons at risk of HIV infection, 87% were symptomatic, and 95% of them sought medical care, yet few had the correct diagnosis made at the first clinic visit.[72] In a prospective study, fever, myalgia, rash, night sweats, and arthralgia occurred more frequently among patients with primary HIV infection, but no targeted symptoms allowed for screening for primary infection.[73] Acute HIV infection should therefore be included in the correct setting in the differential diagnosis of any unexplained febrile illness (see Chapter 122).[76]

The diagnosis of acute HIV infection cannot be made with the commonly available serologic tests (third-generation immunoassays) because they detect antibodies and become positive approximately 3 weeks after the initial infection.[79] Studies of homosexual men,[80,81] persons with hemophilia,[80,82] and intravenous (IV) drug users[83] have consistently demonstrated the development of detectable HIV antibodies within 3 to 12 weeks after infection. Epidemiologic studies and case reports, as well as modeling techniques,[80] suggest that seroconversion beyond 6 months is very uncommon. The laboratory diagnosis of primary HIV infection should be made by requesting a plasma HIV RNA assay, which has a sensitivity of 100% and specificity of 97.4%.[73] The test for the presence of detectable p24 antigen is less sensitive (88.7%) but more specific (100%) than the plasma HIV RNA assay for the diagnosis of primary infection,[73] and the detection of p24 antigen is now used routinely in the screening of blood donors.[84] Therefore the presence of viral p24 antigen or high-titer HIV RNA in a patient with a negative test for HIV-1 antibodies establishes the diagnosis of acute HIV infection (see Chapter 120). False-positive HIV RNA tests have been described, but they are not reproducible and have values less than 3000 copies/mL.[85]

With the availability of fourth-generation HIV tests that detect both p24 antigen and antibodies (immunoglobulins G and M [IgG and IgM]), HIV infection can be identified sooner than with third-generation immunoassays. In a study that did NAAT on HIV-negative specimens after third- and fourth-generation immunoassays, NAAT increased HIV detection rate by 2.2% after a third-generation immunoassay and by only 0.7% after fourth-generation immunoassay.[86]

After primary infection with HIV, the risk for disease progression increases with the duration of infection. Most cohort studies that have evaluated the natural history of HIV infection have been conducted in the United States and Europe and show that AIDS develops in less than 5% of HIV-infected adults within 2 years of infection; without therapy, AIDS develops in approximately 20% to 25% within 6 years of infection and in 50% within 10 years.[87–90] Approximately 5% to 8% of HIV-infected individuals remain clinically asymptomatic, with normal $CD4^+$ T-lymphocyte counts for more than 8 years after infection. These individuals are called "long-term nonprogressors."[91–93]

Differences in the rate of progression may be due to the route of infection, the size of the viral inoculum, the pathogenicity of the infecting viral strain, or the immunologic status of the host. For example, in one analysis of nearly 700 HIV-infected transfusion recipients, the estimated risk for the development of AIDS was 33% for persons within 5 years of infection and 49% within 7 years.[94] Among recipients infected for similar periods, AIDS developed more rapidly in those who received blood from donors who progressed to AIDS soon after donation (50%) than in those who received blood from other HIV-infected donors (26%). In the same study the recipients in whom AIDS developed had received significantly more units of blood at the time of infection than HIV-infected recipients without AIDS did, which raises the possibility that the underlying clinical status leading to multiple transfusions, particularly the degree of immunosuppression, or exposure to other viral cofactors may also have affected disease progression.

AIDS-Indicator Diseases

Three clinical conditions accounted for greater than 75% of all initial AIDS-indicator conditions reported in 1992: *P. jirovecii* pneumonia (42%), HIV wasting syndrome (20%), and candidiasis of the esophagus (15%). The prevalence of several AIDS-indicator diseases was higher in MSM than in heterosexual men or women. In general, the reported frequency of AIDS-indicator diseases is similar for men and women with similar modes of exposure to HIV. However, among PWIDs, esophageal candidiasis, cytomegalovirus (CMV) disease and retinitis, and herpes simplex virus (HSV) disease have been reported more frequently in women than men.[95]

Because most AIDS-indicator infections result from the endogenous reactivation of previously acquired pathogens, the frequency of reported opportunistic infections probably reflects, in part, the geography-specific prevalence of endemic infections. For example, toxoplasmosis and cryptococcosis are more likely to develop in African and Haitian patients.[96] Similarly, the risk of extrapulmonary TB among foreign-born persons with AIDS in the United States is the highest in those from Haiti, the Philippines, Central America, and Africa.[97] Among US-born persons, those at increased risk for extrapulmonary TB include residents of the South and Northeast, blacks and Hispanics, and PWIDs.[98]

Expansion of the surveillance case definition for AIDS in the United States in 1993 to include immunologic criteria (a $CD4^+$ T-lymphocyte cell count of <200/μL) caused a substantial distortion of the trend in the incidence of AIDS-defining diseases. Therefore the CDC developed a procedure for estimating the incidence of AIDS-defining opportunistic infections among persons reported solely on the basis of immunologic criteria; this procedure allowed trends in the incidence of opportunistic infections in persons with AIDS to be estimated as though the case definition had not changed.[98] Changes in the incidence and prevalence trends of AIDS-defining diseases between 1991 and 1996 demonstrated that, for homosexual/bisexual men, significant decreasing trends occurred for 11 opportunistic infections, including *Mycobacterium avium-intracellulare* disease, *P. jirovecii* pneumonia, CMV retinitis, Kaposi sarcoma, esophageal candidiasis, CMV disease, extrapulmonary cryptococcosis, toxoplasmic encephalitis, TB, HSV infection, and disseminated histoplasmosis. In

contrast, for PWIDs decreasing trends were seen for only five opportunistic infections (*P. jirovecii* pneumonia, esophageal candidiasis, TB, chronic HSV infection, and chronic cryptosporidiosis), and an increase occurred for recurrent pneumonia.[99] The decreasing trend for some AIDS-defining opportunistic infections, such as *P. jirovecii* pneumonia, was probably related to the increasing use of ART and prophylaxis against *P. jirovecii* pneumonia. For example, among adults and adolescents with a single AIDS-defining disease reported through 1996, the proportion with *P. jirovecii* pneumonia decreased from 50% in 1988 to 39% in 1996. Although declines were seen in everyone with AIDS during this period, they were the most striking for homosexual/bisexual men and persons with hemophilia or a coagulation disorder. The differences in trends for homosexual/bisexual men and PWIDs may reflect differences in socioeconomic status, access to medical care, or adherence to preventive medications. The increasing use of effective ART, which began in 1995/1996, had caused a dramatic decrease in the incidence of AIDS-defining opportunistic illnesses by the end of 1996,[8] and the incidence of AIDS could no longer be reliably estimated. The decline in AIDS-defining opportunistic illnesses that began in 1996 has continued. With the increasing use of effective ART, AIDS-defining illnesses are occurring mainly among persons with newly diagnosed HIV infection at the time of AIDS, those known to be infected but who do not seek or receive care, and those for whom treatment has failed.[100–103] Among patients who begin ART the unusual presentation of opportunistic infections can occur as a result of immune reconstitution.[104]

In 1993 three new AIDS-defining illnesses were added to the surveillance case definition: recurrent bacterial pneumonia, invasive cervical carcinoma, and pulmonary TB.[16] Several studies have shown that persons with HIV-related immunosuppression are at increased risk of bacterial pneumonia,[105] which can result in significant morbidity and mortality.[19,20] One study among PWIDs found that the annual incidence rate of bacterial pneumonia was five times higher in those who were infected with HIV than in those who were seronegative PWIDs.[105] *Streptococcus pneumoniae* is the most commonly isolated bacterial pathogen and has been reported to precede the onset of other AIDS-defining conditions in 57% to 81% of persons with HIV infection.[106] In a population-based survey in San Francisco, the rate of pneumococcal bacteremia (89% of the HIV-infected patients with bacteremia had pneumonia as a major clinical syndrome) among persons with AIDS was nearly 100 times higher than rates reported before the HIV epidemic.[107] The risk of pneumonia in HIV-infected patients is inversely related to their $CD4^+$ T-lymphocyte counts (see Chapter 123).

Precursor lesions to invasive cervical cancer, such as cervical dysplasia, neoplasia, and genital papillomavirus infection, are more commonly diagnosed in HIV-infected women than in other women (also see Chapter 126).[108] In a study comparing HIV-seropositive with HIV-seronegative women with normal baseline cervical cytology, women positive for oncogenic human papillomavirus had a higher 2-year incidence of squamous intraepithelial lesions than HIV-negative women, regardless of $CD4^+$ count. Among women infected with nononcogenic human papillomavirus types, the incidence of squamous intraepithelial lesions at 2 years was significantly higher among HIV-infected women with a $CD4^+$ count of less than 200 cells/μL than among those with higher $CD4^+$ counts and HIV-negative women.[109] The risk of cervical cancer among HIV-infected patients has not changed with the advent of potent ART.[110]

HIV Infection and Tuberculosis

After several decades of declining incidence, the number of new cases of TB in the United States began to increase in 1986.[111] Many factors contributed to the resurgence of TB, but the HIV/AIDS epidemic was in part a major cause of these excess cases of TB.[112] Now once again, the overall case rates of TB in the United States are declining, with 4.6 new cases per 100,000 population (a total of 13,767 cases) reported in 2006[113] and an estimated 4.0% prevalence of latent TB infection in the general population. The percentage of TB cases with known HIV infection also decreased from 15.0% in 1993 to 6% in 2006[114]; however, the full spectrum of the overlap between HIV and TB is not known, and more than 100,000 persons in the United States are thought to be coinfected with HIV and *Mycobacterium tuberculosis*.[111,112] Comparisons of AIDS and TB registries conducted by the 50 states and Puerto Rico revealed that 14% of persons with TB in 1993 and 1994 (27% among those 25–44 years of age) also appeared in the AIDS registry.[115] The overlap in the demographic and geographic characteristics of the two diseases is evident by surveys of HIV seroprevalence in TB clinics and by the fact that 80% of those with TB and AIDS were found in New York, California, Florida, Georgia, New Jersey, Illinois, and Texas. Both TB and HIV infection disproportionately affect racial and ethnic minorities and the urban poor.[111] In one analysis black and Hispanic adults who died from AIDS were nearly three times more likely than whites to also have TB.[116]

HIV infection is a strong risk factor for the development of active TB in persons with latent *M. tuberculosis* infection. In a prospective study of PWIDs with documented positive tuberculin skin tests, the observed incidence of active TB was 7.9 per 100 person-years for 49 HIV-infected persons versus no cases among 62 HIV-seronegative persons. The risk of active TB in HIV-seropositive persons in this study—14% over 2 years—contrasts strikingly with the estimated 10% lifetime risk in HIV-negative persons with latent TB infection.[117] In addition, HIV-infected persons are at increased risk for the development of active, symptomatic TB after their initial exposure and subsequent infection with *M. tuberculosis*.[118] Outbreaks of TB among HIV-infected individuals in correctional facilities, AIDS clinics, and hospital wards suggest that the development of active TB after exposure is greatly increased among HIV-infected persons. Finally, molecular epidemiology studies conducted in San Francisco and New York suggest that one-third of the cases in San Francisco and 40% in New York are due to recent transmission rather than reactivation.[119,120]

Drug-resistant TB is more common in persons with HIV infection than in those with TB but without HIV infection.[115] In a multivariate analysis conducted by the CDC between 1993 and 1996, being infected with HIV was a risk factor for isoniazid and rifampin monoresistance and multidrug-resistant TB.[121] In a study conducted in New York City the proportion of isolates resistant to one or more anti-TB drugs increased from 10% from 1982–84 to 23% in 1991.[122] Among the isolates of *M. tuberculosis* with primary resistance to isoniazid or rifampin, 75% came from patients known to be infected with HIV.[122] The increased risk of drug-resistant TB among HIV-infected persons may reflect a higher proportion of the disease resulting from recently acquired drug-resistant strains[119,120] and other factors, such as decreased absorption of oral antimycobacterial drugs among HIV-infected persons.[123] Outbreaks of multidrug-resistant TB (e.g., resistant to both isoniazid and rifampin and/or other drugs) have been characterized by (1) a high prevalence of HIV infection among the outbreak cases (range, 20%–100%), (2) a high mortality rate among persons infected with resistant strains (range, 72%–89%), (3) a short median interval between diagnosis and death (range, 4–16 weeks), and (4) nosocomial transmission to health care workers.[115,124–126] The emergence of extensively drug-resistant TB (resistant to both isoniazid and rifampin and to any fluoroquinolone drug and at least one of three second-line injectable drugs [amikacin, kanamycin, or capreomycin]) among HIV-infected persons in South Africa raises concerns about the possibility of epidemics of virtually untreatable TB.[127]

Mortality of Persons With HIV Infections and AIDS

The estimated number of deaths among persons with HIV/AIDS increased steadily through 1995, when approximately 50,000 persons were estimated to have died of AIDS. In 1996 the estimated number of deaths from AIDS decreased to 37,525 and has continued to drop every year since then to 17,347 in 2000, 14,061 in 2006, and 12,287 in 2016 (see Fig. 119.2).[29] Since 2012 the number of deaths reported among persons with stage 3 (AIDS) HIV infection has remained stable, with approximately 13,000 deaths per year and a rate of 4 per 100,000 population.[29] The dramatic declines in AIDS mortality seen after 1996 were largely due to the availability of combination ART[26,128,129] and have been more rapid among whites and homosexual and bisexual men but have occurred in all populations.[10] The percentage decrease in mortality has been the smallest among black women and in the South.

In 1993 HIV infection became the most common cause of death among persons age 25 to 44 years.[130] In 1994 72% of HIV-related deaths occurred in persons age 25 to 44 years, in whom it was the leading cause of death, accounting for 19% of the deaths in this age group. After 1996, when AIDS mortality began to decline, and while HIV infection is no longer a leading cause of death for Americans overall, it remains a leading cause of death among black men age 25 to 44 years.

To put into perspective the impact that AIDS-related mortality has had, the years of potential life lost before the age of 65 years because of AIDS have been calculated.[131] From 1989–90 the years of potential life lost before age 65 years that could be attributed to AIDS and HIV infection increased by 13%. In 1993 AIDS had become the fifth leading cause of years of potential life lost before age 65 years, and in 1994 it became the fourth. That year it was estimated that approximately 49,500 persons died of AIDS.[130] At a population level the improvement in survival for AIDS patients as a result of the introduction of highly active ART in 1996 can be seen in a study conducted in New York City, where the overall cumulative survival at 24 months increased from 43% among patients diagnosed with AIDS from 1990–95 to 76% among those diagnosed from 1996–98.[128] It has been estimated that at least 3 million years of life have been saved in the United States as a direct result of the treatment of HIV infection.[132]

HIV/AIDS IN CHILDREN

Through the end of 2017, a total of 9573 cases of AIDS in children younger than 13 years had been reported in the United States.[29] The number of AIDS diagnoses reported in children younger than 13 years is now quite small in the United States, with 33 cases reported in 2017. HIV diagnosis is also uncommon, with 99 cases and a rate of 0.2 per 100,000 population reported in 2017.[29] The spectrum of AIDS-defining opportunistic infections and malignancies in children overlaps considerably with those that are included in the surveillance case definition for adults and adolescents; however, some differences can be noted (see Chapter 127).[133] Three important exceptions for children younger than 13 years are the inclusion of lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia, recurrent bacterial infections, and the exclusion of a threshold $CD4^+$ T-lymphocyte count (e.g., <200 $CD4^+$ T lymphocytes/μL). Longitudinal evaluations of lymphocyte subsets in both HIV-infected and HIV-uninfected children suggest some measure of prognostic value.[134,135] However, because normal newborns and young infants have prominent lymphocytosis,[136] moderate declines in $CD4^+$ T lymphocytes by adult standards can represent significant impairment in young children.[134,137]

Pediatric cases are ordered into a hierarchy of mutually exclusive exposure categories, and most children reported with AIDS acquire HIV infection perinatally from their mothers.[138] Among the 287 children of age less than 13 years reported through the end of 2016, 86% had acquired HIV infection perinatally. Because most children acquire HIV infection from their mothers, the racial, ethnic, and geographic distributions of children with AIDS parallel those of women with AIDS. Sixty percent of the pediatric HIV infections and 69% of AIDS cases reported in 2017 were among black non-Hispanics.

From 1984–92 the estimated number of children with perinatally acquired AIDS diagnosed each year increased and peaked at 905 in 1992.[138] In 1994, as a result of a clinical trial that demonstrated the efficacy of zidovudine in reducing perinatal HIV transmission by two-thirds,[139] the Public Health Service issued recommendations for the use of zidovudine and counseling and HIV testing of pregnant women in the United States.[140,141] With the implementation of these recommendations, the number of children with perinatally acquired HIV infection has decreased dramatically in the United States, with an estimated 21,956 cases of perinatally acquired HIV presented between 1994 and 2010 (Fig. 119.3).

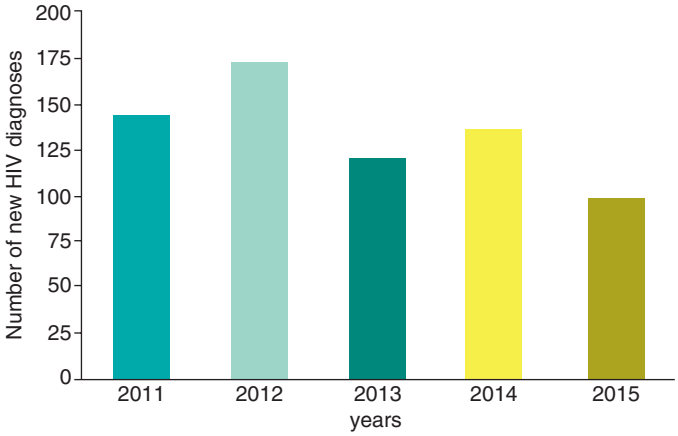

FIG. 119.3 Diagnoses of perinatal HIV infections in the United States, 2011–15. *(From the Centers for Disease Control and Prevention. HIV Among Pregnant Women, Infants, and Children. https://www.cdc.gov/hiv/group/gender/pregnantwomen/index.html. Accessed January 23, 2019.)*

MODES OF TRANSMISSION

More than 2 decades after the initial studies were conducted to determine the ways in which HIV is transmitted, surveillance and epidemiologic data throughout the world continue to support only three primary modes of transmission: sexual contact; exposure to blood, largely through IDU and occasionally through transfusion; and perinatal transmission from infected mothers to their infants.

Sexual Transmission

Sexual contact is the predominant mode of HIV transmission throughout the world. However, the geographic distribution of cases attributable to homosexual and heterosexual transmission varies markedly.[7] Whereas heterosexual transmission is the major mode of spread of HIV infection in Africa and the Caribbean, in North America and Europe male-to-male sexual transmission continues to account for the majority of cases among men, and heterosexual transmission accounts for a smaller number of new infections except among women.[142]

The likelihood of acquiring or transmitting HIV infection through a single sexual contact is directly related to certain correlates of exposure, such as the infectiousness of the source partner, the susceptibility of the exposed individual, the number of partners, and the prevalence of HIV infection in the population. Sexual transmission of HIV is relatively inefficient, but behavioral and biologic factors influence the likelihood of HIV transmission in a given sexual encounter. For example, anal sex has been consistently found to be a greater risk than vaginal sex, which in turn is a higher risk than oral sex,[143] and the coexistence of a sexually transmitted infection (most notably the presence of genital ulcerative disease) greatly increases the infectiousness as well as the susceptibility of the individual.[144–146] Carefully performed longitudinal cohort studies conducted in Africa have helped us understand the risk of HIV transmission per coital act. In a study conducted in Uganda the probability of HIV transmission per coital act was the highest from subjects with early infection (8.2 cases/1000 coital acts), it declined to 0.7 to 1.5 per 1000 coital acts with established infection, and it increased again to 2.8 cases per 1000 coital acts in advanced infection.[147] Index partner HIV viral load was the strongest predictor of transmission at each stage of infection. Taking into consideration that patients with acute infection have extremely high viral loads, the risk for HIV transmission from patients with acute infection has been estimated to be as high as 1 case per 50 coital acts.[148] The estimated per-act HIV transmission risk (expressed as per 10,000 exposures) has been estimated to be 138 for receptive anal intercourse, 11 for insertive anal intercourse, 8 for receptive penile-vaginal intercourse, and 4 for insertive penile-vaginal intercourse.[149] In a prospective cohort study of 2189 high-risk homosexual and bisexual men conducted in San Francisco, Denver, and Chicago with 2633 person-years of follow-up, 60 seroconversions were observed. The estimated per-contact risk of acquiring HIV from unprotected receptive anal intercourse was 0.82% when the partner was known to be HIV infected and 0.27% when partners of unknown serostatus were included.[150] In a systematic review and meta-analysis of the literature on HIV-1 infectiousness through anal intercourse, the per-act risk was 1.4%, and the per-partner risk was 40.4% for unprotected receptive

anal intercourse, with no significant difference between per-act risks for heterosexuals and MSM.[151] The per-partner risk for unprotected insertive anal intercourse and combined unprotected receptive and insertive anal intercourse risks were 21.7% and 39.9%, respectively. These data support that unprotected anal intercourse is a high-risk practice for HIV transmission, but that there is probably substantial variation in infectiousness.

Infectiousness of the Source Partner

The variability in the infectiousness of the source partner has been suggested by observations that some persons appear to be highly efficient transmitters of HIV through sexual contact. Such efficiency is manifested by the infection of a high proportion of an individual's sexual partners,[152] often after only a single contact.[153,154]

It has been thought for some time that HIV transmission appears to be more efficient late in the course of HIV infection.[147,155–159] More recently, primary HIV infection has been recognized as a period associated with increased infectiousness likely related to the much higher viral load in blood and genital secretions of persons with acute infection.[148,160,161] From a public health point of view, this association is extremely important because increased infectiousness would precede recognition of infection by the individual.[162,163] In general, the higher the plasma viral load, the more likely HIV transmission will occur, given similar exposure. In a study conducted in Africa there were no cases of seroconversion among heterosexual discordant partners when the infected partner had serum HIV RNA of less than 1500 copies/mL and the per-person risk of transmitting HIV-1 increased by a factor of 2.5 each time the viral load in the HIV-infected person increased by a factor of 10.[164] In 2008 the Swiss National AIDS Commission published a statement stating that individuals living with HIV who achieved and maintained an undetectable viral load for at least 6 months and did not have other sexually transmitted infections did not transmit HIV through sexual contact.[165] This became known as "The Swiss Statement" and was quite controversial when first published. Since then, results of several studies have provided strong evidence that suppression of HIV viral replication with antiretrovirals (ARVs) dramatically reduces the infectiousness of the HIV-1–infected individual and the subsequent risk of transmission through sexual contact. In a randomized controlled trial conducted among serodiscordant couples, treatment with ART led to a 96% reduction in the probability of HIV transmission and, more important, on long-term follow up of study participants, there were no linked transmissions when the viral load of the infected partner was suppressed.[166,167] Outside of the clinical trial setting the PARTNER study demonstrated zero HIV transmissions among serodiscordant heterosexual and MSM couples when the HIV-infected partner had a suppressed viral load on ART.[168] These and other studies have now confirmed that there is a negligible risk (likely zero risk) of sexual transmission of HIV when the HIV-infected sex partner has durably suppressed viral replication on ART.[169] Taken together, these findings have resulted in the "Undetectable equals Untransmittable (U = U) concept which was accepted by the CDC as a public health principle in 2017.[170]

Similarly, the risk for perinatal transmission of HIV increases as the viral load in the mother increases, and no cases in one study occurred when the maternal viral load in plasma was less than 1000 copies/mL, 16.6% when the viral load was between 1001 and 10,000 copies/mL, 21.3% when the viral load was between 10,001 and 50,000 copies/mL, 30.9% when the viral load was between 50,001 and 100,000 copies/mL, and 40.6% when the viral load was greater than 100,000 copies/mL.[171]

The probability of saliva from HIV-infected persons transmitting HIV through oral-oral or oral-genital sexual contact is low but real.[172] HIV is found in very low concentrations in the saliva of infected persons,[173,174] and since 1987, 21 case reports of 42 potential instances of oral transmission of HIV have appeared.[172] Such transmission is difficult to prove or rule out because most persons with HIV and a history of oral sexual contact report genital contact as well.

Epidemiologic and laboratory data indicate that genital ulcer disease in the source partner is an important factor facilitating HIV transmission. Genital ulcers probably increase the infectiousness of both male and female source partners.[175,176] In a prospective study of more than 400 men who acquired a sexually transmitted disease (STD), including HIV infection, from a group of prostitutes in Nairobi, Kenya, seroconversion to HIV was independently associated with the concurrent acquisition of genital ulcer disease.[177] In a study in Malawi, patients with genital ulcer disease were associated with lower $CD4^+$ T-lymphocyte cell counts and higher plasma HIV RNA than HIV-infected patients without genital ulcer disease.[178] Furthermore, a similar study in Uganda suggested that genital ulcers, caused mainly by HSV-2, are associated with higher viral loads in both incident and prevalent HIV-infected patients.[179] Genital ulcer disease may have augmented the women's infectiousness by increasing viral shedding in the female genital tract through a local inflammatory response mediated by the recruitment and activation of HIV-infected macrophages and lymphocytes to and on the disrupted mucosal surface.[177,180] The recovery of HIV from genital ulcers in HIV-infected women supports this hypothesis.[181] These data suggest that the treatment of genital ulceration and HSV-2 suppressive therapy may be associated with a reduction in HIV viremia, thus potentially reducing HIV transmission and disease progression. However, controlled studies of antiviral therapy for genital HSV infections did not show a reduced risk in the acquisition or transmission of HIV infection.[182–184] In the United States MSM account for the large majority of primary and secondary syphilis cases among males, and having syphilis significantly increases the risk of being diagnosed with HIV in the future.[185]

Nonulcerative STDs may also enhance the sexual transmission of HIV. Among men, urethritis and gonorrhea are associated with the increased detection of HIV in semen,[186,187] and appropriate antibiotic treatment diminishes the amount of HIV present in genital secretions.[188]

Susceptibility of the Recipient Partner

As previously mentioned, the presence of genital and anorectal ulceration or mucosal disruption secondary to infection has emerged as one of the most consistent and biologically plausible factors affecting the transmission and acquisition of HIV infection through sexual contact. Although ulcers that disrupt the genital epithelium can serve simply as a portal of entry for HIV, they may have a more complex role in HIV transmission. Genital ulcers cause an inflammatory response that in turn may increase the number of stimulated T lymphocytes at the surface of the ulceration and thus increase the number of susceptible cells.[178,180]

A number of epidemiologic studies have demonstrated that a history of genital ulcer disease in the recipient partner is a risk factor for acquiring HIV in both heterosexual and homosexual men[180,189] and women.[176,189] Although this association may not be surprising, two seroepidemiologic studies of homosexual men have convincingly demonstrated that genital ulcer disease is not simply a marker for increased sexual activity.[180,190] Instead, infection with HIV was independently associated with serologic evidence of prior syphilis or infection with HSV-2, the two most common causes of genital ulcers among homosexual men in the United States. In another study among female prostitutes in Nairobi, 60% of seroconverting women experienced one or more episodes of genital ulcers before seroconverting.[176]

Nonulcerative STDs, such as gonorrhea and chlamydial infection, also facilitate the acquisition of HIV infection by causing mucosal disruption of the genital tract.[176] Other nonulcerative STDs (e.g., urethritis, cervicitis, balanitis, bacterial vaginosis, and genital warts) also increase the risk of acquiring HIV infection.[191–193] Observational studies over many years strongly suggested that circumcised men were unlikely to acquire HIV. Three randomized trials have demonstrated that circumcision can decrease the acquisition of HIV infection rates by 50% to 60% in circumcised men who largely engaged in heterosexual intercourse.[194–196] However, this benefit has not been confirmed for MSM.[197,198] The higher frequency of balanitis in uncircumcised men has been postulated as a partial explanation for the increased risk of HIV observed among uncircumcised men in developing countries.[177,199,200]

Noninfectious causes of ulceration of the genital tract may also pose a risk for the sexual transmission of HIV. For example, the frequent use of the nonoxynol-9 contraceptive sponge by female prostitutes in Nairobi was associated with increased rates of genital ulcers, vulvitis, and HIV seroconversion in one study.[201] The increased risk for HIV acquisition may be attributable to chemical irritation from the spermicide

or to mechanical trauma, both of which can result in inflammation and ulceration.[202] The importance of the treatment of sexually transmitted infections in the HIV epidemic was made evident by a study in Tanzania showing that prompt management of sexually transmitted infections decreased the incidence of HIV infection by 42%.[203] Certain traumatic sexual practices that result in rectal mucosal disruption and lesions have been associated with HIV infection. Early epidemiologic studies of homosexual men found that receptive anal intercourse, "fisting," and douching increased the risk of HIV transmission.[204–206] Subsequent studies have both supported these findings and extended the association of receptive anal intercourse to the heterosexual transmission of HIV.[157,162,207]

Although cases of AIDS have been reported among lesbian and bisexual women, most were infected through IDU or sex with HIV-infected men.[197–199] Female-to-female transmission of HIV appears to be very rare.[200] However, cases of female-to-female transmission of HIV have been reported.[201–203]

No consistent association between oral contraceptive use by women and acquisition of HIV infection has been found. In one study women who reported taking oral contraceptives had a reduced risk of HIV infection.[158] However, in a longitudinal cohort study of Nairobi prostitutes and a cross-sectional study of sex partners at an STD clinic in Nairobi, oral contraceptive use was an independent risk factor for HIV seroconversion and prevalent infection, respectively.[176,204] In contrast, a study of prostitutes in Zaire[189] and one of pregnant women in a rural US community with a high prevalence of HIV infection[79] found no association between HIV infection and the use of oral contraceptives. The presence of cervical ectopy has been associated with an increased risk of HIV seropositivity among long-term female partners of HIV-positive men in Nairobi.[204] Because oral contraceptives are associated with higher rates of ectopy, the relationship, if any, between oral contraceptives and HIV requires further study.[205] There are growing concerns that hormonal contraceptives, and specifically progestogen-only injectables, such as depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN), may increase the risk of HIV acquisition when used by HIV uninfected women or, when used by women living with HIV, may increase the risk of female to male HIV transmission.[206,208] As a result of these data WHO issued, in 2017, an updated guidance statement for the use of hormonal contraception by women at risk of HIV. In this new document WHO has changed the recommendation for both methods from "use without restriction" to "benefits outweigh theoretical or proven risks."[209] Although anal and vaginal intercourse are the two sex practices associated with the greatest risk of transmission, other sexual activities involving exposure to semen or blood also carry a potential risk of transmission. For example, seroconversion for the HIV antibody has been documented after receptive oral intercourse with ejaculation.[172]

Finally, a mutation in the chemokine receptor gene that may render the rare homozygous host relatively resistant to HIV infection has been identified (see Chapter 121). When this mutation is present in the heterozygous state, it does not prevent infection.[210] The presence of this mutation varies according to race, with 11% and 1.7% homozygosity among whites and blacks, respectively.[160]

Transmission Through Injection Drug Use

Among PWIDs HIV is transmitted by parenteral exposure to HIV-infected blood through sharing of contaminated needles and other injection equipment. Specific factors that have been associated with HIV infection among PWIDs include the duration of IDU, frequency of needle sharing, number of needle-sharing partners, number of injections, median number of injections in "shooting galleries," and prevalence of HIV infection in the area of residence.[34,211–213] The rate of HIV infection among PWIDs varies widely among different geographic areas. In the United States the rate of HIV infection has been the highest in the Northeast.[35,36]

Most studies have found higher rates of HIV infection associated with cocaine and heroin injection than with heroin injection alone, probably because of the greater frequency of cocaine injections.[214–216] Another possible explanation is the greater likelihood of the exchange of sex for drugs among cocaine users.[217] Among PWIDs poor socioeconomic conditions, homelessness, and minority race and ethnicity are associated with an increased frequency of risk behavior and higher rates of HIV infection.[218–221] Among PWIDs enrolled in a study in Baltimore from 1988–89, the 703 HIV-infected users were more likely to have a history of syphilis (16.8%) than the 2218 uninfected PWIDs (11.3%).[222] The higher rates of STD among HIV-infected PWIDs than uninfected users suggests that some infections are transmitted through unsafe sexual practices rather than IDU itself.[43,222,223]

Many PWIDs have changed their drug use behavior to reduce the risk of HIV infection.[224,225] Substance use treatment, street outreach programs, syringe services programs, AIDS educational efforts, and HIV counseling and testing programs have all been shown to be effective in reducing, although not eliminating, the risk of HIV transmission in these populations.[226] However, worldwide coverage of HIV prevention, treatment, and care services for PWIDs is very low, and thus interventions that are known to be effective have not been implemented.[227] ARV drugs given to HIV-negative PWIDs have been shown to decrease HIV-1 incidence by 49%.[228]

Transmission by Blood and Other Tissues

The recipients of unscreened blood or blood products from HIV-infected donors are at high risk for HIV infection. HIV has been transmitted through receipt of whole blood, blood cellular components, plasma, and clotting factors.[229,230] The likelihood of a person becoming infected with HIV after receiving a single-donor blood product documented to be HIV positive approaches 100%.[231,232] Other blood or plasma products, such as hepatitis B immune globulin, immune serum globulin, Rh(D) immune globulin, and hepatitis B vaccine, are prepared by using one of several fractionation processes that inactivate HIV; the use of these products has not been associated with transmission.[233,234]

Before serologic testing for HIV was begun in 1985, 0.04% of 1,200,000 donations in the United States were estimated to be HIV positive.[235] During this time an estimated 29,000 blood or blood product recipients were exposed to HIV; because many died of underlying conditions, 12,000 of these persons were estimated to have survived long enough for AIDS to develop.[236] Confidential unit exclusion and direct donor deferral as well as the institution of HIV antibody screening in 1985, followed by additional tests for antibodies to HIV-2 and p24 antigen in 1996, markedly decreased the risk of HIV infection through blood or blood products. With the implementation of p24 antigen testing, the risk of HIV transmission through the transfusion of screened blood was estimated to be 1 in 200,000 to 1 in 2,000,000 per unit transfused in the United States.[237,238] Further reduction in the risk of transfusion-transmitted HIV in the United States occurred after the US Food and Drug Administration (FDA) approved the implementation of NAAT of blood units in 2002, which reduces the window period to approximately 12 days.[239] In the clinical trials that led to the approval of NAAT by the FDA, a total of 7 HIV-1–positive and 88 hepatitis C virus (HCV)-positive donations that would otherwise not have been diagnosed were detected in more than 20 million donations tested. As a result of additional testing, estimated risk for HIV transmission by blood products is now 1 in 1.4 to 1 in 1.8 million units.[59] The risk of HIV infection for patients with hemophilia who received concentrated clotting factors composed of blood components from potentially thousands of donors was substantial before 1985,[240,241] but now it is exceedingly low. HIV transmission by transplantation of the liver, heart, kidney, pancreas, bone, and possibly skin has been reported.[65,242,243] Relatively avascular tissues, such as corneas and processed tissues, have not been associated with transmission.[65,244,245] AIDS developed in several transplant recipients after receiving a variety of organs from a single HIV-negative cadaver donor. The donor was subsequently found to be HIV infected by culture and PCR.[65]

Perinatal Transmission

Vertical transmission of HIV from an infected woman to her infant can occur during gestation (in utero), at the time of delivery (intrapartum), or postpartum through breastfeeding. Significant progress has been made in elucidating risk factors that influence transmission during these three periods, detecting infection in the newborn earlier and more reliably, and preventing perinatal transmission with the use of ARV drugs (see Chapter 128).

The occurrence of intrauterine infection is supported by the detection of HIV both in fetal tissue as early as 8 weeks[246] and in placental tissue infected in vivo and in vitro.[247] In addition, the 30% to 50% of infected infants who test positive by PCR or HIV culture at birth[248–250] also suggests intrauterine transmission of HIV. The proportion of infants who become infected in each trimester of pregnancy is unknown, but transmission to the infant early in pregnancy would presumably allow viral replication to reach a level sufficient for detection by culture or PCR.[251] HIV-infected infants who test negative by PCR or HIV culture at birth may have become infected late in pregnancy or during the intrapartum period. Accumulating information suggests that a sizable proportion of vertical transmission may occur during the intrapartum period.[252,253] Both vaginal and cesarean deliveries present frequent and varied opportunities for the infant to be exposed to infected maternal blood and cervicovaginal fluids. Although many studies have found statistically similar rates of transmission for vaginal and cesarean section delivery,[254–257] there are data from meta-analysis and randomized clinical trials suggesting that elective cesarean section reduces the risk of perinatal HIV transmission even when accounting for the use of ARV drugs.[258] As a result, the percentage of deliveries performed via elective cesarean section in HIV-infected pregnant women increased from 20% from 1994–98 to 44% from 1998–2000.[259] The isolation of HIV from breast milk,[260] as well as reports of breastfeeding mothers who infected their infants after they had acquired HIV infection through postpartum blood transfusions, provided initial evidence for postnatal HIV transmission.[261] Subsequent evaluation has focused on estimating the added, or attributable, risk of perinatal transmission conveyed by breastfeeding. Several prospective cohort studies that compared breastfed and bottle-fed infants have detected higher rates of HIV infection in breastfed children.[253–255,262,263] The attributable risk of transmission through breastfeeding ranges from 14% to 29% and was determined on the basis of data from developing countries where ART has not been used.[264] Mothers who themselves acquired HIV infection in the postpartum period were more efficient transmitters, presumably because of the increased viral burden associated with primary HIV infection.[265,266] For these reasons it has been recommended in the United States since 1985 that HIV-infected women abstain from breastfeeding their infants. Epidemiologic studies[263] and mathematical models[267] have evaluated the competing risks of acquiring HIV infection by breastfeeding and the increased morbidity and mortality associated with alternatives to breastfeeding in developing countries. Both approaches have found that for children in many developing countries, the benefits from breastfeeding outweigh the risk of HIV transmission through breastfeeding. However, the risk of not breastfeeding varies greatly between and within developing countries, so the situation needs to be considered on an individual basis.

Prospective studies of infants born to women with HIV infection before the use of ARV drugs have found rates of transmission ranging from 13% to 40%,[254–256,268] with the highest rates of perinatally acquired HIV infection, which approach 40%, reported from Africa.[268] The disparity in these rates most likely reflects differences in the severity of the maternal disease stage, nutritional status, rates of breastfeeding, study design, completeness and length of follow-up, and use of different diagnostic criteria.[137] The risk of perinatal transmission appears to vary by the disease stage of the mother. Mothers at both extremes of the clinical spectrum of HIV infection, with either acute primary infection[199,252] or advanced symptomatic disease,[265,268] have been reported to be more likely to transmit HIV to their infants than asymptomatic seropositive women. The most important risk factor to determine the likelihood that an infant will acquire HIV perinatally is the HIV viral load of the mother.[269,270] However, mother-to-child transmission has been observed across the entire range of plasma HIV RNA levels, including in women with very low or undetectable levels of maternal HIV-1 RNA on ART.[271]

In addition to maternal risk factors, obstetric factors that disrupt the maternal-fetal barrier can increase perinatal transmission. In one study among Zairian women the presence of histologic chorioamnionitis and funisitis was associated with an overall twofold increase in the risk of transmission.[272] Preterm delivery, prolonged rupture of membranes (>4 hours), the use of illicit drugs during pregnancy, a low antenatal $CD4^+$ count, and low birth weight are also associated with increased risk for perinatal HIV transmission.[273,274]

Infants born to HIV-infected mothers have passively acquired the maternal antibody to HIV, which persists for 12 to 18 months. For infants 0 to 6 months of age, PCR and viral culture offer the greatest sensitivity and specificity for detecting HIV infection (see Chapters 120 and 127).[275] Nonetheless, these tests can detect only one-half or less of perinatally infected infants, which is a reflection of very low viral burden, sequestration of the virus in other tissues, or recent transmission to the infant either late in the third trimester or at the time of delivery.[276] Other options for diagnosing HIV infection in infants include HIV-specific IgA assays and an in vitro antibody production assay such as the ELISPOT (enzyme-linked immunosorbent spot).[251,277] However, the overall sensitivity and specificity of these tests are less than those of PCR and viral culture, especially for infants younger than 3 months.

Transmission of HIV in Health Care Settings

Percutaneous, mucous membrane, and cutaneous exposure to blood-contaminated body fluids can occur frequently in the health care setting.[278–280] Such exposure has resulted in occupationally acquired HIV infection in health care workers (see Chapter 298).[281–285] Data from several prospective surveillance projects among health care workers indicate that the average risk of seroconversion after a needlestick injury with HIV-infected blood is approximately 0.3%.[281–283] Percutaneous injury, usually inflicted by a hollow-bore needle, is the most common mechanism of occupational HIV transmission. The transmission of HIV has also been reported after mucous membrane and cutaneous exposure to blood, and in those instances the risk is estimated to be 0.09%.[286] As of December 2013 the CDC had received reports of 58 confirmed and 150 possible cases of HIV seroconversion temporally associated with occupational exposure to HIV among health care personnel in the United States.[287] HIV seroconversion temporally associated with an occupational exposure was not documented. In a retrospective study conducted by the CDC it was found that the risk of transmission of HIV to health care workers increased when the device causing the injury was visibly contaminated with blood, the device had been used for insertion into a vein or artery, the device caused a deep injury, or the source patient died within 2 months after the exposure.[288]

Because health care workers are more likely than patients to have contact with blood in the health care setting, the risk of HIV transmission from patient to health care worker clearly exceeds that of health care worker to patient.[289,290] Transmission of HIV from a health care worker to patients has been documented in two instances: in a dental practice in Florida[291,292] and from an orthopedic surgeon in France.[293] In the cluster of cases in Florida the precise events that resulted in the dentist transmitting HIV to 6 of approximately 1100 patients tested for HIV in this practice remain unknown. However, the 6 patients had no confirmed exposure to HIV other than receiving treatment from the dentist, and each was infected with a viral strain that was very similar to that of the dentist but dissimilar from other HIV-infected persons in the local area.[291,292] The very small risk of a health care worker transmitting HIV to a patient probably depends on several factors, including the type of procedure; the technique, skill, and medical condition of the health care worker; and the titer of circulating virus.[289,294,295] Aside from these two instances, the investigation of 22,759 patients of 53 other HIV-infected health care workers has not identified other episodes of transmission of HIV from a health care worker to a patient.[296]

Two patients undergoing nuclear medicine procedures have been reported to have been infected through inadvertent IV injections of blood or other material from HIV-infected patients.[297] In addition, transmission of HIV through percutaneous or mucocutaneous exposure to blood or other body substances has occurred in homes in which health care has been provided.[298,299] Transmission of HIV from patient to patient through improper sterilization or reuse of contaminated needles and syringes has been reported in Romania and the former Soviet Union.[300,301] Similarly, a report from Australia suggested that a breach in infection control precautions caused HIV to be transmitted from one patient to four others during minor surgical procedures

performed on the same day by an HIV-negative surgeon.[302] A more detailed review of transmission in the health care setting can be found in Chapter 298.

Other Modes of Transmission

Although HIV has been isolated from a variety of body fluids,[174,260,303–306] only blood, semen, other genital secretions, and breast milk have been implicated as sources of infection. HIV infection is acquired through exposure to blood, principally through IDU and receipt of contaminated blood, blood products, organs, and tissues. Exposure of nonintact skin to blood after a motor vehicle accident and a sports injury has been reported to result in HIV infection, but these occurrences are rare.[307,308]

Vaginal or anal intercourse is the predominant way in which persons are exposed to HIV-infected semen and cervicovaginal fluids. However, transmission of HIV through intravaginal insemination with unprocessed donor semen[309,310] and intrauterine insemination with processed semen[311] has been reported. Although data regarding the magnitude of the risks are conflicting,[309–311] there is no evidence that any procedure can reliably eliminate HIV from semen.[311]

Laboratory and epidemiologic studies indicate that the infectiousness of saliva from HIV-infected persons through human bites or occupational contact is extremely low. Furthermore, definitive attribution of HIV transmission to contact with saliva is difficult because saliva is often comingled with blood in these settings. The low risk of saliva-mediated HIV transmission is probably attributable to the very low concentrations of HIV in the saliva of infected persons[173,174] as well as the presence of HIV inhibitory activity in saliva.[312] One case report of two siblings infected with HIV suggested a bite as the route of transmission for the previously uninfected child.[313] However, because the bite did not break the skin or result in bleeding, the precise mode of transmission remains uncertain. Multiple epidemiologic studies, including occupational and household contact studies, have found no evidence of transmission via a human bite.[314] Similarly, studies of health care workers monitored prospectively after percutaneous, mucous membrane (e.g., during the administration of cardiopulmonary resuscitation), or nonintact skin exposure to saliva from HIV-infected patients have not detected any instances of HIV antibody seroconversion.[282,315]

To examine the risk of HIV transmission through casual contact, studies have evaluated more than 1000 nonsexual household contacts of both adults and children with HIV infection.[314,316–318] In these households transmission of HIV was found only among sex partners, children born to infected mothers, and persons who themselves had risk factors for HIV infection. However, eight case reports have described household transmission of HIV unassociated with sexual contact, IDU, or breastfeeding. Five of the eight reports were associated with documented or probable blood contact.[299,319–321] Two reports involved nursing care of terminally ill persons with AIDS in which blood exposure might have occurred but was not documented; in both reports skin contact with other secretions and excretions occurred.[299,322] In the last report a bite was suggested but not documented to have resulted in transmission.[313]

Laboratory and epidemiologic studies have produced no evidence of the replication of HIV within insects, in vitro mechanical transmission of HIV, or transmission through biting or bloodsucking insects.[323–325] The potential role of insect-mediated HIV infection was evaluated in a study of residents in a southern Florida community with a high rate of HIV infection.[326] HIV seropositivity was not associated with either epidemiologic or laboratory evidence of exposure to mosquitoes, as measured by the presence of antibodies to five arboviruses. Additional studies in Africa failed to establish an association between the presence of malaria antibodies and HIV.[327]

HIV INFECTION AND AIDS OUTSIDE THE UNITED STATES

HIV infection is pandemic, affecting almost all countries (see Chapter 118). Through December of 2017, United Nations Programme on HIV/AIDS (UNAIDS) and WHO estimate that approximately 36.9 (31.1–43.9) million persons are living with HIV worldwide, including 1.8 (1.3–2.4) million children younger than 15 years. UNAIDS/WHO estimate that in 2017, 21.7 (19.1–22.6) million people living with HIV were on ART, 940,000 (670–1.3 million) died from an AIDS-related illness, and 1.8 (1.4–2.4) million persons were newly infected with HIV, of which 70% occurred in sub-Saharan Africa, the most severely affected region of the world. Greater than 95% of all HIV-infected persons live in low- and middle-income countries (see Chapter 118). The modes of transmission of HIV are similar throughout the world, but the relative frequency varies considerably among countries and regions. In western Europe, North America, and Australia, as well as some parts of South America and the Caribbean, homosexual and bisexual men and PWIDs remain the predominantly affected groups.[328] In northern Europe most AIDS cases have occurred among homosexual and bisexual men, whereas in southern Europe, greater than 60% of persons with AIDS are PWIDs.[329] Although new HIV infections are declining globally, the only region of the world where new HIV infections are increasing is eastern Europe, with two countries, the Russian Federation and Ukraine, contributing 75% of all cases in the WHO European Region and 92% of cases in the East.[329–332]

In sub-Saharan Africa and some areas of the Caribbean, heterosexual contact is the most common mode of transmission.[328,333–339] IDU is now an important route of transmission of HIV in many developing countries and countries in transition, including those of the former Soviet Union.[331] The receipt of contaminated blood products remains a source of HIV transmission in many developing countries where HIV testing of blood and blood products is not regularly available, and medical injections with contaminated medical devices continue to result in some HIV infections.[327,328,332]

A more extensive discussion of AIDS in the developing world is presented in Chapter 118.

HIV-2

HIV-2 is a second human immunodeficiency virus that can result in severe immunodeficiency in some individuals but generally does so less frequently than in HIV-1–infected individuals. Compared with HIV-1 infection, asymptomatic infection is more common in HIV-2–infected individuals, virus loads in blood are lower, and transmission to partners or neonates is less frequent.[342–344]

HIV-2 likely emerged after cross-species transmission of simian immunodeficiency virus (SIV) from sooty mangabeys to humans. Infection with HIV-2 was first reported in western Africa in 1986.[345] Although cases of HIV-2 infection have since been reported in other parts of Africa, several European countries, Canada, the United States, Brazil, and India,[346] the virus continues to be found mostly among heterosexual persons in western Africa, but an increasing number of cases have been recognized in Europe, India, and the United States.[347–349] Data from surveillance and serologic surveys indicate that the prevalence of HIV-2 infection in the United States is extremely low.[337,338] In 1992 the FDA recommended that all blood donations be screened with serologic assays for HIV-1 and HIV-2. The serologic testing of more than 24 million blood donations found no HIV-2–infected persons.[338] Similarly, surveys conducted among persons presumably at increased risk of infection with retroviruses through sexual contact and IDU have found very low rates of HIV-2 infection.[346,349] In one survey, performed from 1988–1990, of 31,533 persons at high risk for HIV infection in the United States, 10% were found to be infected with HIV-1, but only 2 persons (0.006%) were seropositive for HIV-2.[350]

Accumulating information suggests that the modes of transmission for HIV-1 and HIV-2 are similar. Worldwide, HIV-2 infections have been diagnosed predominantly in men and women infected through heterosexual contact and to a lesser extent in homosexual men, PWIDs, transfusion recipients, and persons with hemophilia.[346,351] The lower level of shedding of HIV in genital secretions may help explain the different transmission rates between HIV-1 and HIV-2.[352] Although the perinatal transmission of HIV-2 has been reported, numerous studies suggest that HIV-2 is transmitted less efficiently than HIV-1 from mother to child.[351–356] The natural histories of HIV-1 and HIV-2 infection appear similar in that both are characterized by a broad spectrum of disease. However, the incubation period from the time of initial infection to the eventual development of AIDS may be longer for HIV-2.[351,357–359]

HIV-1 and HIV-2 are genetically and immunologically distinct. However, nucleotide sequence analysis indicates that HIV-1 and HIV-2 share a similar genomic organization, suggesting a common evolutionary origin.[360] Overall, the nucleotide sequence homology for HIV-1 and HIV-2 is approximately 40%; the *gag* and *pol* genes for the two viruses are approximately 60% homologous.[360] These genetic similarities can result in frequent serologic cross-reactions between HIV-1 and HIV-2. Current FDA-approved HIV diagnostic tests do not differentiate between HIV-1 and HIV-2 infection, but because the Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad, Hercules, CA) allows differentiation between HIV-1 and HIV-2 infection, the CDC has proposed a new HIV testing algorithm that first performs a fourth-generation test, followed by an HIV-1/2 differentiation to determine if the patient has antibodies to HIV-1 or HIV-2 (see Chapter 120).[361] HIV-2 is intrinsically resistant to the non-nucleoside reverse-transcriptase inhibitors and enfuvirtide.[362] Although dual infection with both HIV-1 and HIV-2 has been reported, they are uncommon outside endemic areas. In one study from France, among 3700 HIV-infected patients, only 17 were identified as dually infected.[363] Blood donations in the United States are currently tested for evidence of both HIV-1 and HIV-2 antibodies.

PREVENTION OF HIV INFECTION

The prevention of HIV infection must be based on strategies that interrupt sexual, bloodborne, and perinatal transmission of the virus. Such strategies must be grounded in an understanding of the epidemiology of HIV infection and knowledge of the science of human behavior. These science-based strategies are the foundation for the design, implementation, and evaluation of prevention efforts. A number of behavioral interventions have been tested and applied to reduce HIV-associated risk behaviors across a variety of populations. In general, these programs are theory driven and emphasize the development of the cognitive, social, and technical skills associated with safer sex and drug use practices.[364] CDC has compiled a compendium of evidence-based HIV behavioral interventions (EBIs).[365] These interventions have been rigorously evaluated and have demonstrated evidence of efficacy. The current EBIs include 74 HIV risk-reduction behavioral interventions for which there is best evidence for 44 and good evidence for 30.[366] However, it should be noted that these interventions have been proven to reduce HIV-related risky behaviors but not HIV incidence in randomized controlled trials. As a number of biomedical interventions, in particular ARV drugs, have been proven to be effective for HIV prevention, the concept of "combination prevention" has emerged. Combination prevention is defined as rights-based, evidence-informed, and community-owned programs that use a mix of biomedical, behavioral, and structural interventions prioritized to meet the HIV prevention needs of particular individuals and communities and to have the greatest sustained impact on reducing new infections.[367]

Prevention of Sexual Transmission

Strategies for the prevention of the sexual transmission of HIV have focused up to very recently on promoting sexual abstinence, reducing unsafe sexual behavior (unprotected anal intercourse or decreasing the number of partners), encouraging proper condom use, and treating sexually transmitted infections.[368] The consistent use of latex condoms has been shown to be effective for the prevention of HIV transmission at the level of both the individual and the population.[369–371] Multiple epidemiologic studies of heterosexual couples in which one partner is HIV positive and the other HIV negative indicate that the correct and consistent use of latex condoms can significantly reduce the transmission of HIV and other STDs.[372–375] Natural skin condoms do not prevent the transmission of HIV and should not be used. Similarly, petroleum-based lubricants increase the likelihood of rupture of latex condoms and should be avoided.

The effectiveness of condoms to prevent the heterosexual transmission of HIV has been estimated to be 87%, but it may be as low as 60% or as high as 96%.[376,377] Many factors can affect the effectiveness of condoms in reducing the risk of HIV transmission, such as condom breakage, leakage, and slippage. Although condom breakage can occur, it appears to be uncommon, particularly in developed countries, where studies have found breakage rates of 2% or less for vaginal or anal intercourse.[370,372] Similarly, low rates of slippage (i.e., <1%) have been reported.[377] The effectiveness of condoms during anal intercourse is probably lower because condom breakage and slippage may be considerably higher than they are during vaginal intercourse.[378]

Intravaginal pouches ("female condoms") also require correct and consistent use.[379,380] The female condom has been shown to be as effective as the male condom for the prevention of sexually transmitted infections,[380–382] and its contraceptive failure rate has ranged from 11% to 26%, depending on the consistency and correctness of usage.[381] However, the contraceptive failure rate of a condom may not accurately reflect its effectiveness in reducing heterosexual HIV transmission.[370,372]

Currently available spermicides do not protect against the transmission of HIV and other sexually transmitted infections, and nonoxynol-9 might increase the risk for HIV sexual transmission. Three randomized, controlled trials of the use of nonoxynol-9 by commercial sex workers in Africa failed to demonstrate any protection against HIV infection,[383,384] with one showing an increased risk of HIV transmission with the use of a vaginal sponge containing a high dose of nonoxynol-9.[385] Nonoxynol-9–containing contraceptives also failed to protect against infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in two randomized trials, one among prostitutes in Africa and one among US women recruited from an STD clinic.[386,387] The irritative effects of spermicides on the vaginal epithelium may in fact facilitate rather than reduce HIV transmission.[388] Despite these data, contraceptives containing nonoxynol-9 continue to be commonly used in family planning clinics.[389] Several other available topical microbicides that have been studied in clinical trials thus far have also failed to demonstrate efficacy.[390,391] A placebo-controlled study of a polynaphthalene sulphonate gel (PRO2000), completed in 2009 in Malawi, South Africa, Zambia, Zimbabwe, and the United States, reported that HIV infections were reduced by 30% in women who used PRO2000 vaginal gel; however, this difference did not reach statistical significance.[392] The use of a microbicide gel containing the ARV tenofovir has demonstrated efficacy in reducing HIV incidence. In a study conducted in South Africa (CAPRISA 004) this product demonstrated an overall reduction in HIV acquisition of 39% and 54% among women with high gel adherence.[393] This data was not confirmed by the VOICE (MTN-003) trial, where a 1% tenofovir vaginal gel was no better than placebo in preventing HIV acquisition.[394] The quest to develop an effective vaginal microbicide is critically important as female-controlled methods to prevent HIV and STDs that can be safely and effectively used by women are urgently needed.

Despite the demonstrated benefits of condom use, multiple studies have found relatively low rates of consistent condom use among sexually active homosexual men and heterosexual men and women. The factors that influence condom use are complex.[395] Concern about decreased sexual pleasure or a partner's lack of cooperation, inadequate communication skills, the temporal effects of drugs or alcohol, the use of other methods for contraception, and cultural influences have been correlated with low rates of condom use.[395–398]

As previously stated, three randomized trials of male circumcision have demonstrated that circumcision provides a protected benefit of between 50% and 60% against the acquisition of HIV infection among men who engage predominantly in heterosexual intercourse.[194–196] Although these results are clearly encouraging and studies have proven the protective effect of male circumcision, there still remain many challenges in the implementation of this intervention to obtain the full impact of circumcision on HIV incidence among those populations the most heavily affected by HIV.[399]

Partner notification is another mechanism to assist in the prevention of sexual transmission of HIV. Even though many HIV-infected individuals cooperate in notifying at least some of their sex partners, others do not.[400,401] Although the effectiveness of contact tracing and partner notification has been hotly debated,[402] it is probably an effective prevention strategy,[403,404] particularly when it is targeted to acute HIV infection.[405] The efficacy of partner notification by the health department appears to be substantially more effective than notification by the infected person or the patient's physician.[401,406,407]

The control of sexually transmitted infections is also an important intervention to reduce the sexual transmission of HIV. Data from a study in Tanzania in which a syndrome approach was used in the

treatment of symptomatic sexually transmitted infections led to a 42% decrease in HIV incidence.[408] In contrast, in the Rakai district of Uganda a community-based trial of mass treatment for sexually transmitted infections failed to show a difference between the treatment and control arms.[409] The reasons for the lack of consistency in the results of these two trials are multiple and not yet fully explained. Nevertheless, despite lack of proven efficacy in the prevention of HIV infection, the diagnosis and treatment of sexually transmitted infections remains important for the individual as well as for public health.

Preexposure Prophylaxis

ARVs have shown to be highly effective for the prevention of HIV when administered prophylactically to HIV-uninfected but at-risk individuals (preexposure prophylaxis [PrEP]) and when administered after sexual exposure (postexposure prophylaxis).[410] In the iPrEx (Initiativa Profilaxis Pre-Exposición [Preexposure Prophylaxis Initiative]) randomized trial, daily administration of coformulated tenofovir plus emtricitabine as PrEP among MSM decreased the risk of HIV infection by 44%.[411] However, among participants with detectable levels of tenofovir, there was a 92% reduction in risk of HIV acquisition. Subsequent studies using also tenofovir coformulated with emtricitabine have shown as much as an 85% decrease in HIV transmission when adherence is four or more tablets per week.[412] Studies among heterosexual couples have found high level of protection when adherence was also high[413] and no reduction in HIV acquisition when adherence was low.[394,414] The Partners PrEP trial was a randomized placebo-control study of oral daily tenofovir or tenofovir coformulated with emtricitabine for HIV prevention among HIV-uninfected serodiscordant heterosexual couples in Uganda and Kenya. Among participants of both sexes, the efficacy of tenofovir alone was 67% and 75% for tenofovir-emtricitabine. Efficacy estimates were not statistically different between men and women. Among participants assigned to tenofovir-emtricitabine who had detectable drug levels, there was a 90% reduction in HIV acquisition.[413] In contrast, in the FDF2, the FEM-PrEP, and the VOICE studies, low levels of adherence did not reduce the risk of HIV acquisition among participants.[394,414,415] Taken together, these studies suggest that daily oral PrEP with tenofovir-emtricitabine is also effective among heterosexual couples but that adherence needs to be high (Table 119.4). Of importance, in all studies the drugs have been extremely safe and well tolerated. Based on these findings, in 2013 the FDA approved the use of coformulated tenofovir plus emtricitabine for preexposure prophylaxis to prevent sexual acquisition of HIV.[415]

ARVs can also be given after exposure to prevent HIV acquisition (postexposure prophylaxis). In 2005 the CDC published guidelines for ARV postexposure prophylaxis after sexual, IDU, and other nonoccupational exposures to HIV. In these guidelines it is recommended that persons seeking care 72 hours or sooner after nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a person known to have HIV infection be offered a 28-day course of ART.

As previously stated, reducing the viral load through the use of ART dramatically reduces the risk for transmission through sexual contact.[166] In a randomized controlled trial ART given to HIV-infected persons, beginning at a CD4 count of 350 to 550 cells/mm^3, reduced sexual transmission of HIV-1 by 96%. This is by far the most effective intervention to date for the prevention of HIV infection. The realization that treatment is prevention has led to a variety of test-and-treat strategies.[416]

Prevention of Transmission by Injection Drug Use

The prevention and treatment of IDU are critical for reducing HIV transmission among PWIDs,[417] and several studies have documented that significantly lower rates of drug use and related risk behavior are practiced by PWIDs who are in treatment.[418,419] In addition, substance abuse treatment can serve as an entry point for medical care. However, the impact of substance use treatment on HIV infections has been observed only for those users who remain in treatment for at least 1 year.[420] For this reason, brief detoxification programs are not considered effective strategies for HIV prevention unless they are followed by a longer course of treatment. Furthermore, an estimated 80% of active drug users in the United States are not in treatment because of choice or the unavailability of treatment.[421] An integrated approach to service delivery for persons who use drugs that incorporates science-based prevention strategies is critical for the prevention of HIV and other infectious diseases among substance abusers.[422] The removal of restrictions on the purchase of needles and syringes,[423] needle and syringe exchange programs,[424] the proper use of bleach for the disinfection of drug injection equipment,[425] and medication-assisted treatment, such as methadone maintenance programs,[426] are all effective interventions for the prevention of HIV infection among PWIDs. Community outreach-based interventions that include education about HIV transmission and prevention and the distribution of condoms and bleach kits have also demonstrated significant changes in the frequency of drug use and drug-related behaviors.[427] Particularly useful have been risk reduction interventions delivered through social networks by peer educators.[428] Improvement in selected drug use behavior has been reported, including a decrease in the sharing of drug-injection equipment and an increase in the use of bleach for cleaning equipment,[427–431] although the duration of such behavior has not been studied extensively. The overwhelming majority of studies have found that needle exchange programs lead to reduction in the sharing of syringes among program participants,[432,433] do not result in increased drug use among participants or in the recruitment of first-time users, and reduce the transmission of HIV among PWIDs.[434–437] A December 2011 US Congressional ban on the use of federal funds for any program that distributes sterile needles or syringes for hypodermic injection of illegal drugs was lifted in early 2016, largely in response to a severe needle-associated HIV and hepatitis C outbreak in Indiana. PrEP has also proven to be effective among PWIDs. In the Bangkok Tenofovir Study the use of oral tenofovir reduced the acquisition of HIV by 48.9%, and in participants who had detectable tenofovir levels, there was a 73.5% reduction in risk of HIV acquisition. As a result, the CDC published guidelines in 2013 recommending daily oral PrEP with tenofovir-emtricitabine (or tenofovir alone) for PWIDs at

TABLE 119.4 Selected Studies of Preexposure Prophylaxis Using ARV to Prevent HIV Infection

STUDY	ARV	POPULATION	*N*	SITES	EFFICACY ON HIV INCIDENCE
CAPRISA 004[393]	TDF gel	Women	889	South Africa	39% reduction
iPrEx[411]	TDF/FTC	MSM	2499	South America, Africa, South East Asia	44% reduction
Partners PrEP[414]	TDF TDF/FTC	Heterosexual serodiscordant couples	4758	Africa	67% TDF 75% TDF/FTC
TDF2[415]	TDF/FTC	Heterosexual men and women	1200	Botswana	62% efficacy
FEM-PrEP[413]	TDF/FTC	Women	1950	Kenya and South Africa	Stopped for futility
MTN-003 VOICE[394]	TDF tablet and gel 1% TDF/FTC	Women	5029	Uganda, Zimbabwe, South Africa	TDF tablet and gel stopped for futility. TDF/FTC also not effective

ARV, Antiretrovirals; *FTC,* antiretroviral drug emtricitabine; *MSM,* men who have sex with men; *TDF,* antiretroviral drug tenofovir.

risk of HIV infection.[307] In summary, there is clear evidence that a combination of prevention approaches could eliminate HIV transmission among PWIDs. Unfortunately, the implementation of many of these interventions has been limited by public or political opposition.[438]

Prevention of Transmission Through Blood and Other Tissues

The first report of transfusion-associated AIDS was in 1982. In 1983 blood banks initiated the voluntary self-exclusion of donors with risks for HIV infection. In 1985 the first serologic assays for the HIV antibody became available, and the use of these HIV serologic tests to screen blood donations dramatically decreased the risk of transfusion-associated HIV transmission.[236,237] The serologic identification of repeat donors with HIV infection (including the detection of p24 antigen and NAAT), screening of blood for hepatitis C and human T-lymphotropic virus types I and II, and reduction in the number of transfusions performed have also lowered the risk of transmission.[237–239,439] The risk of HIV infection in the United States through the transfusion of blood or blood products is currently extremely low and is estimated to be 1 in 1.4 to 1 in 1.8 million units.[59] Organ and tissue donors should be evaluated and serologically screened in a manner similar to that for blood donors.[440,441] In addition, donations of semen and bone from a living donor may be quarantined until subsequent testing has definitively ruled out the possibility of delayed seroconversion in the donor. The prompt administration of ARV drugs for postexposure prophylaxis after transfusion of contaminated blood prevented HIV infection in one patient.[442]

Prevention of Transmission in the Health Care Setting

The effective prevention of HIV transmission in the health care setting requires a multifaceted approach to reduce the frequency of occupational blood exposure among health care workers. Such a strategy includes engineering controls that do not rely on worker compliance (e.g., self-sheathing needles), safe work practices and techniques, personal protective equipment, and training.[443,444] In particular, a reduction in percutaneous injuries will require the development of puncture-resistant gloves, the redesign of needles and other sharp instruments, or both. In 1987 the CDC recommended that the principle of "universal precautions" be incorporated in programs for infection control.[445] Under universal precautions, blood and certain other body fluids from *all* patients are considered to be potentially infective. Universal precautions include the appropriate use of hand washing and protective barriers, care in the use and disposal of needles and other sharp instruments, and appropriate disinfection and sterilization of reusable equipment. For occupational exposure to HIV among health care workers, the CDC recommended the use of zidovudine for postexposure prophylaxis in 1990.[446] This recommendation was further supported by a case-control study involving health care workers from the United States, France, Italy, and the United Kingdom that showed that the risk of HIV seroconversion after occupational exposure decreased by approximately 81% with the use of zidovudine.[288] Subsequent recommendations have incorporated the newer ARV drugs as well as risk stratification for the type of exposure in the management of occupational exposure to HIV.

Prevention of Perinatal Infection

The primary prevention of perinatally acquired HIV infection must center on routine, voluntary counseling and HIV antibody testing and ART of pregnant women living with HIV (see Chapter 126).[447,448] Because a substantial proportion of women may not initially acknowledge high-risk behavior or know the infection status of their partners, routine HIV testing and counseling must be considered a standard of care when managing pregnant women.[449] In 1994 the results of a randomized, double-blind clinical trial (Pediatric AIDS Clinical Trials Group Protocol 076) found that zidovudine therapy administered to HIV-infected women during pregnancy, at the time of labor, and postpartum to their infants was associated with a 67.5% reduction in the risk of perinatal HIV transmission.[139] Based on these results, a Public Health Service task force issued recommendations for the use of zidovudine for the reduction of perinatal HIV-1 transmission.[140] Several subsequent studies have confirmed the benefits of zidovudine for the prevention of perinatal HIV-1 transmission, even when the drug is given for a much shorter period than it was in the original Protocol 076 trial.[450,451] Advances in understanding the pathogenesis of HIV infection and the availability of laboratory tests to monitor the disease (such as HIV RNA) and better ARV drugs have led to an update in 2008 in the recommendations for the use of ARV drugs in pregnant women.[452] The implementation of these recommendations, which include universal prenatal HIV counseling and testing, ARV prophylaxis, scheduled cesarean delivery, and avoidance of breastfeeding, has resulted in significant public health benefits. The current risk of perinatal HIV transmission in the United States is less than 2%,[453] and the number of children in whom AIDS attributed to perinatal HIV transmission was diagnosed has decreased from a peak of 954 in 1992 to 14 in 2010,[67] and the elimination of perinatal HIV transmission in the United States is a feasible goal. Unfortunately, in most of the world perinatal HIV transmission continues to be an important way in which children acquire HIV infection globally, and further efforts are necessary to reduce mother-to-child HIV transmission.

The prevention of postnatal transmission of HIV infection through breastfeeding must take into account the likelihood of competing risks for morbidity and mortality associated with feeding alternatives in developing countries. In 1985, after the first case report implicating HIV transmission from breast milk and the isolation of HIV from breast milk, the CDC recommended that HIV-seropositive women not breastfeed their infants.[454] This recommendation was intended for mothers in the United States, where alternative, safe, and nutritious substitute feeding methods are readily available.[261] In 1992 WHO and the United Nations International Children's Emergency Fund developed a consensus statement on HIV transmission related to breastfeeding, which stated that "in settings where the primary causes of infant deaths are infectious diseases and malnutrition, breast-feeding should remain the standard advice to pregnant women, including those who are HIV infected."[455] By 1996 UNAIDS had published a revised statement that supported breastfeeding in all populations for whom other safe options are not available, irrespective of HIV infection rates, but recommended counseling for women about the risks of HIV transmission through breastfeeding.[456]

When children born to HIV-infected women can be ensured uninterrupted access to nutritionally adequate breast milk substitutes that are safely prepared and fed to them, they are at less risk of illness and death if they are not breastfed. However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary causes of death during infancy, artificial feeding substantially increases a child's risk of illness and death. In those settings it is preferable for women to provide exclusive breastfeeding to their infants rather than mixed feeding (breast milk plus food supplements) because the risk of HIV transmission is substantially lower when the infant receives only breastfeeding.[457] The importance of providing safe alternatives to breastfeeding among HIV-infected women has been highlighted by several randomized trials on the prevention of perinatal transmission in breastfeeding populations. For example, in the PETRA (PErinatal TRAnsmission) trial, the benefits of combination ART diminished considerably as a result of breastfeeding.[458] In the South African Intrapartum Nevirapine Trial (SAINT), breastfeeding was the most significant risk factor for transmission from mother to child when ART was administered to prevent intrapartum and early postpartum HIV transmission.[459] Recent trials providing ART to the mother during breastfeeding have proven to be an effective approach to reducing HIV infection through breast milk.[460]

COUNSELING AND HIV ANTIGEN/ANTIBODY TESTING

Early recognition of HIV infection through HIV antibody testing has been one of the primary objectives of HIV prevention efforts. However, with the realization that treatment of HIV infection has prevention benefits, HIV testing has become an even more important preventive intervention.[461,462] The major benefits of HIV testing programs are (1) linkage to care and prevention services of HIV-seropositive persons, (2) counseling to promote the behavior change necessary to reduce

HIV transmission, and (3) referral to PrEP programs of high-risk individuals found to be HIV uninfected when these programs are available.

Physicians have an essential role in this public health effort. As the principal providers of primary health care, they are the most frequently named by the general public as the desired source for HIV testing.[463] The number of persons who have been tested for HIV has increased significantly in recent years, and it is now estimated that 46% of adults and adolescents in the United States report having ever been tested for HIV infection.[464] However, many who are tested for HIV do not return for their results. The CDC estimates that 31% of those who tested HIV positive in 2000 at publicly funded testing sites of the CDC failed to return for their results.[461] The approval by the FDA of rapid HIV tests, such as the OraQuick HIV rapid test (OraSure Technologies, Bethlehem, PA) and the subsequent CLIA (Clinical Laboratory Improvement Amendment) waiver of this test, offers the possibility for more persons to be tested for HIV and receive their results on the same day, eliminating the need for a second visit.[465] Although some concerns have been expressed about the reliability of rapid tests, several studies have demonstrated that the sensitivity and specificity of the commercially available rapid tests are comparable to those of standard EIA testing (see Chapter 120).[466] Rapid tests may have poor positive-predictive value in low-prevalence settings.[467]

In an effort to make HIV testing more accessible and available in clinical settings, the CDC issued counseling and referral guidelines in 2006.[447] These guidelines recommend that an "opt-out" approach be implemented for HIV testing in health care settings, in which all patients between the ages of 13 to 64 are notified that they will be tested for HIV unless they decline. Prevention counseling is no longer a part of routine HIV testing but is still recommended for persons known to engage in behaviors that increase their risk of acquiring HIV infection. The guidelines also recommend annual testing for persons considered to be at high risk. Although this approach has been shown to be cost-effective in several studies,[468,469] it has still not gained wide acceptance as a screening strategy.[470] In 2013 the US Preventive Services Task Force updated their 2005 recommendations on HIV screening and recommended that clinicians screen adolescents and adults age 15 to 65 years and that younger adolescents and older adults who are at increased risk should also be screened. Both these recommendations received a grade A recommendation.[471]

Couples voluntary counseling and testing (CVCT) has been used as an HIV prevention intervention for heterosexual couples in Africa for more than 20 years.[472] The critical difference between the CVCT model and the conventional model of individual HIV testing is that the couple receives all counseling and testing at the level of the dyad and allows the implementation of prevention and care interventions based on their joint HIV status. CVCT has recently been adopted for male-male couples in the United States.[473]

Health care workers who perform invasive procedures that are considered prone to exposure (e.g., procedures that include digital palpation of a needle tip in a body cavity or the simultaneous presence of the health care worker's fingers and a needle or other sharp object in a poorly visualized or highly confined anatomic site) should know their HIV antibody status. The mandatory testing of health care workers for the HIV antibody is not recommended.[474]

The use of short-term case management to link newly diagnosed HIV infected persons into care has been shown to be effective and is a recommended intervention to decrease the possibility that HIV-infected persons may fail to enter care.[475,476] HIV-infected persons should also be instructed to notify sex or needle-sharing partners and refer them for HIV counseling and testing. If HIV-infected persons are reluctant to directly inform their partners, physicians may offer to inform the partners or seek the assistance of the local health department. Confidentiality is very important, to protect these individuals and not discourage them from seeking HIV testing.

Persons found to be HIV seropositive should be referred for medical evaluation, including immunologic ($CD4^+$ T-lymphocyte cell counts) and virologic (quantitation of HIV RNA) monitoring, screening for other STDs, prophylaxis against certain opportunistic illnesses, vaccinations, ART, and other preventive and therapeutic services.[477]

VACCINES FOR HIV TYPE 1 INFECTION

The development of a safe and effective HIV-1 vaccine is one of the highest biomedical research priorities. Effective vaccination offers the best hope for the ultimate control of the HIV-1 epidemic,[478] but no vaccine is near clinical use despite more than 35 years of intensive research in this field. HIV-1 vaccine development presents unprecedented scientific challenges.[479,480] Among the most important roadblocks is our current lack of understanding of the immune correlates of protection against HIV-1 and our inability to induce broadly reactive neutralizing antibody (NAb) responses by vaccination. In addition, enormous genetic variation exists among HIV-1 strains worldwide. Nevertheless, new vaccine candidates aimed at eliciting virus-specific cellular and humoral immune responses have been able to afford partial protection in certain nonhuman primate models, and several novel passive and active immunization strategies are currently being tested for clinical efficacy. In this chapter we review recent progress in the clinical development of candidate HIV-1 vaccines.

Animal Models

The lack of an accepted small animal model for HIV-1 infection has slowed vaccine development. Nonhuman primates have therefore been required for the preclinical evaluation of candidate HIV-1 vaccines. Chimpanzees can be infected with HIV-1, but most viruses are nonpathogenic in this species.[481,482] The most extensively studied nonhuman primate model involves SIV infection of rhesus macaques (*Macaca mulatta*).[483] SIV and HIV-1 are similar in genetic structure and organization, and certain pathogenic strains of SIV cause an AIDS-like disease in macaques, including opportunistic infections.[484,485] As a result, SIV infection of rhesus macaques has emerged as a popular model for testing HIV-1 vaccines. A related model, involving chimeric simian-human immunodeficiency virus (SHIV) infection of macaques, has also been used.

The importance of humoral immune responses is illustrated by studies in rhesus macaques in which passive infusions of HIV-1–specific neutralizing monoclonal antibodies afforded complete protection against infection with pathogenic SHIV isolates.[486,487] Although vaccine-elicited antibody responses have been shown to provide a degree of protection against homologous and heterologous viral challenges in certain settings,[488–492] it has proven extraordinarily difficult to generate broadly reactive NAbs by vaccination using recombinant envelope proteins.

Vector-based strategies have also been explored in rhesus macaques. Poxviruses have been explored extensively as candidate HIV-1 vaccine vectors but have proven only weakly immunogenic.[493–498] Replication-incompetent, recombinant adenovirus serotype 5 (rAd5) vectors have been shown to elicit robust cellular immune responses in nonhuman primates[499,500] but have shown no protection against SIVmac251 challenges.[9,10,118] Studies with Ad26/Env vaccines have shown partial protection against both SIVmac251 and SHIV-SF162P3 challenges in rhesus macaques, with functional non-NAbs as the correlate of protection in these models.[488,501] Another promising vaccine study showed that CMV vectors afforded early and profound virologic control in approximately half of the vaccinated animals after SIV challenge.[502]

Human Trials

More than 50 candidate HIV-1 vaccines have been studied in more than 30,000 HIV-1–uninfected healthy volunteers since 1987. The study of candidate HIV-1 vaccines in humans poses several unique problems above and beyond those encountered in studies of other experimental vaccines. Volunteers need to be fully informed of the potential hazards of immunization and of the limitations of our knowledge regarding HIV-1 transmission, pathogenesis, and immune control. Volunteers must be made aware that they may become seropositive for HIV-1 by conventional screening assays,[503–507] and the recent adoption of an "opt-out" policy for routine HIV-1 testing increases the potential for false-positive results to occur.[508,509] Volunteers must also be counseled not to abandon behaviors to reduce risk for acquisition of HIV-1 infection because of a presumption that the vaccine under study will prove effective. A detailed description of the procedures used in the conduct of phase I studies of HIV-1 candidate vaccines in humans, including measures taken to address the preceding issues, has been published.[510]

The purpose of phase I studies is to examine the immunogenicity and safety of vaccine candidates in humans. A wide variety of different types of vaccine candidates have been evaluated in humans. For most phase I and phase II studies (Table 119.5), individuals at low risk for acquisition of HIV-1 infection are enrolled to avoid the potentially confounding effects of intercurrent HIV-1 infections. In contrast, phase IIb and III studies are carried out in participants at higher risk for acquisition of HIV-1 infection (Table 119.6).[511–518]

Purified envelope protein,[513–515,519,520] synthetic peptides,[521–530] live vector–based,[531–559] and DNA[560–564] vaccines have been explored in clinical trials. In addition, various adjuvant strategies have been studied, including alum, MF59, and plasmid cytokines, such as granulocyte-macrophage colony-stimulating factor, IL-2, IL-12, and IL-15. Various delivery modalities have also been assessed for DNA vaccines, including intramuscular injection, bioinjector (compressed air injection system), and electroporation.[510,565–573]

Phase II Clinical Studies

Six phase II studies of candidate HIV-1 vaccines by the AIDS Vaccine Evaluation Group (AVEG) and its successor, the HIV Vaccine Trials

TABLE 119.5 Phase II Studies of Candidate HIV-1 Vaccines in HIV-1–Seronegative Volunteers

VACCINE	COMPOSITION	HIV-1 STRAINS	SPONSOR	REFERENCES
rgp120	Protein	SF-2 + MN	Chiron/Biocine, Aventis Pasteur	574
vCP205, rgp120	Canarypox prime, protein boost	MN/LAI (vCP205), SF-2 (rgp120)	Aventis Pasteur, Chiron/Biocine	575
vCP1452, rgp120	Canarypox prime, protein boost	MN/LAI (vCP1452), MN + GNE8 (rgp120)	Aventis Pasteur, VaxGen	76
VRC-HIVDNA-016-00-VP, VRC-HIVADV014-00-VP	DNA prime, rAd5 boost	Clade B HXB2 *gag,* NL4-3 *pol,* NY5/BRU *nef*; clade A 92rw020, clade B HXB2/BaL, clade C 97ZA012 *env*	NIH VRC	77
pGA2/JS7, MVA/HIV62	DNA prime, rMVA boost	BH10, IIIB, HXB-2/ADA *gag,* protease, reverse transcriptase, *env, tat, vpu, rev*	Geovax	578
Ad26.Mos.HIV, MVA.Mos, and clade C Env gp140	rA26 prime, rAd26, rMVA, ± protein boost	Synthetic bivalent mosaic inserts (*env, gag,* and *pol*)	Janssen, NIH, MHRP	579

MHRP, Military HIV Research Program; *NIH VRC,* National Institutes of Health Vaccine Research Center; *rAD5,* recombinant adenovirus serotype 5; *rgp120,* recombinant glycoprotein 120; *rMVA,* modified vaccinia Ankara (vaccine); *vCP205,* canarypox vector 205.

TABLE 119.6 Completed Efficacy Studies (Phase IIb, III) of Candidate HIV-1 Vaccines in HIV-1–Seronegative Volunteers

VACCINE	START	SAMPLE SIZE	LOCATION	TARGET POPULATION	HIV INFECTION RATE IN VACCINE GROUP (%)	HIV INFECTION RATE IN PLACEBO GROUP (%)	VACCINE APPROACH; HIV-1 STRAINS	VACCINE DEVELOPER	REFERENCES
AIDSVAX B/B	1998	5403	North America, Netherlands	MSM	6.7	7.0	rgp120: MN, GNE-8	VaxGen	513
AIDSVAX B/E	1999	2546	Thailand	IVDU	8.4	8.3	rgp120: MN, A244	VaxGen	516
Step Study (HVTN 502)	2004	3000	North America, Caribbean, Australia	MSM; sexual exposure	4.6[a]	3.1	Ad5 *gag/pol/nef*: clade B *gag*-CAM-1, *pol*-IIIB, *nef*-JR-FL	Merck	511
Phambili Study (HVTN 503)	2006	3000[b]	South Africa	Sexual exposure	Stopped early 4.54[c]	Stopped early 3.70	Ad5 *gag/pol/nef*: clade B *gag*-CAM-1, *pol*-IIIB, *nef*-JR-FL	Merck	517
ALVAC-HIV (vCP1521) AIDSVAX B/E (RV144)	2003	16,402	Thailand	Sexual exposure	0.192[d]	0.279	Canarypox and rgp120	Sanofi Pasteur, VaxGen	601
DNA/Ad5 (HVTN 505)	2009	2504	United States	MSM	2.8%[e]	2.3%	DNA prime, Ad5 boost. Clade B HXB2 *gag,* NL4-3 *pol,* NY5/BRU *nef*; clade A 92rw020, clade B HXB2/BaL, clade C 97ZA012 *env*	NIH VRC	518

Ad5, Adenovirus serotype 5; *HVTN,* HIV Vaccine Trials Network; *IVDU,* intravenous drug user; *MSM,* men who have sex with men; *rgp120,* recombinant glycoprotein 120; *VAX,* vaccine; *vCP,* canarypox vector.

[a]Yearly HIV-1 incidence in MSM population (n = 1836) as of October 17, 2007.

[b]Target enrollment was 3000. Actual enrollment was 801 before study termination on September 19, 2007 and unblinded in October 2007. At the time the study was stopped, 56 (7%) of subjects had received all three planned injections.

[c]Yearly HIV-1 incidence per 100 person-years, through August 31, 2009.

[d]Yearly HIV-1 incidence per 100 person-years.

[e]Stopped early April 22, 2013 by the Data Safety Monitoring Board because futility criteria were met. Study was also unblinded.

Network (HVTN), have been performed. The first study (AVEG 201) evaluated two recombinant glycoprotein 120 (rgp120) subunit vaccines in 296 HIV-1–seronegative subjects in six demographic groups: four with higher-risk behavior and two with lower-risk behavior.[574] After three immunizations, greater than 87% of subjects developed NAbs to the homologous isolate, which persisted for at least 2 years in 57% of subjects who were tested. However, the study showed somewhat lower antibody responses to one of the vaccines (HIV-1_{SF-2} gp120) in the IV drug user group and, to a lesser extent, in heterosexual partners of HIV-1–infected individuals. The reasons for this have not been explained, but this study illustrates the importance of assessing immunogenicity in groups other than low-risk subjects.

The second phase II study was a collaboration between AVEG and HIVNET (AVEG 202–HIVNET 014).[575] This study examined a prime-boost regimen consisting of the canarypox vector vCP205 with an rgp120 (SF-2) boost in 435 subjects, of whom 60 were lower risk and 375 were higher risk. The vaccines were generally well tolerated in these groups. Greater than 90% of subjects who received the prime-boost regimen developed NAbs against the homologous T-cell line adapted (TCLA) virus, and one-third of those who received regimens containing vCP205 developed HIV-1–specific $CD8^+$ T-lymphocyte responses. There appeared to be no significant difference in immune responses between the higher- and lower-risk groups in this study.

The HVTN completed a phase II study of vCP1452, which expressed gp120, the transmembrane portion of gp41, *gag*, a portion of *pol*, and several $CD8^+$ T-lymphocyte epitopes from *nef* and *pol* (HVTN 203). The vector was administered at a dose of $10^{7.26}$ mean tissue culture infectious dose ($TCID_{50}$) at a regimen of 0, 1, 3, and 6 months to 330 subjects. The vaccine was well tolerated, but the overall immunogenicity was disappointing. Vaccinees developed HIV-1–specific $CD8^+$ T-lymphocyte responses at a cumulative frequency of less than 30% at any point throughout the study and less than 15% at any single time point.[227] Why vCP1452 was less immunogenic in this phase II study than other canarypox constructs in phase I studies is not clear. Raising the dose of vCP1452 to 10^8 significantly increased reactogenicity but did not augment immunogenicity.[576]

The second phase II trial conducted by the HVTN assessed the safety and immunogenicity of a DNA prime/rAd5 boost regimen developed by the National Institutes of Health Vaccine Research Center (NIH VRC; HVTN 204). This vaccine contained six DNA plasmids (*gag, pol*, and *nef* from clade B and *env* from clades A, B, and C) and four rAd5 vectors (*gag-pol* from clade B and *env* from clades A, B, and C). This placebo-controlled study enrolled 480 subjects irrespective of baseline Ad5 titer in the Americas (United States, Brazil, Jamaica, and Haiti) and South Africa and administered 4 mg of DNA at 0, 1, and 2 months, followed by an rAd5 boost (1×10^{10} viral particles) at month 6. The vaccine regimen was well tolerated and moderately immunogenic with cellular immune responses directed at global potential T-cell epitopes, detected to *env* and *gag* in 54% and 55% of subjects, respectively. This regimen also induced modest binding antibody responses in subjects to the envelope glycoprotein Con S (95%), clade A (84%), clade B (95%), and clade C (93%) gp140 oligomers, but limited NAb responses to Tier 1 viruses.[577] This regimen was advanced into a phase IIb efficacy study (HVTN 505) in Ad5-seronegative, circumcised MSM and who are at high risk for acquiring HIV-1 (which is described later).

A third phase II trial has been conducted by the HVTN, which assessed the safety and immunogenicity of an modified vaccinia Ankara (MVA) alone and a DNA prime/MVA boost regimen (HVTN 205). These vaccines, pGA2/JS7 DNA (expressing *gag, pol, env, tat, rev,* and *vpu* genes) and MVA/HIV62 (expressing *gag, pol*, and *env* genes), were studied in 300 vaccinia-naïve individuals, of whom 75 received placebo. The vaccines were given in two different regimens—3 mg of DNA given at 0 and 2 months, followed by MVA given at 4 and 6 months (DDMM regimen) versus three doses of the MVA given at 0, 2, and 6 months (MMM regimen). Both of these regimens were found to be generally safe and well tolerated. However, differences in the immune responses elicited were observed, with the DDMM regimen eliciting higher rates of T-cell responses and the MMM regimen inducing higher rates of antibody responses.[578] Further studies of these products are being planned.

A fourth phase II trial assessed the safety and immunogenicity of a bivalent mosaic HIV-1 construct including Env/Gag/Pol antigens delivered by a recombinant adenovirus serotype 26 (Ad26) vector as a prime and boosted with Ad26 or MVA vectors expressing homologous mosaic Env/Gag/Pol antigens with or without a clade C envelope gp140 protein.[579] The mosaic inserts are bioinformatically derived complimentary antigens designed to cover the majority of globally circulating HIV-1 strains.[580–582] In this multiarm study the Ad26 prime/Ad26+gp140 regimen was found to be the most immunogenic (with antibody and T-cell responses identified in 80% to 100% of participants) and has been selected for further assessment (see later).

Phase IIb and III Efficacy Studies

Determination of the efficacy of a candidate HIV-1 vaccine requires the conduct of large-scale, rigorously controlled clinical trials. Such trials present formidable scientific and logistic challenges and require extensive resources. As a result, the criteria to determine that a candidate HIV-1 vaccine has sufficient promise to proceed into an efficacy trial remain a matter of substantial controversy. Nevertheless, it is also appreciated that properly conducted efficacy trials may provide important information regarding correlates of protection that may not be obtained otherwise, even if the candidate vaccine is only minimally effective. This information could then be "fed back" to investigators for appropriate modification or revision of vaccine development efforts.

The first phase III trial of a candidate HIV-1 vaccine involved the VaxGen AIDSVAX B/B vaccine.[513] This vaccine consisted of rgp120 proteins from two clade B isolates (MN and GNE-8) in alum and was administered at months 0, 1, 6, 12, 18, 24, and 30 in a multicenter study. The experimental design was a double-blinded, randomly allocated, placebo-controlled study (vaccine-to-placebo ratio of 2:1 in 5403 subjects, of whom 5109 were MSM and 308 were women at heterosexual risk for HIV-1 infection. At the end of the 3-year period of observation, the rate of the major study end point (HIV-1 infection) was virtually the same in the vaccine group (6.7%) and the placebo group (7%) (see Table 119.6).

A second phase III study was conducted in Thailand with a similar rgp120 vaccine (AIDSVAX B/E) derived from a clade B isolate (MN) and a primary clade E isolate (CM244).[515] The experimental design was similar to that described previously, except that the vaccine-to-placebo ratio was 1:1, and the study population consisted of 2546 PWIDs. The 3-year cumulative rate of infection was 8.3% in the placebo group and 8.4% in vaccine recipients. Taken together, these studies indicate that the rgp120 approach offered no evidence for protection against acquiring HIV-1 infection.

A phase III trial (RV144) of a prime-boost vaccine regimen consisting of the canarypox vector vCP1521 expressing HIV-1 *gag* and *pol* (subtype B) and CRF01_AE (subtype E) gp120 boosted by AIDSVAX B/E has been conducted in Thailand. The vaccine regimen involved administration of the canarypox ALVAC vector at months 0, 1, 3, and 6 and the rgp120 protein at months 3 and 6. Each subject was followed for 3 years to assess for both acquisition of HIV-1 infection and HIV-1 disease progression. This study enrolled a community-based population of 16,402 (1:1 randomization) subjects not at especially high risk for HIV-1 acquisition (see Table 119.6). The modified intention-to-treat analysis (excluding HIV-1 infections present at baseline) showed a modest vaccine efficacy of 31.2% ($P = .04$) but no effect on viral load setpoint in those subjects who became HIV-1 infected.[516] This observation of modest vaccine efficacy triggered an exhaustive search for potential correlates of efficacy, which identified IgG responses to the variable regions (particularly V2) of the HIV-1 envelope as potentially protective immune responses (see Table 119.6).[583–585]

In 2016 a phase IIb/3 study was initiated in South Africa (HVTN 702) to assess the RV144 regimen in another context to verify the RV144 finding noted earlier. The vaccines were slightly modified from the RV144 regimen to resemble the circulating strains in South Africa. In HVTN 702, ALVAC-HIV (vCP2438) is given as a prime (months 0 and 1) and boosted with ALVAC-HIV and an MF59 adjuvanted bivalent subtype C gp120 protein (months 3, 6, and 12; NCT#02968849). This study is fully enrolled ($n = 5400$ women) and is in active follow-up (Table 119.7).

TABLE 119.7 Efficacy Studies of Candidate HIV-1 Vaccines or bNAbs in HIV-1–Seronegative Volunteers Currently Underway

VACCINE/bNAb	NAME	START	SAMPLE SIZE	LOCATION	TARGET POPULATION	NCT#
ALVAC (vCP2438), bivalent clade C gp120/MF59	HVTN 702	2016	5400	South Africa	Men/women	2968849
VRC01[a]	HVTN 703/ HPTN 081	2016	1900	sub-Saharan Africa	Women	2568215
VRC01[a]	HVTN 704/ HPTN 085	2016	2700	Americas	MSM, transgender	2716675
Tetravalent Ad26.Mosaic, clade C gp140/alum	HVTN 705	2018	2600	sub-Saharan Africa	Women	3060629

[a]bNAb.
Ad26, Adenovirus serotype 26; *bNAbs,* broadly neutralizing antibodies; *gp120,* glycoprotein 120; *HPTN,* HIV Prevention Trials Network; *HVTN,* HIV Vaccine Trials Network; *MSM,* men who have sex with men; *NCT,* ClinicalTrials.gov identifier number; *vCP,* canarypox vector.

Two phase IIb efficacy studies of the Merck rAd5-*gag/pol/nef* vaccine given at months 0, 1, and 6 have also been conducted. These studies aimed to determine whether the HIV-1–specific cellular immune responses elicited by this vaccine[586] would reduce either HIV-1 acquisition or viral load setpoint after infection. One study was conducted in the Americas, the Caribbean, and Australia (HVTN 502 or "Step") and enrolled 3000 participants at high risk for HIV-1 infection. A parallel study was begun in South Africa (HVTN 503 or "Phambili"). The Step Study was terminated early at the first Data Safety Monitoring Board meeting in September 2007 because of a determination of futility in finding significant protection from infection between the vaccine and placebo groups. The rates of infection in the vaccine and placebo groups were not significantly different (see Table 119.6), and HIV-1 viral loads were not reduced in vaccinees compared with placebo subjects, despite the induction of HIV-1–specific cellular immune responses in most vaccinees.[511,512,587] In addition, the data suggested that vaccinees who had preexisting Ad5 immunity and who were uncircumcised may have had increased risk for HIV-1 acquisition, especially during the early period after vaccination.[588] Subsequent analyses, using an HIV-1 sieve approach, suggested that the vaccine may have elicited immune responses that exerted immunologic pressure on the infecting HIV-1 virus in vaccine recipients who became HIV-1 infected.[589,590] No increased HIV-1 acquisition was observed in vaccinees who did not have preexisting Ad5 immunity and who were circumcised. A second study of this vaccine regimen was carried out in Phambili. It was halted and unblinded shortly after it was initiated due to the results from the Step trial—with 801 of the planned 3000 participants enrolled. An evaluation of HIV-1 acquisition of these limited data found no evidence for vaccine benefit in preventing HIV-1 acquisition or on HIV-1 viral load setpoint (see Table 119.6).[591] Although the biologic basis for the potentially increased rate of HIV-1 acquisition in the Step Study remains unclear, these data suggest potential advantages of using vaccine vectors that are not subject to substantial preexisting vector immunity.

The fourth concept to be tested in an efficacy trial is HVTN 505, a phase IIb study of a DNA prime followed by rAd5 boost HIV-1 vaccine regimen (DNA/rAd5) developed by the VRC at the NIH. This vaccine included envelope antigens from HIV-1 clades A, B, and C. This study enrolled 2504 volunteers in the United States who were MSM or transgender volunteers at high risk for acquiring HIV-1. At the first planned interim Data Safety Monitoring Board review for efficacy in April 2013, the study was stopped for lack of efficacy because futility criteria had been met for both coprimary end points: HIV-1 acquisition and reduction in HIV-1 viral load setpoint in those who became HIV-1 infected.[592] At present, no further development of rAd5-based HIV-1 vaccine candidates is planned. It is unclear whether the failure of these rAd5 vector-based vaccines represents the failure of these specific vaccine products or the failure of the T-cell–based vaccine concept in general.

A fifth concept (phase IIb, HVTN 705) is undergoing field testing based on the bivalent mosaic antigen concept delivered by an Ad26 vector and boosted with an alum adjuvanted clade C gp140 protein (NCT#03060629). This study is recruiting 2600 women in sub-Saharan Africa at risk for HIV-1 infection. The primary end point is prevention of HIV-1 infection. This study is ongoing.

Broadly Neutralizing Antibodies Against HIV-1

The development of single-cell antibody cloning techniques has led to the recognition and eventual generation of monoclonal broadly neutralizing antibodies (bNAbs) against HIV-1 from patients infected with HIV-1. This has led to consideration of their use in immunoprophylaxis and immunotherapy of HIV infection.[593] Passive transfer of bNAbs to macaques has been shown to prevent infection of macaques with SHIV[594] and also to suppression of SHIV in infected animals.[595] Properties of bNAbs, such as extensive somatic hypermutation, make it extraordinarily difficult to elicit them by conventional immunization approaches.

bNAbs have been administered to uninfected[596] as well as HIV-1 infected volunteers[597,598] in phase 1 trials. The most extensively studied of the bNAbs, VRC01, is undergoing phase 2b studies to determine its efficacy in prevention of acquisition of HIV-1 infection. Both studies were initiated in 2016 in persons at increased risk for the acquisition of HIV-1 infection. The first study is in the Americas in men and transgender persons who have sex with men (n = 2700; HVTN 704/HPTN085, NCT#02716675).[599] The companion study is evaluating the prophylactic efficacy in women (n = 1900) in sub-Saharan Africa (HVTN703/HPTN081, NCT#02568215).[599]
Both of these studies are fully enrolled and in active follow-up. Multiple bNAbs with improved breadth and prolonged half-life have been developed and are in phase I testing[600] (NCT#03387150).

Early Phase Clinical Trials

A number of novel HIV-1 vaccine concepts are currently being pursued in early phase clinical trials. Studies are planned to evaluate novel vectors, such as CMV vectors, and novel Env immunogens that aim to induce bNAb responses. Although such immunogens do not yet exist, early phase clinical trials are in progress to evaluate native-like Env trimers and to determine whether engineered immunogens can trigger germline variable antibody genes that are believed to be required for neutralization breadth. In addition, studies will determine whether a series of immunogens can recapitulate B-cell development pathways that have been defined for broadly neutralizing monoclonal antibodies. Meanwhile, a series of early phase clinical trials are underway to evaluate whether cocktails of broadly neutralizing monoclonal antibodies can be used for passive protection.

Summary

Multiple HIV-1 vaccine approaches have been evaluated, and several large clinical efficacy trials are currently underway to evaluate novel HIV-1 vaccine strategies that should inform the field over the next several years. Future priorities of the field involve the development of vaccines that elicit broadly reactive NAbs and antibody cocktails for passive protection.

Key References

The complete reference list is available online at Expert Consult.

3. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*. 1983;220:868–871.
27. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63:1–10.
28. Centers for Disease Control and Prevention. Estimated HIV Incidence and Prevalence in the United States, 2010 – 2015. HIV Surveillance Supplemental Report 2018; 23(No. 1); published March 2018. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-23-1.pdf.
29. Centers for Disease Control and Prevention. Diagnoses of HIV Infection in the United States and Dependent Areas, 2017. HIV Surveillance Report, 2017, Vol 29; published November 2018. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2017-vol-29.pdf. Accessed December 12, 2018.
151. Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. *Int J Epidemiol*. 2010;39:1048–1063.
161. Cohen MS, Shaw GM, McMichael AJ, et al. Acute HIV-1 infection. *N Engl J Med*. 2011;364:1943–1954.
166. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.
167. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375:830–839.
228. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013;381:2083–2090.
394. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2015;372:509–519.
411. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587–2599.
413. Beaten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367:399–410.
414. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012;367:411–422.
415. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012;367:423–434.
471. Moyer VA, U.S Preventive Services Task Force. Summaries for patients: screening for HIV: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2013;159:1–36.
476. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care Panel. *Ann Intern Med*. 2012;156:817–833.
579. Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicenter, randomized, double-blinded, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). *Lancet*. 2018;392:232–243.
580. Fisher W, Perkins S, Theiler J, et al. Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants. *Nat Med*. 2007;13:100–106.
581. Barouch DH, O'Brien KL, Simmons NL, et al. Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys. *Nat Med*. 2010;16:319–323.
582. Santra S, Liao H, Zhang R, et al. Mosaic vaccines elicit CD8+ T lymphocyte responses in monkeys that confer enhanced immune coverage of diverse HIV strains. *Nat Med*. 2010;16:324–328.
596. Ledgerwood JE, Coates EE, Yamshchikov G, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. *Clin Exp Immunol*. 2015;182:289–301.
600. Caskey M, Klein F, Lorenzi JCC, et al. Viraemia suppressed in HIV-1 infected humans by broadly neutralizing antibody 3BNC117. *Nature*. 2015;522:487–491.

References

1. Centers for Disease Control and Prevention. *Pneumocystis* pneumonia—Los Angeles. *MMWR Morb Mortal Wkly Rep*. 1981;30:250–252.
2. Centers for Disease Control and Prevention. Kaposi's sarcoma and *Pneumocystis* pneumonia among homosexual men—New York City and California. *MMWR Morb Mortal Wkly Rep*. 1981;30:305–308.
3. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*. 1983;220:868–871.
4. Gallo RC, Sarin PS, Gelmann EP, et al. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). *Science*. 1983;220:865–867.
5. Zhu T, Korber BT, Nahmias AJ, et al. An African HIV-1 sequence from 1959 and implications for the origin of the epidemic. *Nature*. 1998;391:594–597.
6. Worobey M, Gemmel M, Teuwen DE, et al. Direct evidence of extensive diversity in Kinshasa by 1960. *Nature*. 2008;455:661–664.
7. Joint United Nations Programme on HIV/AIDS (UNAIDS). Report on the Global HIV/AIDS Epidemic 2008. Geneva: World Health Organization/UNAIDS; 2008.
8. Pallela F, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1998;338:853–860.
9. Centers for Disease Control and Prevention. HIV Infection Risk, Prevention, and Testing Behaviors among Mem Who Have Sex with Men – National HIV Behavioral Surveillance, 20 cities, 2014. HIV Surveillance Special Report 15; published January 2016. http://www.cdc.gov/hiv/library/reports/surveillance/#panel12.
10. Karon JM, Fleming PL, Steketee RW, et al. HIV in the United States at the turn of the century: an epidemic in transition. *Am J Public Health*. 2001;91:1060–1068.
11. Hall HI, Song R, Rhodes P, et al; HIV Incidence Surveillance Group. Estimation of HIV incidence in the United States. *JAMA*. 2008;300:520–529.
12. Nakashima AK, Fleming PL. HIV/AIDS surveillance in the United States, 1981-2001. *J Acquir Immune Defic Syndr*. 2003;32(suppl 1):S68–S85.
13. Centers for Disease Control and Prevention. Update on acquired immune deficiency syndrome (AIDS)—United States. *MMWR Morb Mortal Wkly Rep*. 1982;31:507–508, 513–514.
14. Centers for Disease Control and Prevention. Revision of the case definition of acquired immunodeficiency syndrome for national reporting—United States. *MMWR Morb Mortal Wkly Rep*. 1985;34:373–375.
15. Centers for Disease Control and Prevention. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep*. 1987;36(suppl):S1–S15.
16. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992;41(RR–17):1–19.
17. Centers for Disease Control and Prevention. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged < 18 months and for HIV infection and AIDS among children 18 months to <13 years—United States, 2008. *MMWR Recomm Rep*. 2008;57(RR–10):1–12.
18. Rosenblum LS, Buehler JW, Morgan MW, et al. The completeness of AIDS case reporting, 1988: a multisite collaborative surveillance project. *Am J Public Health*. 1992;82:1495–1499.
19. Buehler JW, Devine OJ, Berkelman RL, et al. Impact of the human immunodeficiency virus epidemic on mortality trends in young men, United States. *Am J Public Health*. 1990;80:1080–1086.
20. Chu SY, Buehler JW, Berkelman RL. Impact of the human immunodeficiency virus epidemic on mortality in women of reproductive age, United States. *JAMA*. 1990;264:225–229.
21. Buehler JW, Berkelman RL, Stehr-Green JK. The completeness of AIDS surveillance. *J Acquir Immune Defic Syndr*. 1992;5:257–264.
22. Doyle T, Glynn K, Groseclose S. Completeness of notifiable infectious diseases reporting in the United States: an analytical review. *Am J Epidemiol*. 2002;155:866–874.
23. Vogt RL, Clark SW, Kappel S. Evaluation of the state surveillance system using hospital discharge diagnoses, 1982-83. *Am J Epidemiol*. 1986;123:197–198.
24. Centers for Disease Control and Prevention. Guidelines for national human immunodeficiency virus case surveillance, including monitoring for human immunodeficiency virus infection and acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep*. 1999;48:1–28.
25. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection. *MMWR Recomm Rep*. 1999;48(RR–13):29–31.
26. World Health Organization (WHO). *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. Geneva: WHO Press; 2007. http://www.who.int/hiv/pub/guidelines/hivstaging/en/index.html.
27. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63:1–10.
28. Centers for Disease Control and Prevention. Estimated HIV Incidence and Prevalence in the United States, 2010 – 2015. HIV Surveillance Supplemental Report 2018; 23(No. 1); published March 2018. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-23-1.pdf.
29. Centers for Disease Control and Prevention. Diagnoses of HIV Infection in the United States and Dependent Areas, 2017. HIV Surveillance Report, 2017, Vol 29; published November 2018. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2017-vol-29.pdf. Accessed December 12, 2018.
30. Janssen R, Satten G, Stramer S, et al. New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. *JAMA*. 1998;280:42–48.
31. Vu MQ, Steketee RW, Valleroy L, et al. HIV incidence in the United States, 1978-1999. *J Acquir Immune Defic Syndr*. 2002;31:188–201.
32. Woodring J, Kruszon-Moran D, McQuillan G. HIV infection in U.S. household population aged 18-59: data from the National Health and Nutrition Examination Survey, 2007-2012. *Natl Health Stat Report*. 2015;83:1–13.
33. Hahn RA, Onorato IM, Jones TS, et al. Prevalence of HIV infection among intravenous drug users in the United States. *JAMA*. 1989;261:2677–2684.
34. Des Jarlais DC, Friedman SR, Novick DM, et al. HIV-1 infection among intravenous drug users in Manhattan, New York City, from 1977 through 1987. *JAMA*. 1989;261:1008–1012.
35. Allen DM, Onorato IM, Green TA, et al. HIV infection in intravenous drug users entering drug treatment, United States, 1988 to 1989. *Am J Public Health*. 1992;82:541–546.
36. Prevots DR, Allen DM, Lehman JS, et al. Trends in human immunodeficiency virus seroprevalence among injection drug users entering drug treatment centers, United States, 1988-1993. *Am J Epidemiol*. 1996;143:733–742.
37. Battjes RJ, Pickens RW, Brown LS Jr. HIV infection and AIDS risk behaviors among injecting drug users entering methadone treatment: an update. *J Acquir Immune Defic Syndr*. 1995;10:90–96.
38. Centers for Disease Control and Prevention. HIV diagnoses among injection-drug users in states with HIV surveillance—25 states, 1994-2000. *MMWR Morb Mortal Wkly Rep*. 2003;52:634–636.
39. Centers for Disease Control and Prevention. HIV Infection, Risk, Prevention, and Testing Behaviors Among Persons Who Inject Drugs – National HIV Behavioral Surveillance: Injection Drug Use, 20 U.S. Cities, 2015. HIV Surveillance Special Report 18. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html.
40. Van Handel MM, Rose CE, Hallisey EJ, et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. *J Acquir Immune Defic Syndr*. 2016;73:323–331.
41. Lee LM, Fleming PL. Trends in human immunodeficiency virus diagnoses among women in the United States, 1994-1998. *J Am Med Womens Assoc*. 2001;56:94–99.
42. Pence BW, Reif S, Whetten K, et al. Minorities, the poor, and survivors of abuse: HIV-infected patients in the US Deep South. *South Med J*. 2007;100:1114–1122.
43. Strathdee SA, Galai N, Safaiean M, et al. Sex differences in risk factors for HIV seroconversion among injection drug users: a 10-year perspective. *Arch Intern Med*. 2001;161:1281–1288.
44. Janssen RS, St. Louis ME, Satten GA, et al. HIV infection among patients in U.S. acute care hospitals: strategies for the counseling and testing of hospital patients. *N Engl J Med*. 1992;327:445–452.
45. Miller RS, Green LA, Nutting PA, et al. Human immunodeficiency virus seroprevalence in community-based primary care practices, 1990-1992: a report from the Ambulatory Sentinel Practice Network. *Arch Fam Med*. 1995;4:1042–1047.
46. Walensky RP, Losina E, Steger-Craven KA, et al. Identifying undiagnosed human immunodeficiency virus: the yield of routine, voluntary inpatient testing. *Arch Intern Med*. 2002;162:887–892.
47. Weis SE, Foresman B, Cook PE, et al. Universal HIV screening at a major metropolitan TB clinic: HIV prevalence and high-risk behaviors among TB patients. *Am J Public Health*. 1999;89:73–75.
48. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings. *MMWR Recomm Rep*. 2006;55(RR14):1–17, quiz CE 1–4.
49. Blocker ME, Levine WC, St. Louis ME. HIV prevalence in patients with syphilis, United States. *Sex Transm Dis*. 2000;27:53–59.
50. Centers for Disease Control and Prevention. HIV Prevalence and Trends in Selected Populations in the United States: Results from National Serosurveillance, 1993-1997. Atlanta: Centers for Disease Control and Prevention; 2001:1-51.
51. Withum DG, Guerena-Burgueno F, Gwinn M, et al. High HIV prevalence among female and male prisoners in the United States, 1989-1992: implications for prevention and treatment strategies. Abstract POC213115. In: Abstracts of the Ninth International Conference on AIDS/Fourth STD World Congress. Vol. 2. Berlin, 1993:736.
52. Centers for Disease Control and Prevention. National HIV Serosurveillance Summary—Results Through 1992. Publication No. HIV/NCID/1193/036. Atlanta: U.S. Department of Health and Human Services, Public Health Service; 1993.
53. Mikl J, Dzierbicki A, Smith PF, et al. Trends in HIV infection rates among New York State prison entrants, 1987-97. Abstract 2356. Presented at the Twelfth International Conference on AIDS. Geneva, June 28-July 3, 1998.
54. Sabin KM, Frey RL Jr, Horsley R, et al. Characteristics and trends of newly identified HIV infections among incarcerated populations: CDC HIV voluntary counseling, testing, and referral system, 1992-1998. *J Urban Health*. 2001;78:241–255.
55. Westergaad RP, Spaulding AC, Flanigan TP. HIV among persons incarcerated in the US: a review of evolving concepts in testing, treatment and linkage to community care. *Curr Opin Infect Dis*. 2013;26:10–16.
56. Pilcher CD, McPherson JT, Leone PA, et al. Real-time, universal screening for acute HIV infection in a routine HIV counseling and testing population. *JAMA*. 2002;288:216–221.
57. Rutherford GW, Schwarcz SK, McFarland W. Surveillance for incident HIV infection: new technology and new opportunities. *J Acquir Immune Defic Syndr*. 2000;25(suppl 2):S115–S119.
58. Selik RM, Ward JW, Buehler JW. Trends in transfusion-associated acquired immune deficiency syndrome in the United States, 1982 through 1991. *Transfusion*. 1993;33:890–893.
59. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA*. 2003;289:959–962.
60. Neal JJ, Fleming PL, Green TA, et al. Trends in heterosexually acquired AIDS in the United States, 1988 through 1995. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;14:465–474.
61. Nwanyanwu OC, Conti LA, Ciesielski CA, et al. Increasing frequency of heterosexually transmitted AIDS in southern Florida: artifact or reality? *Am J Public Health*. 1993;83:571–573.
62. Klevens RM, Fleming PL, Neal JJ, et al. Is there really a heterosexual AIDS epidemic in the United States? Findings from a multisite validation study, 1992-1995. Mode of Transmission Validation Study Group. *Am J Epidemiol*. 1999;149:75–84.
63. Green TA, Karon JM, Nwanyanwu OC. Changes in AIDS incidence trends in the United States. *J Acquir Immune Defic Syndr*. 1992;5:547–555.
64. Castro KG, Lifson AR, White CR, et al. Investigations of AIDS patients with no previously identified risk factors. *JAMA*. 1988;259:1338–1342.
65. Simonds RJ, Holmberg SD, Hurwitz RL, et al. Transmission of human immunodeficiency virus type 1 from a seronegative organ and tissue donor. *N Engl J Med*. 1992;326:726.
66. Centers for Disease Control and Prevention. Update: trends in AIDS incidence, deaths and prevalence—United States, 1996. *MMWR Morb Mortal Wkly Rep*. 1997;46:165–173.
67. Centers for Disease Control and Prevention. HIV Surveillance Report, 2010. Vol 22. http://www.cdc.gov/hiv/topics/surveillance/resources/reports/.
68. Diaz T, Buehler JW, Castro KG, et al. AIDS trends among Hispanics in the United States. *Am J Public Health*. 1993;83:504–509.

69. Centers for Disease Control and Prevention. Risks for HIV infection among persons residing in rural areas and small cities—selected sites, southern United States, 1995-1996. *MMWR Morb Mortal Wkly Rep*. 1998;47:974–978.
70. Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report 2003. Vol. 15. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2004:5-46.
71. Greenberg AE, Thomas PA, Landesman SH, et al. The spectrum of HIV-1-related disease among outpatients in New York City. *AIDS*. 1992;6:849–859.
72. Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiological features of primary HIV infection. *Ann Intern Med*. 1996;125:257–264.
73. Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med*. 2001;134:25–29.
74. Hardy WD, Daar ES, Sokolov RT Jr, et al. Acute neurologic deterioration in a young man. *Rev Infect Dis*. 1991;13:745–750.
75. Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. *AIDS*. 1991;5: 1–14.
76. Kahn JO, Walker BD. Current concepts: acute human immunodeficiency virus type 1 infection. *N Engl J Med*. 1998;339:33–39.
77. Fox R, Eldred LJ, Fuchs EJ, et al. Clinical manifestations of acute infection with human immunodeficiency virus in a cohort of gay men. *AIDS*. 1987;1:35–38.
78. Pedersen C, Lindhardt BO, Jensen BL, et al. Clinical course of primary HIV infection: consequences for subsequent course of infection. *BMJ*. 1989;299:154–157.
79. Busch MP, Lee LL, Shatten GA, et al. Time course of detection of viral and serologic markers preceding human immunodeficiency virus type 1 seroconversion: implications for screening of blood and tissue donors. *Transfusion*. 1995;35:91–97.
80. Horsburgh CR Jr, Ou CY, Jason J, et al. Duration of human immunodeficiency virus infection before detection of antibody. *Lancet*. 1989;2:637–640.
81. Pan LZ, Sheppard HW, Winkelstein W, et al. Lack of detection of human immunodeficiency virus in persistently seronegative homosexual men with high or medium risks for infection. *J Infect Dis*. 1991;164:962–964.
82. Simmonds P, Lainson FAL, Cuthbert R, et al. HIV antigen and antibody detection: variable responses to infection in the Edinburgh haemophiliac cohort. *BMJ*. 1988;296:593–598.
83. Yerly S, Chamot E, Deglon JJ, et al. Absence of chronic human immunodeficiency virus infection without seroconversion in intravenous drug users: a prospective and retrospective study. *J Infect Dis*. 1991;164:965–968.
84. Alter HJ, Epstein JS, Swenson SG, et al. Prevalence of human immunodeficiency virus type 1 p24 antigen in the US blood donors—an assessment of the efficacy of testing in donor screening. The HIV-Antigen Study Group. *N Engl J Med*. 1990;323:1312–1317.
85. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS*. 2002;16:1119–1129.
86. Patel P, Mackellar D, Simmons P, et al. Detecting acute human immunodeficiency virus infection using 3 different screening immunoassays and nucleic acid amplification testing for human immunodeficiency virus RNA, 2006-2008. *Arch Intern Med*. 2010;170:66–74.
87. Centers for Disease Control and Prevention. Projections of the number of persons diagnosed with AIDS and the number of immunosuppressed HIV-infected persons—United States, 1992-1994. *MMWR Recomm Rep*. 1992;41(RR–18):1–29.
88. Ragni MV, Kingsley LA. Cumulative risk for AIDS and other HIV outcomes in a cohort of hemophiliacs in western Pennsylvania. *J Acquir Immune Defic Syndr*. 1990;3:708–713.
89. Kuo JM, Taylor JMG, Detels R. Estimating the AIDS incubation period from a prevalent cohort. *Am J Epidemiol*. 1991;133:1050–1057.
90. Rutherford GW, Lifson AR, Hessol NA, et al. Course of HIV-1 infection in a cohort of homosexual and bisexual men: an 11 year follow up study. *BMJ*. 1990;301:1183–1188.
91. Lifson AR, Buchbinder SP, Sheppard HW, et al. Long-term human immunodeficiency virus infection in asymptomatic homosexual and bisexual men with normal CD4+ lymphocyte counts: immunologic and virologic characteristics. *J Infect Dis*. 1991;163:959–965.
92. Learmont J, Tindall B, Evans L, et al. Long-term symptomless HIV-1 infection in recipients of blood products from a single donor. *Lancet*. 1992;340:863–867.
93. Ashton JJ, Carr A, Cunningham PM, et al. Predictors of progression in long-term non-progressors. Australian Long-term Non-progressor Study Group. *AIDS Res Hum Retroviruses*. 1998;14:117–121.
94. Ward JW, Bush TJ, Perkins HA, et al. The natural history of transfusion-associated infection with human immunodeficiency virus. *N Engl J Med*. 1989;321:947–952.
95. Fleming PL, Ciesielski CA, Byers RH, et al. Gender differences in reported AIDS-indicative diagnoses. *J Infect Dis*. 1993;168:61–67.
96. Kreiss JK, Castro KG. Special considerations for managing suspected human immunodeficiency virus infection and AIDS in patients from developing countries. *J Infect Dis*. 1990;162:955–960.
97. Slutsker L, Castro KG, Ward JW, et al. Epidemiology of extra-pulmonary tuberculosis among persons with AIDS in the United States. *Clin Infect Dis*. 1993;16:513–518.
98. Karon JM, Green TA, Hanson DL, et al. Estimating the number of AIDS-defining opportunistic illness diagnoses from data collected under the 1993 AIDS surveillance definition. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;16:116–121.
99. Jones JL, Hanson DL, Dworkin MS, et al. Trends in AIDS-related opportunistic infections among men who have sex with men and among injecting drug users, 1991-96. *J Infect Dis*. 1998;178:114–120.
100. Holtzer CD, Jacobson MA, Hadley WK, et al. Decline in the rate of specific opportunistic infections at the San Francisco General Hospital, 1994-1997. *AIDS*. 1998;12:1931–1933.
101. Gebo KA, Fleishman JA, Reilly ED, et al. High rates of primary *Mycobacterium avium* complex and *Pneumocystis jiroveci* prophylaxis in the United States. *Med Care*. 2005;43(suppl 9):III23–III30.
102. Jacobson MA, Franch M. Altered natural history of AIDS- related opportunistic infections in the era of potent combination antiretroviral therapy. *AIDS*. 1998;12(supplA):S157–S163.
103. Mouron Y, Alfandari S, Valette M, et al. Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centers. *AIDS*. 1997;11:F101–F105.
104. French MA. Immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis*. 2009;48:101–107.
105. Selwyn PA, Feingold AR, Hartel D, et al. Increased risk of bacterial pneumonia in HIV-infected intravenous drug users without AIDS. *AIDS*. 1988;2:167–172.
106. Janoff EN, Breiman RF, Daley CL, et al. Pneumococcal disease during HIV infection: epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med*. 1992;117:314–324.
107. Redd SC, Rutherford GW 3rd, Sande MA, et al. The role of human immunodeficiency virus infection in pneumococcal bacteremia in San Francisco residents. *J Infect Dis*. 1990;162:1012–1017.
108. Laga M, Icenogle JP, Marsella R, et al. Genital papillomavirus infection and cervical dysplasia—opportunistic complications of HIV infection. *Int J Cancer*. 1992;50:45–48.
109. Harris TG, Burk RD, Palefsky JM, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. *JAMA*. 2005;293:1471–1476.
110. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States, 1980-2002. *AIDS*. 2006;20:1645–1654.
111. Barnes PF, Bloch AB, Davidson PT, et al. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med*. 1991;324:1644–1650.
112. Raviglione MC, Narain JP, Kochi A. HIV-associated tuberculosis in developing countries: clinical features, diagnosis, and treatment. *Bull World Health Organ*. 1992;70:515–526.
113. Centers for Disease Control and Prevention. Trends in tuberculosis incidence—United States, 2006. *MMWR Morb Mortal Wkly Rep*. 2007;56:245–250.
114. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2007. Atlanta: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2008.
115. Centers for Disease Control and Prevention. Prevention of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *MMWR Recomm Rep*. 1998;47(RR–20):1–58.
116. Braun MM, Cote TR, Rabkin CS. Trends in death with tuberculosis during the AIDS era. *JAMA*. 1993;269:2865–2868.
117. Rieder HL, Snider DE Jr. Tuberculosis and the acquired immunodeficiency syndrome [editorial]. *Chest*. 1986;90:469–470.
118. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med*. 1998;340:367–373.
119. Small PM, Hopewell PC, Singh SP, et al. The epidemiology of tuberculosis in San Francisco: a population based study using conventional and molecular methods. *N Engl J Med*. 1994;330:1703.
120. Alland D, Kalbut GE, Moss AR, et al. Transmission of tuberculosis in New York City: an analysis of DNA fingerprinting and conventional epidemiologic methods. *N Engl J Med*. 1994;330:1710.
121. Moore M, Onorato IM, McCoy E, et al. Trends in drug-resistant tuberculosis in the United States, 1993-1996. *JAMA*. 1997;278:833–837.
122. Frieden TR, Sterling T, Pablos-Mendez A, et al. The emergence of drug-resistant tuberculosis in New York City. *N Engl J Med*. 1993;328:521–526.
123. Peloquin C, MacPhee AA, Berning SE. Malabsorption of anti-mycobacterial medications [letter]. *N Engl J Med*. 1993;329:1122.
124. Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;326:1514–1521.
125. Pearson ML, Jereb JA, Frieden TR, et al. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis: a risk to patients and health care workers. *Ann Intern Med*. 1992;117:191–196.
126. Beck-Sagué C, Dooley SW, Hutton MD, et al. Hospital outbreak of multidrug-resistant Mycobacterium tuberculosis infections: factors in transmission to staff and HIV-infected patients. *JAMA*. 1992;268:1280–1286.
127. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death among patients co-infected with tuberculosis and HIV in a rural area in South Africa. *Lancet*. 2006;368:1575–1580.
128. Fordyce EJ, Singh TP, Nash D, et al. Survival rates in NYC in the era of combination ART. *J Acquir Immune Defic Syndr*. 2002;30:111–118.
129. Murphy EL, Collier AC, Kallish LA, et al. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Ann Intern Med*. 2001;135:17–26.
130. Centers for Disease Control and Prevention. Update: mortality attributable to HIV-infection among persons aged 25-44 years—United States, 1994. *MMWR Morb Mortal Wkly Rep*. 1996;45:121–125.
131. Centers for Disease Control and Prevention. Years of potential life lost before age 65-United States, 1990 and 1991. *MMWR Morb Mortal Wkly Rep*. 1993;42:251–252.
132. Walensky RP, Paltiel AD, Losina E, et al. The survival benefits of AIDS treatment in the United States. *J Infect Dis*. 2006;194:1–5.
133. Turner BJ, Eppes S, McKee LJ, et al. A population-based comparison of the clinical course of children and adults with AIDS. *AIDS*. 1995;9:65–72.
134. Duliege AM, Messiah A, Blanche S, et al. Natural history of human immunodeficiency virus type 1 infection in children: prognostic value of laboratory tests on the bimodal progression of the disease. *Pediatr Infect Dis J*. 1992;11:630–635.
135. McKinney RE Jr, Wilfert CM. Lymphocyte subsets in children younger than 2 years old: normal values in a population at risk for human immunodeficiency virus infection and diagnostic and prognostic application to infected children. *Pediatr Infect Dis J*. 1992;11:639–644.
136. Waecker NJ Jr, Ascher DP, Robb ML, et al. Age-adjusted CD4+ lymphocyte parameters in healthy children at risk for infection with human immunodeficiency virus. *Clin Infect Dis*. 1993;17:123–125.
137. Quinn TC, Ruff A, Modlin J. HIV infection and AIDS in children. *Annu Rev Public Health*. 1992;13:1–30.
138. Centers for Disease Control and Prevention. AIDS among children—United States, 1996. *MMWR Morb Mortal Wkly Rep*. 1996;45:1005–1010.
139. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med*. 1994;331:1173–1180.
140. Centers for Disease Control and Prevention. Recommendations of the US Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus. *MMWR Recomm Rep*. 1994;43(RR–11):1–20.
141. Centers for Disease Control and Prevention. US Public Health Service recommendations for human immunodeficiency virus counseling and testing for pregnant women. *MMWR Recomm Rep*. 1995;44(RR–7):1–15.
142. Chin J, Sato PA, Mann JM. Projections of HIV infections and AIDS cases to the year 2000. *Bull World Health Organ*. 1990;68:1–11.
143. Samuel MC, Hessol N, Shiboski S, et al. Factors associated with human immunodeficiency virus seroconversion in homosexual men in three San Francisco cohorts. *J Acquir Immune Defic Syndr*. 1993;6:303–312.

144. Cohen MS. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet*. 1998;351(suppl 3):S5–S7.
145. Quinn TC. Association of sexually transmitted diseases and infection with the human immunodeficiency virus: biological cofactors and markers of behavioral interventions. *Int J STD AIDS*. 1996;7(suppl 2):S17–S24.
146. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. 1999;75:3–17.
147. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, Rakai, Uganda. *J Infect Dis*. 2005;191:1403–1409.
148. Cohen MS, Pilcher CD. Amplified HIV transmission and new approaches to HIV prevention. *J Infect Dis*. 2005;191:1391–1393.
149. Patel P, Borkowf CB, Brooks JT, et al. Estimating per-act HIV transmission risk: a systematic review. *AIDS*. 2014;28:1509–1519.
150. Vittinghoff E, Douglas J, Judson F, et al. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *Am J Epidemiol*. 1999;150:306–311.
151. Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. *Int J Epidemiol*. 2010;39:1048–1063.
152. Clumeck N, Taelman H, Hermans P, et al. A cluster of HIV infection among heterosexual people without apparent risk factors. *N Engl J Med*. 1989;321:1460–1462.
153. Peterman TA, Stoneburner RL, Allen JR, et al. Risk of human immunodeficiency virus transmission from heterosexual adults with transfusion-associated infections. *JAMA*. 1988;59:55–58.
154. Johnson AM, Petherick A, Davidson SJ, et al. Transmission of HIV to heterosexual partners of infected men and women. *AIDS*. 1989;3:367–372.
155. Seidlin M, Vogler M, Lee E, et al. Heterosexual transmission of HIV in a cohort of couples in New York City. *AIDS*. 1993;7:1247.
156. Goedert JJ, Eyster ME, Bigger RJ, et al. Heterosexual transmission of human immunodeficiency virus: association with severe depletion of T-helper lymphocytes in men with hemophilia. *AIDS Res Hum Retroviruses*. 1987;3:355–361.
157. European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. *BMJ*. 1992;304:809–813.
158. Lazzarin A, Saracco A, Musicco M, et al. Man-to-woman sexual transmission of the human immunodeficiency virus: risk factors related to sexual behavior, man's infectiousness, and woman's susceptibility. *Arch Intern Med*. 1991;151:2411–2416.
159. Laga M, Taelman H, Van der Stuyft P, et al. Advanced immunodeficiency as a risk factor for heterosexual transmission of HIV. *AIDS*. 1989;3:361–366.
160. Pilcher CD, Eron JJ Jr, Vernazza PL, et al. Sexual transmission during the incubation period of primary HIV infection. *JAMA*. 2001;286:1713–1714.
161. Cohen MS, Shaw GM, McMichael AJ, et al. Acute HIV-1 infection. *N Engl J Med*. 2011;364:1943–1954.
162. Cates W Jr, Chesney MA, Cohen MS. Primary HIV infection—a public health opportunity. *Am J Public Health*. 1997;87:1928–1930.
163. Pilcher CD, Eron JJ, Galvin S, et al. Acute HIV revised: new opportunities for treatment and prevention. *J Clin Invest*. 2004;113:937–945.
164. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med*. 2000;342:921–929.
165. Vernazza P, Hirschel B, Bernasconi E, et al. Les personnes seropositives ne souffrant d'aucune autre MST et suivant un traitment antiretroviral efficace ne transmettent pas le VIH voie sexuelle. *Bulletin Medecins Suisses*. 2008;89:165–169.
166. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.
167. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375:830–839.
168. Roger A, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*. 2016;316:171–181.
169. LeMessurier J, Traversy G, Varsaneux O, et al. Risk of sexual transmission of human immunodeficiency virus with antiretroviral therapy, suppressed viral load and condom use: a systematic review. *CMAJ*. 2018;190:E1350–E1360.
170. McCray E, Mermin JH. CDC Dear Colleague Letter, September 27, 2017. https://www/cdc/gov/hiv/library/dcl/dcl/092717.html.
171. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. *N Engl J Med*. 1999;341:394–402.
172. Rothenberg RB, Scarlett M, del Rio C, et al. Oral transmission of HIV. *AIDS*. 1998;12:2095–2105.
173. Goto Y, Yeh CK, Notkins AL, et al. Detection of proviral sequences in saliva of patients infected with human immunodeficiency virus type 1. *AIDS Res Hum Retroviruses*. 1991;7:343–347.
174. Levy JA, Greenspan D. HIV in saliva [letter]. *Lancet*. 1988;2:1248.
175. Piot P, Laga M. Genital ulcers, other sexually transmitted diseases, and the sexual transmission of HIV: the first two may be important risk factors for the third. *BMJ*. 1989;298:623–624.
176. Plummer FA, Simonsen JN, Cameron DW, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *J Infect Dis*. 1991;163:233–239.
177. Cameron DW, Simonsen JN, D'Costa LJ, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet*. 1989;2:403–407.
178. Dyer JR, Eron JJ, Hoffman IF, et al. Association of CD4 cell depletion and elevated blood and seminal plasma human immunodeficiency virus type 1 (HIV-1) RNA concentrations with genital ulcer disease in HIV-1-infected men in Malawi. *J Infect Dis*. 1998;177:224–227.
179. Hray RH, Wawer MJ, Li X, et al. Determinants of HIV viral load in incident and prevalent infections, Rakai, Uganda. Abstract 908. In: Program and Abstracts 10th Conference on Retrovirus and Opportunistic Infections. Boston, February 10-14, 2003.
180. Stamm WE, Handsfield HH, Rompalo AM, et al. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA*. 1988;260:1429–1433.
181. Kreiss KJ, Coombs R, Plummer F, et al. Isolation of human immunodeficiency virus from genital ulcers in Nairobi prostitutes. *J Infect Dis*. 1989;160:380–384.
182. Watson-Jones D, Weiss HA, Rusizoka M, et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. *N Engl J Med*. 2008;358:1560–1571.
183. Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371:2109–2119.
184. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010;362:427–439.
185. Pathela P, Braunstein SL, Blank S, et al. HIV incidence among men with and those without sexually transmitted infections: estimates from matching against an HIV case registry. *Clin Infect Dis*. 2013;57:1203–1209.
186. Moss GB, Overbaugh J, Welch M, et al. Human immunodeficiency virus DNA in urethral secretions in men: association with gonococcal urethritis and CD4 depletion. *J Infect Dis*. 1995;172:1469–1474.
187. Atkins MC, Carlin EM, Emery VC, et al. Fluctuations of HIV load in semen of HIV-positive patients with newly acquired sexually transmitted diseases. *BMJ*. 1996;313:341–342.
188. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDSCAP Malawi Research Group. *Lancet*. 1997;349:1868–1873.
189. Greenblatt RM, Lukehart SA, Plummer FA, et al. Genital ulceration as a risk factor for human immunodeficiency virus infection. *AIDS*. 1988;2:47–50.
190. Holmberg SD, Stewart JA, Gerber AR, et al. Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA*. 1988;259:1048–1050.
191. Laga M, Manoka A, Kivuvu M, et al. Non-ulcerative sexually transmitted diseases as risk factor for HIV-1 transmission in women: results from a cohort study. *AIDS*. 1993;7:95–102.
192. Kapiga SH, Shao JF, Lwihula GK, et al. Risk factors for HIV infection among women in Dar es Salaam, Tanzania. *J Acquir Immune Defic Syndr*. 1994;7:301–309.
193. Cohen CR, Duerr A, Pruithithada N, et al. Bacterial vaginosis and HIV seroprevalence among female commercial sex workers in Chiang Mai, Thailand. *AIDS*. 1995;9:1093–1097.
194. Auvert B, Ralijaard D, Lagarde E, et al. Randomized, controlled intervention trial of male circumcision for the reduction of HIV infection risk: the ANRS 1265 trial. *PLoS Med*. 2005;2:e298.
195. Gray RH, Kigozi G, Servadda D, et al. Male circumcision for HIV prevention in Rakai, Uganda: a randomized trial. *Lancet*. 2007;369:657–666.
196. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet*. 2007;369:643–656.
197. Chu SY, Hammett TA, Buehler JW. Update: epidemiology of reported cases of AIDS in women who report sex only with other women, United States, 1980-1991. *AIDS*. 1992;6:518–519.
198. Kral AH, Lorvick J, Bluthenthal RN, et al. HIV risk profile of drug-using women who have sex with women in 19 United States cities. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;16:211–217.
199. Marrazzo JM, Koutsky LA, Handsfield HH. Characteristics of female sexually transmitted disease clinic clients who report same-sex behaviour. *Int J STD AIDS*. 2001;12:41–46.
200. Petersen LR, Doll L, White C, et al. No evidence for female-to-female HIV transmission among 960,000 female blood donors. *J Acquir Immune Defic Syndr*. 1992;5:853–855.
201. Marmor M, Weiss LR, Lyden M, et al. Possible female-to-female transmission of human immunodeficiency virus [letter]. *Ann Intern Med*. 1986;105:969.
202. Monzon OT, Capellan JMB. Female-to-female transmission of HIV [letter]. *Lancet*. 1987;2:40–41.
203. Rich JD, Buck A, Tuomala RE, et al. Transmission of human immunodeficiency virus infection presumed to have occurred via female-homosexual contact. *Clin Infect Dis*. 1993;17:1003–1005.
204. Moss GB, Clemetson D, D'Costa L, et al. Association of cervical ectopy with heterosexual transmission of human immunodeficiency virus: results of a study of couples in Nairobi, Kenya. *J Infect Dis*. 1991;164:588–591.
205. Stephenson JM. Systematic review of hormonal contraception and risk of HIV transmission: when to resist meta-analysis. *AIDS*. 1998;12:545–553.
206. Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis*. 2012;12:19–26.
207. Padian NS, Shiboski SC, Jewell NP. The effect of number of exposures on the risk of heterosexual HIV transmission. *J Infect Dis*. 1990;161:883–887.
208. Haddad LB, Polis CB, Sheth AN, et al. Contraceptive methods and risk of HIV acquisition or female-to-male transmission. *Curr HIV/AIDS Rep*. 2014;11:447–458.
209. World Health Organization. Hormonal Contraceptive Eligibility for Women at High Risk of HIV. Guidance Statement; 2017. http://apps.who.int/iris/bitstream/handle/10665/254662/WHO-RHR-17.04-eng.pdf;jsessionid=464B4C944D8A02800C6A3CA11C390111?sequence=1. Accessed July 1, 2018.
210. Dean M, Carrington M, Winkler C, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. *Science*. 1996;273:1856–1862.
211. Centers for Disease Control and Prevention. Human immunodeficiency virus infection in the United States: a review of current knowledge. *MMWR Morb Mortal Wkly Rep*. 1987;36(suppll 6):S1–S48.
212. Schoenbaum EE, Hartel D, Selwyn PA, et al. Risk factors for human immunodeficiency virus infection in intravenous drug users. *N Engl J Med*. 1989;321:874–879.
213. Lange WR, Snyder FR, Lozovsky D, et al. The geographic distribution of human immunodeficiency virus markers in parenteral drug abusers. *Am J Public Health*. 1988;78:443–446.
214. Friedman SR, Lieb S, Tempalski B, et al. HIV among injection drug users in large metropolitan areas, 1998. *J Urban Health*. 2005;83:434–445.
215. Anthony JC, Vlahov D, Nelson KE, et al. New evidence on intravenous cocaine use and the risk of infection with human immunodeficiency virus type 1. *Am J Epidemiol*. 1991;134:1175–1189.
216. Koblin BA, McCusker J, Lewis BF, et al. Racial/ethnic differences in HIV-1 seroprevalence and risky behaviors among intravenous drug users in a multisite study. *Am J Epidemiol*. 1990;132:837–846.
217. Fernando D, Schilling RF, Fontdevila J, et al. Predictors of sharing drugs among injection drug users in the South Bronx: implications for HIV transmission. *J Psychoactive Drugs*. 2003;35:227–236.
218. Centers for Disease Control and Prevention. National HIV Prevalence Surveys, 1997 Summary. Atlanta: Centers for Disease Control and Prevention; 1998:1-25.
219. Kral AH, Bluthenthal RN, Booth RE, et al. HIV seroprevalence among street-recruited injection drug and

crack cocaine users in 16 US municipalities. *Am J Public Health*. 1998;88:108–113.

220. Selik RM, Castro KG, Pappaioanou M, et al. Birthplace and the risk of AIDS among Hispanics in the United States. *Am J Public Health*. 1989;79:836–839.
221. McCusker J, Koblin B, Lewis BF, et al. Demographic characteristics, risk behaviors, and HIV seroprevalence among intravenous drug users by site of contact: results from a communitywide HIV surveillance project. *Am J Public Health*. 1990;80:1062–1067.
222. Nelson KE, Vlahov D, Cohn S, et al. Sexually transmitted diseases in a population of intravenous drug users: association with seropositivity to the human immunodeficiency virus (HIV). *J Infect Dis*. 1991;164:457–463.
223. Rolfs RT, Goldberg M, Sharrar RG. Risk factors for syphilis: cocaine use and prostitution. *Am J Public Health*. 1990;80:853–857.
224. Magura S, Grossman JI, Lipton DS, et al. Determinants of needle sharing among intravenous drug users. *Am J Public Health*. 1989;79:459–462.
225. Guydish JR, Abramowitz A, Woods W, et al. Changes in needle sharing behavior among intravenous drug users: San Francisco, 1986-88. *Am J Public Health*. 1990;80:995–997.
226. Neaigus A, Sufian M, Friedman SR, et al. Effects of outreach intervention on risk reduction among intravenous drug users. *AIDS Educ Prev*. 1990;2:253–271.
227. Mathers BM, Deganhardt L, Ali H, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional and national coverage. *Lancet*. 2010;375:1014–1026.
228. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013;381:2083–2090.
229. Curran JW, Lawrence DN, Jaffe H, et al. Acquired immunodeficiency syndrome (AIDS) associated with transfusions. *N Engl J Med*. 1984;310:69–75.
230. Evatt BL, Ramsey RB, Lawrence DN, et al. The acquired immunodeficiency syndrome in patients with hemophilia. *Ann Intern Med*. 1984;100:499–504.
231. Donegan E, Stuart M, Niland JC, et al. Infection with human immunodeficiency virus type 1 (HIV1) among recipients of antibody-positive blood donations. *Ann Intern Med*. 1990;113:733–739.
232. Ward JW, Deppe DA, Samson S, et al. Risk of human immunodeficiency virus infection from blood donors who later developed the acquired immunodeficiency syndrome. *Ann Intern Med*. 1987;106:61–62.
233. Centers for Disease Control and Prevention. Safety of therapeutic immune globulin preparations with respect to transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus infection. *MMWR Morb Mortal Wkly Rep*. 1986;35:231–233.
234. Wells MA, Wittek AE, Epstein JS, et al. Inactivation and partition of human T-cell lymphotrophic virus, type III, during ethanol fractionation of plasma. *Transfusion*. 1986;26:210–213.
235. Ward JW, Grindon AJ, Feorino PM, et al. Laboratory and epidemiologic evaluation of an enzyme immunoassay for antibodies to HTL V-III. *JAMA*. 1986;256:357–361.
236. Peterman TA, Lui KJ, Lawrence DN, et al. Estimating the risks of transfusion-associated acquired immune deficiency syndrome and human immunodeficiency virus infection. *Transfusion*. 1987;27:371–374.
237. Lackritz EM, Satten GA, Aberle-Grasse J, et al. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. *N Engl J Med*. 1995;333:1721–1725.
238. Schreiber GB, Bush MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. *N Engl J Med*. 1996;334:1635–1690.
239. U.S. Food and Drug Administration. FDA Approves First Nucleic Acid Test (NAT) System to Screen Whole Blood Donors for Infections With Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV). www.fda.gov/bbs/topics/ANSWERS/2002/ANS01140.html.
240. Stehr-Green JK, Jason JM, Evatt BL, et al. Geographic variability of hemophilia-associated AIDS in the United States: effect of population characteristics. *Am J Hematol*. 1989;32:178–183.
241. Eyster ME, Gail MH, Ballard ID, et al. Natural history of human immunodeficiency virus infection in hemophiliacs: effects of T-cell subsets, platelet counts and age. *Ann Intern Med*. 1987;107:1–6.
242. Erice A, Rhame FS, Heussner RC, et al. Human immunodeficiency virus infection in patients with solid-organ transplants: report of five cases and review. *Rev Infect Dis*. 1991;13:537–547.
243. Clarke JA. HIV transmission and skin grafts. *Lancet*. 1987;1:983.
244. Pepose JS, McRae S, Quinn TC, et al. Serologic markers after the transplantation of corneas from donors infected with human immunodeficiency virus. *Am J Ophthalmol*. 1987;103:798–801.
245. Glasser DB. Serologic testing of cornea donors. *Cornea*. 1998;17:123–128.
246. Lewis SH, Reynolds-Kohler C, Fox HE, et al. HIV-1 in trophoblastic and villous Hofbauer cells, and haematological precursors in eight-week fetuses. *Lancet*. 1990;335:565–568.
247. Douglas GC, King BF. Maternal-fetal transmission of human immunodeficiency virus: a review of possible routes and cellular mechanisms of infection. *Clin Infect Dis*. 1992;15:678–691.
248. Krivine A, Firtion G, Cao L, et al. HIV replication during the first weeks of life. *Lancet*. 1992;339:1187–1189.
249. Rogers MF, Ou CY, Rayfield M, et al. Use of the polymerase chain reaction for early detection of the proviral sequences of human immunodeficiency virus in infants born to seropositive mothers. *N Engl J Med*. 1989;320:1649–1654.
250. Burgard M, Mayaux MJ, Blanche S, et al. The use of viral culture and p24 antigen testing to diagnose human immunodeficiency virus infection in neonates. *N Engl J Med*. 1992;327:1192–1197.
251. Rogers MF, Schochetman G, Hoff R. Advances in diagnosis of HIV infection in infants. In: Pizzo PA, Wilfert CM, eds. *Pediatric AIDS: The Challenge of HIV Infection in Infants, Children and Adolescents*. 2nd ed. Baltimore: Williams & Wilkins; 1994:219–238.
252. Ehrnst A, Lindgren S, Dictor M, et al. HIV in pregnant women and their offspring: evidence for late transmission. *Lancet*. 1991;338:203–207.
253. European Collaborative Study. Risk factors for mother-to-child transmission of HIV-1. *Lancet*. 1992;339:1007–1012.
254. Gabiano C, Tovo PA, de Martino M, et al. Mother-to-child transmission of human immunodeficiency virus type 1: risk of infection and correlates of transmission. *Pediatrics*. 1992;90:369–374.
255. Blanche S, Rouzioux C, Moscato MLG, et al. A prospective study of infants born to women seropositive for human immunodeficiency virus type 1. *N Engl J Med*. 1989;320:1643–1648.
256. Hutto C, Parks WP, Lai S, et al. A hospital-based prospective study of perinatal infection with human immunodeficiency virus type 1. *J Pediatr*. 1991;118:347–353.
257. Goedert JJ, Duliege AM, Amos CI, et al. High risk of HIV-1 infection for firstborn twins. *Lancet*. 1991;338:1471–1475.
258. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1-A meta-analysis of 15 prospective cohort studies. *N Engl J Med*. 1999;340:977–987.
259. Dominguez KL, Lindegren ML, D'Almada PJ, et al. Increasing trend of cesarean deliveries in HIV-infected women in the United States from 1994 to 2000. *J Acquir Immune Defic Syndr*. 2003;33:232–238.
260. Thiry L, Sprecher-Goldberger S, Jonchkheer T, et al. Isolation of AIDS virus from cell-free breast milk of three healthy virus carriers [letter]. *Lancet*. 1985;2:891–892.
261. Oxtoby MJ. Human immunodeficiency virus and other viruses in human milk: placing the issues in broader perspective. *Pediatr Infect Dis J*. 1988;7:825–835.
262. Phuapradit W. Timing and mechanism of perinatal human immunodeficiency virus-1 infection. *Aust N Z J Obstet Gynaecol*. 1998;38:293–297.
263. Ryder RW, Manzila T, Baende E, et al. Evidence from Zaire that breastfeeding by HIV-1 seropositive mothers is not a major route for perinatal HIV-1 transmission but does decrease morbidity. *AIDS*. 1991;5:709–714.
264. Dunn DT, Newell ML, Ades AE, et al. Risk of human immunodeficiency virus type 1 transmission through breastfeeding. *Lancet*. 1992;340:585–588.
265. Van de Perre P, Simonon A, Msellati P, et al. Postnatal transmission of human immunodeficiency virus type 1 from mother to infant: a prospective cohort study in Kigali, Rwanda. *N Engl J Med*. 1991;325:593–598.
266. Palasithran P, Ziegler JB, Stewart GJ, et al. Breastfeeding during primary human immunodeficiency virus infection and risk of transmission from mother to infant. *J Infect Dis*. 1993;167:441–444.
267. Hu DJ, Heyward WL, Byers RH Jr, et al. HIV infection and breastfeeding: policy implications through a decision analysis model. *AIDS*. 1992;6:1505–1513.
268. Ryder RW, Nsa W, Hassig SE, et al. Perinatal transmission of the human immunodeficiency virus type 1 to infants of seropositive women in Zaire. *N Engl J Med*. 1989;320:1637–1642.
269. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. *N Engl J Med*. 1999;341:385–393.
270. Jamieson DJ, Sibailly TS, Sadek R, et al. HIV-1 viral load and other risk factors for mother-to-child transmission of HIV-1 in a breast-feeding population in Côte d'Ivoire. *J Acquir Immune Defic Syndr*. 2003;34:430–436.
271. Warszawski J, Tubiana R, LeChenadee J, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS*. 2008;22:289–299.
272. St. Louis ME, Kamenga M, Brown C, et al. Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic, and placental factors. *JAMA*. 1993;269:2853–2859.
273. Kuhn L, Steketee RW, Weedon J, et al. Distinct risk factors for intrauterine and intrapartum human immunodeficiency virus transmission and consequences for disease progression in infected children. *J Infect Dis*. 1999;179:52–58.
274. Landsman SH, Kalish LA, Burns DN, et al. Obstetrical factors and the transmission of human immunodeficiency virus type 1 from mother to child. *N Engl J Med*. 1996;334:1617–1623.
275. Borkowsky W, Krasinski K, Pollack H, et al. Early diagnosis of human immunodeficiency virus infection in children 6 months of age: comparison of polymerase chain reaction, culture, and plasma antigen capture techniques. *J Infect Dis*. 1992;166:616–619.
276. Report of a Consensus Workshop, Siena, Italy, January 17-18, 1992. Early diagnosis of HIV infection in infants. *J Acquir Immune Defic Syndr*. 1992;5:1169–1178.
277. Nesheim S, Lee F, Sawyer M, et al. Diagnosis of human immunodeficiency virus infection by enzyme-linked immunospot assays in a prospectively followed cohort of infants of human immunodeficiency virus-seropositive women. *Pediatr Infect Dis J*. 1992;11:635–639.
278. Tokars JI, Bell DM, Culver DH, et al. Percutaneous injuries during surgical procedures. *JAMA*. 1992;267:2899–2904.
279. Marcus R, Culver DH, Bell DM, et al. Risk of human immunodeficiency virus infection among emergency department workers. *Am J Med*. 1993;94:363–370.
280. Wong ES, Stotka JL, Chinchilli VM, et al. Are universal precautions effective in reducing the number of occupational exposures among health care workers? A prospective study of physicians on a medical service. *JAMA*. 1991;265:1123–1128.
281. Tokars JI, Marcus R, Culver DH, et al. Surveillance of HIV infection and zidovudine use among health care workers after occupational exposure to HIV-infected blood. *Ann Intern Med*. 1993;118:913–919.
282. Henderson DK, Fahey BJ, Willy M, et al. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV 1) associated with clinical exposures: a prospective evaluation. *Ann Intern Med*. 1990;113:740–746.
283. Gerberding JL. Incidence and prevalence of human immunodeficiency virus, hepatitis B virus, hepatitis C virus and cytomegalovirus among health care personnel at risk for blood exposure: final report from a longitudinal study. *J Infect Dis*. 1994;170:1410–1417.
284. Ippolito G, Puro V, De Carli G. The risk of occupational human immunodeficiency virus infection in health care workers: Italian multicenter study. *Arch Intern Med*. 1993;153:1451–1458.
285. Chamberland ME, Conley LJ, Bush TJ, et al. Health care workers with AIDS: national surveillance update. *JAMA*. 1991;266:3459–3462.
286. Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep*. 2001;50:1–52.
287. Joyce PM, Kuhar D, Brooks JT. Occupationally acquired HIV infection among health care workers – United States, 1985 – 2013. *MMWR Morb Mortal Wkly Rep*. 2015;63:1245–1246.
288. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health-care workers after percutaneous exposure. *N Engl J Med*. 1997;337:1485–1490.
289. Chamberland ME, Bell DM. HIV transmission from health care worker to patient: what is the risk [editorial]? *Ann Intern Med*. 1992;116:871–873.
290. Gerberding J. Provider-to-patient HIV transmission: how to keep it exceedingly rare. *Ann Intern Med*. 1999;130:1–6.
291. Ciesielski C, Marianos D, Ou CY, et al. Transmission of human immunodeficiency virus in a dental practice. *Ann Intern Med*. 1992;116:798–805.
292. Centers for Disease Control and Prevention. Update: investigations of patients who have been treated by

HIV-infected healthcare workers—United States. *MMWR Morb Mortal Wkly Rep*. 1993;42:329–337.
293. Lot F, Séguier JC, Fégueux S, et al. Probable transmission of HIV from an orthopedic surgeon to a patient in France. *Ann Intern Med*. 1999;130:1–6.
294. Ou CY, Ciesielski CA, Myers G, et al. Molecular epidemiology of HIV transmission in a dental practice. *Science*. 1992;256:1165–1171.
295. Bell DM, Shapiro CN, Gooch BF. Preventing HIV transmission to patients during invasive procedures. *J Public Health Dent*. 1993;53:170–173.
296. Robert LM, Chamberland ME, Cleveland JL, et al. Investigations of patients of health care workers infected with HIV: the Centers for Disease Control and Prevention database. *Ann Intern Med*. 1995;122: 653–657.
297. Centers for Disease Control and Prevention. Patient exposures to HIV during nuclear medicine procedures. *MMWR Morb Mortal Wkly Rep*. 1992;41:575–578.
298. Centers for Disease Control and Prevention. HIV infection in two brothers receiving intravenous therapy for hemophilia. *MMWR Morb Mortal Wkly Rep*. 1992;41:228–231.
299. Centers for Disease Control and Prevention. Human immunodeficiency virus transmission in household settings—United States. *MMWR Morb Mortal Wkly Rep*. 1994;43:353–356.
300. Hersh BS, Popovici F, Apetrei RC, et al. Acquired immunodeficiency syndrome in Romania. *Lancet*. 1991;338:645–649.
301. Pokrovsky VV, Eramova EU. Nosocomial outbreak of HIV infection in Elista, USSR. Abstract W.A.O.5. Presented at the Fifth International Conference on AIDS. Montreal, June 4-9, 1989.
302. Chant K, Lowe D, Rubin G, et al. Patient-to-patient transmission of HIV in private surgical consulting rooms [letter]. *Lancet*. 1993;342:1548–1549.
303. Vernazza PL, Eron JJ, Cohen MS, et al. Detection and biologic characterization of infectious HIV-1 in semen of seropositive men. *AIDS*. 1994;8:1325–1329.
304. Fujikawa LS, Salahuddin SZ, Palestine AG, et al. Isolation of human T-lymphotropic virus type III from the tears of a patient with the acquired immunodeficiency syndrome. *Lancet*. 1985;2:529–530.
305. Ho DD, Rota TR, Schooley RT, et al. Isolation of HTL V-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med*. 1985;313:1493–1497.
306. Mundy DC, Schinazi RF, Gerber AR, et al. Human immunodeficiency virus isolated from amniotic fluid [letter]. *Lancet*. 1987;2:459–460.
307. Hill DR. HIV infection following motor vehicle trauma in central Africa. *JAMA*. 1989;261:3282–3283.
308. Torre D, Sampietro C, Ferraro G, et al. Transmission of HIV-1 infection via sports injury [letter]. *Lancet*. 1990;335:1105.
309. Stewart GJ, Tyler JPP, Cunningham AL, et al. Transmission of human T-cell lymphotropic virus type III (HTL V-III) by artificial insemination by donor. *Lancet*. 1985;2:581–585.
310. Chiasson MA, Stoneburner RL, Joseph SC. Human immunodeficiency virus transmission through artificial insemination. *J Acquir Immune Defic Syndr*. 1990;3:69–72.
311. Centers for Disease Control and Prevention. HIV-1 infection and artificial insemination with processed semen. *MMWR Morb Mortal Wkly Rep*. 1990;39:255–256.
312. Yeh CK, Handelman B, Fox PC, et al. Further studies of salivary inhibition of HIV-1 infectivity. *J Acquir Immune Defic Syndr*. 1992;5:898–903.
313. Wahn V, Kramer HH, Voit T, et al. Horizontal transmission of HIV infection between two siblings [letter]. *Lancet*. 1986;2:694.
314. Rogers MF, White CR, Sanders R, et al. Lack of transmission of human immunodeficiency virus from infected children to their household contacts. *Pediatrics*. 1990;85:210–214.
315. Saviteer SM, White GC, Cohen MS, et al. HTLV-III exposure during cardiopulmonary resuscitation [letter]. *N Engl J Med*. 1985;313:1606–1607.
316. Lifson AR. Do alternate modes for transmission of human immunodeficiency virus exist? A review. *JAMA*. 1988;259:1353–1356.
317. Gershon RRM, Vlahov D, Nelson KE. The risk of transmission of HIV-1 through nonpercutaneous, nonsexual modes—a review. *AIDS*. 1990;4:645–650.
318. Lusher JM, Operskalski EA, Aledort LM, et al. Risk of human immunodeficiency virus type 1 infection among sexual and nonsexual household contacts of persons with congenital clotting disorders. *Pediatrics*. 1991;88:242–249.
319. Centers for Disease Control and Prevention. Apparent transmission of human T-lymphotrophic virus type III/ lymphadenopathy-associated virus from a child to a mother providing health care. *MMWR Morb Mortal Wkly Rep*. 1986;35:76–79.
320. Centers for Disease Control and Prevention. HIV transmission between two adolescent brothers with hemophilia. *MMWR Morb Mortal Wkly Rep*. 1993;42:948–951.
321. Fitzgibbon JE, Gaur S, Frenkel LD, et al. Transmission from one child to another of human immunodeficiency virus type 1 with a zidovudine-resistance mutation. *N Engl J Med*. 1993;329:1835–1846.
322. Grint P, McEvoy M. Two associated cases of the acquired immunodeficiency syndrome (AIDS). *Commun Dis Rep*. 1985;42:4.
323. Srinivasan A, York D, Bohan C. Lack of HIV replication in arthropod cells [letter]. *Lancet*. 1987;1:1094–1095.
324. Miike L. Do Insects Transmit AIDS? Washington, DC: Health Program, Office of Technology Assessment, U.S. Congress; 1987:1-43.
325. Webb PA, Happ CM, Maupin GO, et al. Potential for insect transmission of HIV: experimental exposure of *Cimex hemipterus* and *Toxorhynchites amboinensis* to human immunodeficiency virus. *J Infect Dis*. 1989;160:970–977.
326. Castro KG, Lieb S, Jaffe HW, et al. Transmission of HIV in Belle Glade, Florida: lessons for other communities in the United States. *Science*. 1988;239:193–197.
327. Greenberg AE, Nguyen-Dinh P, Mann JM, et al. The association between malaria, blood transfusions, and HIV seropositivity in a pediatric population in Kinshasa, Zaire. *JAMA*. 1988;259:545–549.
328. Joint United Nations Programme on HIV/AIDS. 2008 Report on the Global AIDS Epidemic. http://www.unaids.org/sites/default/files/media_asset/jc1510_2008globalreport_en_0.pdf. Accessed April 12, 2019.
329. Mertens TE, Belsey E, Stoneburner RL, et al. Global estimates of HIV infections and AIDS: further heterogeneity in spread and impact. *AIDS*. 1995;9(suppl 1):S251.
330. European Centre for Disease Prevention and Control, WHO Regional Office for Europe. HIV/AIDS Surveillance in Europe 2018 – 2017 Data. Copenhagen: WHO Regional Office for Europe; 2018. https://ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2018-2017-data#no-link. Accessed October 1, 2018.
331. Field MG. HIV and AIDS in the Former Soviet Bloc. *N Engl J Med*. 2004;351:117–120.
332. Ompad DC, Wang J, Dumchev K, et al. Patterns of harm reduction service utilization and HIV incidence among people who inject drugs in Ukraine: a two-part latent profile analysis. *Int J Drug Policy*. 2017;43:7–15.
333. Torrey BB, Way PO. Seroprevalence of HIV in Africa: Winter 1990. CIR Staff Paper No. 55. Washington, DC: Center for International Research, U.S. Bureau of the Census; 1990.
334. Rwandan HIV Seroprevalence Study Group. Nationwide community based serological survey of HIV-1 and other human retrovirus infections in a central African country. *Lancet*. 1989;1:941–943.
335. Serwadda D, Wawer MJ, Musgrave SD, et al. HIV risk factors in three geographic strata of rural Rakai District, Uganda. *AIDS*. 1992;6:983–989.
336. Miotti PG, Dallabetta GA, Ndovi E, et al. HIV-1 and pregnant women: associated factors, prevalence, estimate of incidence and role in fetal wastage in Central Africa. *AIDS*. 1990;4:733–736.
337. Allen S, Lindan C, Serufilira A, et al. Human immunodeficiency virus infection in urban Rwanda: demographic and behavioral correlates in a representative sample of childbearing women. *JAMA*. 1991;226:1657–1663.
338. N'Galy B, Ryder RW. Epidemiology of HIV infection in Africa. *J Acquir Immune Defic Syndr*. 1988;1:551–558.
339. Dallabetta GA, Miotti PG, Chiphangwi JD, et al. High socioeconomic status is a risk factor for human immunodeficiency virus type 1 (HIV-1) infection but not for sexually transmitted diseases in women in Malawi: implications for HIV-1 control. *J Infect Dis*. 1993;167:36–42.
340. Deleted in review.
341. Lackritz EM. Prevention of HIV transmission by blood transfusion in the developing world: achievements and continuing challenges. *AIDS*. 1998;12(supplA):S81.
342. Marlink R, Kanki P, Thior I, et al. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. *Science*. 1994;265:1587–1590.
343. Berry N, Jaffar S, Schim van der Loeff M, et al. Low level viremia and high CD4% predict normal survival in a cohort of HIV type-2-infected villagers. *AIDS Res Hum Retroviruses*. 2002;18:1167–1173.
344. Leligdowicz A, Yindom LM, Onyango C, et al. Robust Gag-specific T cell responses characterize viremia control in HIV-2 infection. *J Clin Invest*. 2007;117:3067–3074.
345. Clavel F, Guetard D, Brun-Vezinet F, et al. Isolation of a new human retrovirus from West African patients with AIDS. *Science*. 1986;233:343–346.
346. Centers for Disease Control and Prevention. Testing for antibodies to human immunodeficiency virus type 2 in the United States. *MMWR Recomm Rep*. 1992;41(RR–12):1–9.
347. DeCock KM, Adjorlolo G, Ekpini E, et al. Epidemiology and transmission of HIV-2: why there is no HIV-2 pandemic. *JAMA*. 1993;270:2083–2086.
348. Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency (HIV)-2 infection. *Clin Infect Dis*. 2011;52:780–787.
349. O'Brien TR, George JR, Holmberg SD. Human immunodeficiency virus type 2 infection in the United States: epidemiology, diagnosis, and public health implications. *JAMA*. 1992;267:2775–2779.
350. Onorato IM, O'Brien TR, Schable CA, et al. Sentinel surveillance for HIV-2 infection in high-risk US populations. *Am J Public Health*. 1993;83:515–519.
351. Markovitz DM. Infection with the human immunodeficiency virus type 2. *Ann Intern Med*. 1993;118:211–218.
352. Hawes SE, Sow PS, Stern JE, et al. Lower levels of HIV-2 than HIV-1 in the female genital tract: correlates and longitudinal assessment of viral shedding. *AIDS*. 2008;22:2517–2525.
353. Poulsen AG, Kvinesdal BB, Aaby P, et al. Lack of evidence of vertical transmission of human immunodeficiency virus type 2 in a sample of the general population in Bissau. *J Acquir Immune Defic Syndr*. 1992;5:25–30.
354. Centers for Disease Control and Prevention. Compendium of HIV Prevention Interventions with Evidence for Effectiveness. Atlanta: CDC; 1999 [revised August 31, 2001].
355. Del Mistro A, Chotard J, Hall AJ, et al. HIV-1 and HIV-2 seroprevalence rates in mother-child pairs living in The Gambia (West Africa). *J Acquir Immune Defic Syndr*. 1992;5:19–24.
356. Adjorlolo-Johnson G, DeCock KM, Ekpini E, et al. Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. *JAMA*. 1994;272:462.
357. Dufoort G, Courouce AM, Ancelle-Park R, et al. No clinical signs 14 years after HIV-2 transmission via blood transfusion [letter]. *Lancet*. 1988;2:510.
358. Pepin J, Morgan G, Dunn D, et al. HIV-2-induced immunosuppression among asymptomatic West African prostitutes: evidence that HIV-2 is pathogenic, but less so than HIV-1. *AIDS*. 1991;5:1165–1172.
359. Marlink R, Thior I, Travers K, et al. Reduced virulence of HIV-2 compared to HIV-1. *Science*. 1994;265:1587.
360. Guyader M, Emerman M, Sonigo P, et al. Genome organization and transactivation of the human immunodeficiency virus type 2. *Nature*. 1987;326:662–669.
361. Alexander TS. Human immunodeficiency virus diagnostic testing: 30 years of evolution. *Clin Vaccine Immunol*. 2016;23:249–253.
362. Heneine W. Susceptibility of HIV-2, SIV and SHIV to various anti-HIV-1 compounds: implications for treatment and postexposure prophylaxis. *Antivir Ther*. 2004;9:57–65.
363. Landman R, Damond F, Gerbe J, et al. Immunological and therapeutic follow-up of HIV-1/HIV-2 dually seropositive patients. *AIDS*. 2009;23:426–428.
364. DiClemente RJ. Looking forward: future directions for HIV prevention research. In: Peterson JL, DiClemente RJ, eds. *Handbook of HIV Prevention*. New York: Kluwer Academic/Plenum; 2000:311–324.
365. Lyles CM, Kay LS, Crepaz N, et al. Best-evidence interventions: findings from a systematic review of HIV behavioral interventions for US populations at high risk, 2000-2004. *Am J Public Health*. 2007;97:133–143.
366. Centers for Disease Control and Prevention. Compendium of Evidence-Based HIV Behavioral Interventions. http://www.cdc.gov/hiv/prevention/research/compendium/rr/complete.html. Accessed June 1, 2013.
367. Hankins CA, de Zalduondo BO. Combination prevention: a deeper understanding of effective HIV prevention. *AIDS*. 2010;24(suppl 4):S70–S80.
368. Chen MS, Dellabeta G, Laga M, et al. A new deal in HIV prevention: lessons from the global approach. *Ann Intern Med*. 1994;120:340–341.
369. Johnson AM. Condoms and HIV transmission. *N Engl J Med*. 1994;331:391–392.
370. Centers for Disease Control and Prevention. Update: barrier protection against HIV infection and other sexually transmitted diseases. *MMWR Morb Mortal Wkly Rep*. 1993;42:589–591.

371. National Institute of Allergy and Infectious Diseases. Workshop Summary: Scientific Evidence on Condom Effectiveness for Sexually Transmitted Disease (STD) Prevention. www.niaid.nih.gov/dmid/stds/condomreport.pdf. Accessed July 20, 2001.
372. Thompson JL, Yager TJ, Martin JL. Estimated condom failure and frequency of condom use among gay men. *Am J Public Health*. 1993;83:1409–1413.
373. Weller SC. A meta-analysis of condom effectiveness in reducing sexually transmitted HIV. *Soc Sci Med*. 1993;36:1635–1644.
374. Saracco A, Musicco M, Nicolosi A, et al. Man-to-women sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. *J Acquir Immune Defic Syndr*. 1993;6:497–502.
375. De Vincenzi I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Heterosexual Transmission of HIV. *N Engl J Med*. 1994;331:341–346.
376. Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. *Fam Plann Perspect*. 1999;31:272–279.
377. Weller SC, Davis KR. Condom Effectiveness in Reducing Heterosexual HIV Transmission. [Cochrane Review]. Issue 1. Oxford: Update Software; 2004.
378. Silverman BG, Gross TP. Use and effectiveness of condoms during anal intercourse. *Sex Transm Dis*. 1997;24:11–17.
379. Rosenberg MJ, Gollub EL. Commentary: methods women can use that may prevent sexually transmitted disease, including HIV. *Am J Public Health*. 1992;82:1473–1478.
380. French P, Latka M, Gollub EL, et al. Female condoms as effective as male condoms in preventing sexually transmitted diseases. Abstract 60730. Presented at the Twelfth International Conference on AIDS. Geneva, June 28-July 3, 1998.
381. Fontan AL, Saba J, Chandelying V, et al. Protection against sexually transmitted diseases by granting sex workers in Thailand the choice of using the male or female condom: results from a randomized controlled trial. *AIDS*. 1998;12:1851–1859.
382. French PP, Latka M, Gollub EL, et al. Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. *Sex Transm Dis*. 2003;30:433–439.
383. Roddy R, Zekeng L, Ryan K, et al. A controlled trial of nonoxynol-9-film to reduce male-to-female transmission of sexually transmitted diseases. *N Engl J Med*. 1998;339:504–510.
384. Van Damme L. Advances in topical microbicides. Presented at the Thirteenth International AIDS Conference. Durban, South Africa, July 9-14, 2000.
385. Kreiss J, Ngugi E, Holmes K, et al. Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *JAMA*. 1992;268:477–482.
386. Louv WC, Austin H, Alexander WJ, et al. A clinical trial of nonoxynol-9 for preventing gonococcal and chlamydial infections. *J Infect Dis*. 1988;158:513–523.
387. Roddy RE, Zekeng L, Ryan KA, et al. Effect of nonoxynol-9 gel on urogenital gonorrhea and chlamydial infection—a randomized controlled trial. *JAMA*. 2002;287:1117–1122.
388. Stone KM, Peterson HB. Spermicides, HIV, and the vaginal sponge [editorial]. *JAMA*. 1992;268:521–523.
389. Centers for Disease Control and Prevention. Nonoxynol-9 spermicide contraception use—United States, 1999. *MMWR Morb Mortal Wkly Rep*. 2002;51:389–392.
390. Feldblum PJ, Adeiga A, Bakare R, et al. SAVVY vaginal gel (C31G) for prevention of HIV infection: a randomized controlled trial in Nigeria. *PLoS ONE*. 2008;3:e1474.
391. Van Damme L, Govinden R, Mirembe FM, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. *N Engl J Med*. 2008;359:463–472.
392. Abdool KS, Coletti A, Richardson B, et al. Safety and effectiveness of vaginal microbicides BufferGel and 0.5% PRO 2000/5 Gel for the prevention of HIV infection in women: results of the HPTN 035 Trial. *AIDS*. 2011;25:957–966.
393. Abdool Karim Q, Abbdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329:1168–1174.
394. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2015;372:509–519.
395. Roper WL, Peterson HB, Curran JW. Commentary: condoms and HIV/STD prevention—clarifying the message. *Am J Public Health*. 1993;83:501–503.
396. Centers for Disease Control and Prevention. Heterosexual behaviors and factors that influence condom use among patients attending a sexually transmitted disease clinic—San Francisco. *MMWR Morb Mortal Wkly Rep*. 1990;39:685–689.
397. Peterson JL, Coates TJ, Catania JA, et al. High-risk sexual behavior and condom use among gay and bisexual African-American men. *Am J Public Health*. 1992;82:1490–1494.
398. Catania JA, Coates TJ, Kegeles S, et al. Condom use in multiethnic neighborhoods of San Francisco: the population-based AMEN (AIDS in Multiethnic Neighborhoods) study. *Am J Public Health*. 1991;81:284–287.
399. Sawires SR, Dworkin SL, Fiamma A, et al. Male circumcision and HIV/AIDS: challenges and opportunities. *Lancet*. 2007;369:708–713.
400. Marks G, Richardson JL, Maldonado N. Self-disclosure of HIV infection to sexual partners. *Am J Public Health*. 1991;81:1321–1323.
401. Landis SE, Schoenbach VJ, Weber DJ, et al. Results of a randomized trial of partner notification in cases of HIV infection in North Carolina. *N Engl J Med*. 1992;326:101–106.
402. Bayer R, Toomey KE. HIV prevention and the two faces of partner notification. *Am J Public Health*. 1992;82:1158–1164.
403. Pavia AT, Benyo M, Niler L, et al. Partner notification for control of HIV: results after 2 years of a statewide program in Utah. *Am J Public Health*. 1993;83:1418–1424.
404. Golen MR. HIV partner notification: a neglected prevention intervention. *Sex Transm Dis*. 2002;29:472–475.
405. Pilcher CD, Fiscus SA, Nguyen TQ, et al. Detection of acute infections during HIV testing in North Carolina. *N Engl J Med*. 2005;352:1873–1883.
406. Macke BA, Maher JE. Partner notification in the United States: an evidence-based review. *Am J Prev Med*. 1999;17:230–242.
407. Giesecke J, Ramstedt K, Granath F, et al. Efficacy of partner notification for HIV infection. *Lancet*. 1991;338:1096–1100.
408. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomized controlled trial. *Lancet*. 1995;346:530–536.
409. Wawer MJ, Sewankambo NK, Serwadda D, et al. Control of sexually transmitted diseases and AIDS prevention in Uganda: a randomized community trial. *Lancet*. 1999;353:525–535.
410. Centers for Disease Control and Prevention. US Public Health Service: Preexposure Prophylaxis for the Prevention of HIVB Infection in the United States – 2017 Update: A Clinical Practice Guideline; published March 2018. https://www.cdc.gov/hiv/prep/cdc-hiv-prep-guidelines-2017.pdf.
411. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587–2599.
412. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis*. 2014;14:820–829.
413. Beaten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367:399–410.
414. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012;367:411–422.
415. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012;367:423–434.
416. Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373:48–57.
417. The Twin Epidemics of Substance Use and HIV. Washington, DC: National Commission on AIDS; 1991.
418. Metzger DS, Navaline H, Woody GE. Drug-abuse treatment as AIDS prevention. *Public Health Rep*. 1998;113(suppl 1):S97–S106.
419. Gossop M, Marsden J, Stewart D, et al. Reduced injection risk and sexual risk behaviours after drug misuse treatment: results from the National Treatment Outcome Research Study. *AIDS Care*. 2002;14:77–93.
420. Metzger DS, Navaline H. HIV prevention among injection drug users: the need for integrated models. *J Urban Health*. 2003;80:iii59–iii66.
421. Centers for Disease Control and Prevention. Update: reducing HIV transmission in intravenous-drug users not in drug treatment—United States. *MMWR Morb Mortal Wkly Rep*. 1990;39:97–101.
422. Centers for Disease Control and Prevention. Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted infections and tuberculosis for persons who use drugs illicitly: summary guidance from CDC and the U.S. Department of Health and Human Services. *MMWR Morb Mortal Wkly Rep*. 2012;61:1–43.
423. Groseclose SL, Weinstein B, Jones S, et al. Legal purchase of clean needles and syringes in Connecticut: do they make a difference? Abstract POD274185. In: Abstracts of the Ninth International Conference on AIDS/Fourth STD World Congress. Vol. 2. Berlin: International AIDS Society; 1993:915.
424. U.S. General Accounting Office (USGAO). Needle Exchange Programs: Research Suggests Promise as an AIDS Prevention Strategy. Report to the Chairman, Select Committee on Narcotics Abuse and Control, House of Representatives. Washington, DC: USGAO, Human Resources Division; 1993.
425. Centers for Disease Control and Prevention. Use of bleach for disinfection of drug injection equipment. *MMWR Morb Mortal Wkly Rep*. 1993;42:418–419.
426. Yancovitz SR, Des Jarlais DC, Peyser NP, et al. A randomized trial of an interim methadone maintenance clinic. *Am J Public Health*. 1991;81:1185–1191.
427. Coyle SL, Needle RH, Normand J. Outreach-based HIV prevention for injecting drug users: a review of published outcome data. *Public Health Rep*. 1998;113(suppl 1):S19–S30.
428. Latkin CA. Outreach in natural settings: the use of peer leaders for HIV prevention among injecting drug users' networks. *Public Health Rep*. 1998;113(suppl 1):S151–S159.
429. Stephens RC, Feucht TE, Roman SW. Effects of an intervention program on AIDS-related drug and needle behavior among intravenous drug users. *Am J Public Health*. 1991;81:568–571.
430. Negigus A, Friedman SR, Curtis R, et al. Relevance of drug injectors' social networks and risk networks for understanding and preventing HIV infection. *Soc Sci Med*. 1994;38:67–78.
431. Des Jarlais DC, Friedman SR, Friedman P, et al. HIV/AIDS related behavior change among injecting drug users in different national settings. *AIDS*. 1995;9:611–617.
432. Hagan H, McGough JP, Thiede H, et al. Reduced injection frequency and increased entry and retention in substance abuse treatment associated with needle-exchange participation in Seattle drug injectors. *J Subst Abuse Treat*. 2000;19:247–252.
433. Strathdee SA, Celentano DD, Shah N, et al. Needle exchange attendance and health care utilization promote entry into detoxification. *J Urban Health*. 1999;76:448–460.
434. School of Public Health, University of California, Berkeley and the Institute for Health Policy Studies, University of California, San Francisco. The Public Health Impact of Needle Exchange Programs in the United States and Abroad: Summary, Conclusions, and Recommendations. Report prepared for the Centers for Disease Control and Prevention. Atlanta: Centers for Disease Control and Prevention; 1993.
435. Vlahov D, Junge B. The role of needle exchange programs in HIV prevention. *Public Health Rep*. 1998;113(suppl 1):S75–S80.
436. Hurley S, Jolley D, Kaldor J. Effectiveness of needle-exchange programmes for prevention of HIV infection. *Lancet*. 1997;349:1797.
437. Des Jarlais D, Perlis T, Arasteh K, et al. HIV incidence among injection drug users in New York City, 1990 to 2002: use of serologic test algorithm to assess expansion of HIV prevention services. *Am J Public Health*. 2005;95:1539–1544.
438. Reddon H, Marshall BD, Milloy MJ. Elimination of HIV transmission through novel and established prevention strategies among people who inject drugs. *Lancet HIV*. 2019;6:e128–e136.
439. Dodd RY, Notari EP IV, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion*. 2002;42:975–979.
440. Centers for Disease Control and Prevention. Semen banking, organ and tissue transplantation, and HIV antibody testing. *MMWR Morb Mortal Wkly Rep*. 1988;37:57–58, 63.
441. Centers for Disease Control and Prevention. Transmission of HIV through bone transplantation: case report and public health recommendations. *MMWR Morb Mortal Wkly Rep*. 1988;37:597–599.
442. Katzenstein TL, Dickmeiss E, Aladdin H, et al. Failure to develop HIV infection after receipt of HIV-contaminated

blood and postexposure prophylaxis. *Ann Intern Med*. 2000;133:31–34.
443. Bell DM. Human immunodeficiency virus transmission in health care settings: risk and risk reduction. *Am J Med*. 1991;91(suppl 3B):S294–S300.
444. Do AN, Ciesielski CA, Metler RP, et al. Occupationally acquired human immunodeficiency virus (HIV) infection: national case surveillance data during 20 years of the HIV epidemic in the United States. *Infect Control Hosp Epidemiol*. 2003;24:86–96.
445. Centers for Disease Control and Prevention. Recommendations for prevention of HIV transmission in healthcare settings. *MMWR Morb Mortal Wkly Rep*. 1987;36(suppl 2S):S1–S18.
446. Centers for Disease Control and Prevention. Public Health Service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine postexposure use. *MMWR Morb Mortal Wkly Rep*. 1990;39:1–14.
447. Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR–14):1–17.
448. Institute of Medicine. *Reducing the Odds: Preventing Perinatal Transmission of HIV in the United States*. Washington, DC: National Academy Press; 1998.
449. Lindsay MK, Peterson HB, Feng TI, et al. Routine antepartum human immunodeficiency virus infection screening in an innercity population. *Obstet Gynecol*. 1989;74:289–294.
450. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*. 1998;339:1409–1414.
451. Centers for Disease Control and Prevention. Administration of zidovudine during late pregnancy and delivery to prevent perinatal HIV transmission—Thailand, 1996-1998. *MMWR Morb Mortal Wkly Rep*. 1998;47:1551–1554.
452. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. http://aidsinfo.nih.gov/contentfiles/lyguidelines/PerinatalGL.pdf. Accessed June 1, 2013.
453. Cooper ER, Charurat M, Mofenson LM, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1 infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr Hum Retrovirol*. 2002;29:484–494.
454. Centers for Disease Control and Prevention. Recommendations for assisting in the prevention of perinatal transmission of human T-lymphotrophic type III/lymphadenopathy-associated virus. *MMWR Morb Mortal Wkly Rep*. 1985;34:721–726, 731–732.
455. World Health Organization. Consensus statement from the WHO/UNICEF consultation on HIV transmission and breastfeeding. *Wkly Epidemiol Rec*. 1992;67:177–179.
456. United Nations AIDS Program. HIV and infant feeding: an interim statement. *Wkly Epidemiol Rec*. 1996;71:289–291.
457. Iliff PJ, Piwoz EG, Tavengwa NV, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS*. 2005;19:699–708.
458. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2002;359:1178–1186.
459. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of HIV-1. *J Infect Dis*. 2003;187:725–735.
460. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce HIV-1 transmission. *N Engl J Med*. 2008;359:119–129.
461. Centers for Disease Control and Prevention. Advancing HIV prevention: new strategies for a changing epidemic—United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52:329–332.
462. Janssen RS, Holtgrave DR, Valdiserri RO, et al. The serostatus approach to fighting the HIV epidemic: prevention intervention strategies for infected individuals. *Am J Public Health*. 2001;91:1019–1024.
463. Valdiserri RO, Holtgrave DR, Brackbill RM. American adults' knowledge of HIV testing availability. *Am J Public Health*. 1993;83:525–528.
464. Kaiser Family Foundation. Percentage of Persons Aged 18 – 64 Who Reported Ever Receiving an HIV Test. https://www.kff.org/other/state-indicator/hiv-testing-rate-ever-tested/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D. Accessed October 30, 2018.
465. Centers for Disease Control and Prevention. Notice to readers: approval of a new rapid test for HIV antibody. *MMWR Morb Mortal Wkly Rep*. 2002;51:1051–1052.
466. Wesolowski LG, MacKellar DA, Facente SN, et al. Post-marketing surveillance of OraQuick whole blood and oral fluid rapid testing. *AIDS*. 2006;20:1661–1666.
467. Delaney KP, Branson BM, Uniyal A, et al. Performance of an oral fluid rapid HIV-1/2 test: experience from four CDC studies. *AIDS*. 2006;20:1655–1660.
468. Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med*. 2005;352:570–585.
469. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States—an analysis of cost-effectiveness. *N Engl J Med*. 2005;352:586–595.
470. Chou R, Huffman LH, Fu R, et al; US Preventive Services Task Force. Screening for HIV: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2005;143:55–73.
471. Moyer VA, U.S. Preventive Services Task Force. Summaries for patients: screening for HIV: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2013;159:1–36.
472. Painter TM. Voluntary counseling and testing for couples: a high-leverage intervention for HIV/AIDS prevention in sub-Saharan Africa. *Soc Sci Med*. 2001;53:1397–1411.
473. Sullivan PS, White D, Rosenberg ES, et al. Safety and acceptability of couples HIV testing and counseling for US men who have sex with men: a randomized prevention study. *J Int Assoc Provid AIDS Care*. 2014;13:135–144.
474. Centers for Disease Control and Prevention. Recommendations for preventing transmission of human immunodeficiency virus and hepatitis B virus to patients during exposure-prone invasive procedures. *MMWR Morb Mortal Wkly Rep*. 1991;40:1–9.
475. Gardner LI, Metsch LR, Anderson-Mahoney P, et al. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. *AIDS*. 2005;19:423–431.
476. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care Panel. *Ann Intern Med*. 2012;156:817–833.
477. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed November 25, 2018.
478. Fauci AS. An HIV vaccine is essential for ending the HIV/AIDS pandemic. *JAMA*. 2017;318:1535–1536.
479. Barouch DH. Challenges in the development of an HIV-1 vaccine. *Nature*. 2008;455:613–619.
480. Cohen YZ, Dolin R. Novel HIV vaccine strategies: overview and perspective. *Ther Adv Vaccines*. 2013;1:99–112.
481. Villinger F, Brar SS, Brice GT, et al. Immune and hematopoietic parameters in HIV-1 infected chimpanzees during clinical progression toward AIDS. *J Med Primatol*. 1997;26:11–18.
482. Novembre FJ, Saucier M, Anderson DC, et al. Development of AIDS in a chimpanzee infected with human immunodeficiency virus type 1. *J Virol*. 1997;71:4086–4091.
483. Letvin NL, King NW. Immunologic and pathologic manifestations of the infection of rhesus monkeys with simian immunodeficiency virus of macaques. *J Acquir Immune Defic Syndr*. 1990;3:1023–1040.
484. Desrosiers RC. The simian immunodeficiency viruses. *Annu Rev Immunol*. 1990;8:557–558.
485. Kodama T, Wooley DP, Naidu YM, et al. The significance of premature stop codons in env of SIV. *J Virol*. 1989;63:4709–4714.
486. Moldt B, Rakasz EG, Schultz N, et al. Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo. *Proc Natl Acad Sci USA*. 2012;109:18921–18925.
487. Frey G, Peng H, Rits-Volloch S, et al. A fusion-intermediate state of HIV-1 gp41 targeted by broadly neutralizing antibodies. *Proc Natl Acad Sci USA*. 2008;105:3739–3744.
488. Barouch DH, Liu J, Li H, et al. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. *Nature*. 2012;482:89–93.
489. Letvin NL, Rao SS, Montefiori DC, et al. Immune and genetic correlates of vaccine protection against mucosal infection by SIV in monkeys. *Sci Transl Med*. 2011;3:81ra36.
490. Letvin NL, Montefiori DC, Yasutomi Y, et al. Potent, protective anti-HIV immune responses generated by bimodal HIV envelope DNA plus protein vaccination. *Proc Natl Acad Sci USA*. 1997;94:9378–9383.
491. Earl PL, Sugiura W, Montefiori DC, et al. Immunogenicity and protective efficacy of oligomeric human immunodeficiency virus type 1 gp140. *J Virol*. 2001;75:645–653.
492. Cho MW, Kim YB, Lee MK, et al. Polyvalent envelope glycoprotein vaccine elicits a broader neutralizing antibody response but is unable to provide sterilizing protection against heterologous simian/human immunodeficiency virus infection in pigtailed macaques. *J Virol*. 2001;75:2224–2234.
493. Seth A, Ourmanov I, Schmitz JE, et al. Immunization with a modified vaccinia virus expressing simian immunodeficiency virus (SIV) Gag-Pol primes for an anamnestic Gag-specific cytotoxic T-lymphocyte response and is associated with reduction of viremia after SIV challenge. *J Virol*. 2000;74:2502–2509.
494. Ourmanov I, Brown CR, Moss B, et al. Comparative efficacy of recombinant modified vaccinia virus Ankara expressing simian immunodeficiency virus (SIV) Gag-Pol and/or Env in macaques challenged with pathogenic SIV. *J Virol*. 2000;74:2740–2751.
495. Amara RR, Villinger F, Altman JD, et al. Control of a mucosal challenge and prevention of clinical AIDS in rhesus monkeys by a multiprotein DNA/MVA vaccine. *Science*. 2001;292:69–74.
496. Amara RR, Villinger F, Staprans SI, et al. Different patterns of immune responses but similar control of a simian-human immunodeficiency virus 89.6P mucosal challenge by modified vaccinia virus Ankara (MVA) and DNA/MVA vaccines. *J Virol*. 2002;76:7625–7631.
497. Barouch DH, Santra S, Kuroda MJ, et al. Reduction of simian-human immunodeficiency virus 89.6P viremia in rhesus monkeys by recombinant modified vaccinia virus Ankara vaccination. *J Virol*. 2001;75:5151–5158.
498. Vaccari M, Keele BF, Bosinger SE, et al. Protection afforded by an HIV vaccine candidate in macaques depends on the dose of SIVmac251 at challenge exposure. *J Virol*. 2013;87:3538–3548.
499. Shiver JW, Emini EA. Recent advances in the development of HIV-1 vaccines using replication-incompetent adenovirus vectors. *Annu Rev Med*. 2004;55:355–372.
500. Shiver JW, Fu TM, Chen L, et al. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature*. 2002;415:331–335.
501. Barouch DH, Alter G, Broge T, et al. Protective efficacy of adenovirus/protein vaccines against SIV challenges in rhesus monkeys. *Science*. 2015;349:320–324.
502. Hansen SG, Ford JC, Lewis MS, et al. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature*. 2011;473:523–527.
503. Ackers ML, Parekh B, Evans TG, et al. Human immunodeficiency virus (HIV) seropositivity among uninfected HIV vaccine recipients. *J Infect Dis*. 2003;187:879–886.
504. Fuchs J, Durham M, McLellan-Lemal E, et al. Negative social impacts among volunteers in an HIV vaccine efficacy trial. *J Acquir Immune Defic Syndr*. 2007;46:362–368.
505. Khurana S, Needham J, Park S, et al. Novel approach for differential diagnosis of HIV infections in the face of vaccine-generated antibodies: utility for detection of diverse HIV-1 subtypes. *J Acquir Immune Defic Syndr*. 2006;43:304–312.
506. Silbermann B, Tod M, Desaint C, et al. Short communication: long-term persistence of vaccine-induced HIV seropositivity among healthy volunteers. *AIDS Res Hum Retroviruses*. 2008;24:1445–1448.
507. Cooper CJ, Metch B, Dragavon J, et al. Vaccine-induced HIV seropositivity/reactivity in noninfected HIV vaccine recipients. *JAMA*. 2010;304:275–283.
508. Bartlett JG, Branson BM, Fenton K, et al. Opt-out testing for human immunodeficiency virus in the United States: progress and challenges. *JAMA*. 2008;300:945–951.
509. Quirk EK, Mogg R, Brown DD, et al. HIV seroconversion without infection after receipt of adenovirus-vectored HIV type 1 vaccine. *Clin Infect Dis*. 2008;47:1593–1599.
510. Dolin R, Graham B, Greenberg S, et al; and the AIDS Vaccine Clinical Trials Network. Safety and immunogenicity of an HIV-1 recombinant gp160 candidate vaccine in humans. *Ann Intern Med*. 1991;114:119–127.
511. Buchbinder SP, Mehrotra DV, Duerr A, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine

(the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet*. 2008;372:1881–1893.
512. McElrath MJ, De Rosa SC, Moodie Z, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. *Lancet*. 2008;372:1894–1905.
513. Flynn NM, Forthal DN, Harro CD, et al. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *J Infect Dis*. 2005;191:654–665.
514. Gilbert PB, Peterson ML, Follmann D, et al. Correlation between immunologic responses to a recombinant glycoprotein 120 vaccine and incidence of HIV-1 infection in a phase 3 HIV-1 preventive vaccine trial. *J Infect Dis*. 2005;191:666–677.
515. Pitisuttithum P, Gilbert P, Gurwith M, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. *J Infect Dis*. 2006;194:1661–1671.
516. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 2009;361:2209–2220.
517. Gray GE, Allen M, Moodie Z, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomized, placebo-controlled test-of-concept phase 2b study. *Lancet Infect Dis*. 2011;11:507–515.
518. Hammer SM, Sobieszczyk ME, Janes H, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med*. 2013;369:2083–2092.
519. Selwyn PA, Feingold AR, Hartel D, et al. Increased risk of bacterial pneumonia in HIV-infected intravenous drug users without AIDS. *AIDS*. 1988;2:167–172.
520. Janoff EN, Breiman RF, Daley CL, et al. Pneumococcal disease during HIV infection: epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med*. 1992;117:314–324.
521. Goepfert PA, Tomaras GD, Horton H, et al. Durable HIV-1 antibody and T-cell responses elicited by an adjuvanted multiprotein recombinant vaccine in uninfected human volunteers. *Vaccine*. 2007;25:510–518.
522. Gorse GJ, Keefer MC, Belshe RB, et al. A dose-ranging study of a prototype synthetic HIV-1 V3 branched peptide vaccine. *J Infect Dis*. 1996;173:330–339.
523. Sarin PS, Mora CA, Naylor PH, et al. HIV-1 p17 synthetic peptide vaccine HGP-30: induction of immune response in human subjects and preliminary evidence of protection against HIV challenge in SCID mice. *Cell Mol Biol*. 1995;41:401–407.
524. Kahn JO, Stites DP, Scillian J, et al. A phase I study of HGP-30, a 30 amino acid subunit of the human immunodeficiency virus (HIV) p17 synthetic peptide analogue subunit vaccine in seronegative subjects. *AIDS Res Hum Retroviruses*. 1992;8:1321–1325.
525. Naylor PH, Sztein MB, Wada S, et al. Preclinical and clinical studies on immunogenicity and safety of the HIV-1 p17 based synthetic peptide AIDS vaccine: HGP-30-KLH. *Int J Immunopharmacol*. 1991;13(suppl 1):117–127.
526. Li D, Forrest BD, Li Z, et al. International clinical trials of HIV vaccines, II. Phase I trial of an HIV-1 synthetic peptide vaccine evaluating an accelerated immunization schedule in Yunnan, China. *Asian Pac J Allergy Immunol*. 1997;15:105–113.
527. Kelleher AD, Emery S, Cunningham P, et al. Safety and immunogenicity of UBI HIV-1 (MN) octameric V3 peptide vaccine administered by subcutaneous injection. *AIDS Res Hum Retroviruses*. 1997;13:29–32.
528. Phanuphak P, Teeratakulpixarn S, Sarangbin S, et al. International clinical trials of HIV vaccines, I. Phase I trial of an HIV-1 synthetic peptide vaccine in Bangkok, Thailand. *Asian Pac J Allergy Immunol*. 1997;15:41–48.
529. Gorse GJ, Baden LR, Wecker M, et al. Safety and immunogenicity of cytotoxic T-lymphocyte polyepitope, DNA plasmid (EP HIV-1090) vaccine in healthy, human immunodeficiency virus type 1 (HIV-1)-uninfected adults. *Vaccine*. 2008;26:215–223.
530. Spearman P, Kalams S, Elizaga M, et al. Safety and immunogenicity of a CTL multiepitope peptide vaccine for HIV with or without GM-CSF in a phase I trial. *Vaccine*. 2009;27:243–249.
531. Cooney EL, Collier AC, Greenberg PD, et al. Safety and immunologic response to a recombinant vaccinia virus vaccine expressing HIV envelope glycoprotein. *Lancet*. 1991;337:567–572.
532. Graham BS, Belshe RB, Clements ML, et al. Vaccination of vaccinia-naïve adults with human immunodeficiency virus type 1 gp160 recombinant vaccinia virus in a blinded, controlled randomized clinical trial. *J Infect Dis*. 1992;166:244–252.
533. Walsh SR, Dolin R. Vaccinia viruses: vaccines against smallpox and vectors against infectious diseases and tumors. *Expert Rev Vaccines*. 2011;10:1221–1240.
534. Elizaga ML, Vasan S, Marovich MA, et al. Prospective surveillance for cardiac adverse events in healthy adults receiving modified vaccinia Ankara vaccines: a systematic review. *PLoS ONE*. 2013;8:e54407.
535. Keefer MC, McElrath MJ, Weinhold K, et al. A phase I trial of vaccinia-env/gag/pol (TBC-3B) given by alternative routes, boosted with rgp120MN [AVEG 014C]. Poster presentation. Twelfth World AIDS Conference. Geneva, Switzerland, June 28-July 3, 1998.
536. Graham BS, Gorse GJ, Schwartz DH, et al. Determinants of antibody response after recombinant gp160 boosting in vaccinia-naïve volunteers primed with gp160-recombinant vaccinia virus. *J Infect Dis*. 1994;170:782–786.
537. Zagury D, Bernard J, Cheynier R, et al. A group specific anamnestic immune reaction against HIV-1 induced by a candidate vaccine against AIDS. *Nature*. 1988;332:728–731.
538. Stanhope PE, Clements ML, Siliciano RF. Human CD4+ cytolytic T lymphocyte responses to a human immunodeficiency virus type 1 gp160 subunit vaccine. *J Infect Dis*. 1993;168:92–100.
539. Clements-Mann ML, Weinhold K, Matthews TJ, et al. Immune responses to human immunodeficiency virus (HIV) type 1 induced by canarypox expressing HIV-1MN gp120, HIV-1SF-2 recombinant gp120, or both vaccines in seronegative adults. *J Infect Dis*. 1998;177:1230–1246.
540. Pialoux G, Excler JL, Riviere Y, et al. A prime-boost approach to HIV preventive vaccine using a recombinant canarypox virus expressing glycoprotein 160 (MN/LAI). *AIDS Res Hum Retroviruses*. 1995;11:373–381.
541. Fleury B, Janvier G, Pialoux G, et al. Memory cytotoxic T lymphocyte responses in human immunodeficiency virus type I (HIV-1)-negative volunteers immunized with a recombinant canarypox expressing gp160 of HIV-1 and boosted with a recombinant gp160. *J Infect Dis*. 1996;174:734–738.
542. Guimaraes-Walker A, Mackie N, McCormack S, et al. Lessons from IAVI-006, a Phase I clinical trial to evaluate the safety and immunogenicity of the pTHr HIVA DNA and MVA HIVA vaccines in a prime-boost strategy to induce HIV-1 specific T-cell responses in healthy volunteers. *Vaccine*. 2008;26:6671–6677.
543. Jaoko W, Nakwagala FN, Anzala O, et al. Safety and immunogenicity of recombinant low-dosage HIV-1 A vaccine candidates vectored by plasmid pTHr DNA or modified vaccinia virus Ankara (MVA) in humans in East Africa. *Vaccine*. 2008;26:2788–2795.
544. Mulligan MJ, Russell ND, Celum C, et al. Excellent safety and tolerability of the human immunodeficiency virus type 1 pGA2/JS2 plasmid DNA priming vector vaccine in HIV type 1 uninfected adults. *AIDS Res Hum Retroviruses*. 2006;22:678–683.
545. Peters BS, Jaoko W, Vardas E, et al. Studies of a prophylactic HIV-1 vaccine candidate based on modified vaccinia virus Ankara (MVA) with and without DNA priming: effects of dosage and route on safety and immunogenicity. *Vaccine*. 2007;25:2120–2127.
546. Sandstrom E, Nilsson C, Hejdeman B, et al. Broad immunogenicity of a multigene, multiclade HIV-1 DNA vaccine boosted with heterologous HIV-1 recombinant modified vaccinia virus Ankara. *J Infect Dis*. 2008;198:1482–1490.
547. Vasan S, Schlesinger SJ, Chen Z, et al. Phase 1 safety and immunogenicity of ADMVA, a multigenic, modified vaccinia Ankara-HIV-1 B'/C candidate vaccine. *PLoS ONE*. 2010;5:e8816.
548. Walsh SR, Seaman MS, Grandpre LE, et al. Impact of anti-orthopoxvirus neutralization antibodies induced by a heterologous prime-boost HIV-1 vaccine on insert-specific immune responses. *Vaccine*. 2012;31:114–119.
549. Harari A, Bart PA, Stohr W, et al. An HIV-1 clade C DNA prime, NYVAC boost vaccine regimen induces reliable, polyfunctional, and long-lasting T cell responses. *J Exp Med*. 2008;205:63–77.
550. Bart PA, Goodall R, Barber T, et al. EV01: a phase I trial in healthy HIV negative volunteers to evaluate a clade C HIV vaccine, NYVAC-C undertaken by the EuroVacc Consortium. *Vaccine*. 2008;26:3153–3161.
551. McCormack S, Stohr W, Barber T, et al. EV02: a Phase I trial to compare the safety and immunogenicity of HIV DNA-C prime-NYVAC-C boost to NYVAC-C alone. *Vaccine*. 2008;26:3162–3174.
552. Kibler KV, Gomez CE, Perdiguero B, et al. Improved NYVAC-based vaccine vectors. *PLoS ONE*. 2011;6:e25674.
553. Perreau M, Welles HC, Harari A, et al. DNA/NYVAC vaccine regimen induces HIV-specific CD4 and CD8 T-cell responses in intestinal mucosa. *J Virol*. 2011;85:854–862.
554. Abbink P, Lemckert AA, Ewald BA, et al. Comparative seroprevalence and immunogenicity of six rare serotype recombinant adenovirus vaccine vectors from subgroups B and D. *J Virol*. 2007;81:4654–4663.
555. Vogels R, Zuijdgeest D, van Rijnsoever R, et al. Replication-deficient human adenovirus type 35 vectors for gene transfer and vaccination: efficient human cell infection and bypass of preexisting adenovirus immunity. *J Virol*. 2003;77:8263–8271.
556. Barouch DH, Pau MG, Custers JH, et al. Immunogenicity of recombinant adenovirus serotype 35 vaccine in the presence of preexisting anti-Ad5 immunity. *J Immunol*. 2004;172:6290–6297.
557. Baden LR, Walsh SR, Seaman MS, et al. First-in-human evaluation of the safety and immunogenicity of a recombinant adenovirus serotype 26 HIV-1 Env vaccine (IPCAVD001). *J Infect Dis*. 2013;207:240–247.
558. Barouch DH, Liu J, Peter L, et al. Characterization of humoral and cellular immune responses elicited by a recombinant adenovirus serotype 26 HIV-1 Env vaccine in healthy adults (IPCAVD 001). *J Infect Dis*. 2013;207:248–256.
559. Keefer MC, Gilmour J, Hayes P, et al. A phase I double blind, placebo-controlled, randomized study of a multigenic HIV-1 adenovirus subtype 35 vector vaccine in healthy uninfected adults. *PLoS ONE*. 2012;7:e41936.
560. Boyer JD, Cohen AD, Vogt S, et al. Vaccination of seronegative volunteers with a human immunodeficiency virus type 1 env/rev DNA vaccine induces antigen specific proliferation and lymphocyte production of B chemokines. *J Infect Dis*. 2000;181:476–483.
561. Mulligan M, Goepfert P, Corey L, et al. AVEG 031: Phase 1 evaluation of a gag-pol facilitated DNA vaccine for HIV-1 prevention. Poster presentation. Twelfth World AIDS Conference. Geneva, Switzerland, June 28-July 3, 1998.
562. Emini E. A potential HIV vaccine using a replication defective adenoviral vaccine vector. Presented at the Ninth Conference on Retroviruses and Opportunistic Infections, session 12. Seattle, WA, February 24-28, 2002.
563. Catanzaro AT, Roederer M, Koup RA, et al. Phase I clinical evaluation of a six-plasmid multiclade HIV-1 DNA candidate vaccine. *Vaccine*. 2007;25:4085–4092.
564. Eller MA, Eller LA, Opollo MS, et al. Induction of HIV-specific functional immune responses by a multiclade HIV-1 DNA vaccine candidate in healthy Ugandans. *Vaccine*. 2007;25:7737–7742.
565. Kahn JO, Sinangil F, Baenziger J, et al. Clinical and immunologic responses to human immunodeficiency virus (HIV) type 1 SF2 gp120 subunit vaccine combined with MF59 adjuvant with or without muramyl tripeptide dipalmitoyl phosphatidyl-ethanolamine in non-HIV-infected human volunteers. *J Infect Dis*. 1994;170:1288–1291.
566. Schwartz DH, Gorse G, Clements ML, et al. Induction of HIV-1 neutralising and syncytium-inhibiting antibodies in uninfected recipients of HIV-IIIB rgp120 subunit vaccine. *Lancet*. 1993;342:69–73.
567. Belshe RB, Graham BS, Keefer MC, et al. Neutralizing antibodies to HIV-1 in seronegative volunteers immunized with recombinant gp120 from the MN strain of HIV-1. *JAMA*. 1994;272:475–480.
568. Gorse GJ, McElrath MJ, Matthews TJ, et al. Modulation of immunologic responses to HIV-1 recombinant gp160 vaccine by dose and schedule of administration. *Vaccine*. 1998;16:493–506.
569. Gorse GJ, Corey L, Patel GB, et al. HIVMN recombinant glycoprotein 160 vaccine-induced cellular and humoral immunity boosted by HIV-1MN recombinant glycoprotein 120 vaccine. *AIDS Res Hum Retroviruses*. 1999;2:115–132.
570. Keefer MC, Graham BS, Belshe RB, et al. Studies of high doses of a human immunodeficiency virus type 1 recombinant glycoprotein 160 candidate vaccine in HIV-1 seronegative humans. *AIDS Res Hum Retroviruses*. 1994;10:1713–1723.
571. Graham BS, Keefer MC, McElrath MJ, for the NIAID AIDS Vaccine Evaluation Group. Safety and immunogenicity of a candidate HIV-1 vaccine in healthy adults: recombinant glycoprotein (rgp)120. A randomized, double-blind trial. *Ann Intern Med*. 1996;125:270–279.
572. Belshe RB, Stevens C, Gorse G, et al; (NIAID AVEG, HIVNET Vaccine Development Groups). Safety and immunogenicity of a canarypox vectored HIV-1 vaccine with or without gp120 in higher and lower risk volunteers. *J Infect Dis*. 2001;183:1343–1352.
573. Evan TG, McElrath MJ, Matthews T, et al. QS-21 promotes a dose-sparing adjuvant effect during HIV-1 subunit immunization. *Vaccine*. 2001;19:2080–2091.

574. McElrath MJ, Corey L, Montefiori D, et al. A phase II study of two HIV type 1 envelope vaccines, comparing their immunogenicity in populations at risk for acquiring HIV type 1 infection. AIDS Vaccine Evaluation Group. *AIDS Res Hum Retroviruses*. 2000;16:907–919.
575. Belshe RB, Stevens C, Gorse G, et al; (NIAID AVEG, HIVNET Vaccine Development Groups). Safety and immunogenicity of a canarypox vectored HIV-1 vaccine with or without gp120 in higher and lower risk volunteers. *J Infect Dis*. 2001;183:1343–1352.
576. Goepfert PA, Horton H, McElrath MJ, et al. High-dose recombinant canarypox vaccine expressing HIV-1 protein, in seronegative human subjects. *J Infect Dis*. 2005;192:1249–1259.
577. Churchyard GJ, Morgan C, Adams E, et al. A phase IIA randomized clinical trial of a multi-clade HIV-1 DNA prime followed by a multi-clade rAd5 HIV-1 vaccine boost in healthy adults (HVTN 204). *PLoS ONE*. 2011;6:e21225.
578. Goepfert PA, Elizaga M, Montefiori D, et al. Phase 2a safety and immunogenicity testing of DNA and recombinant modified vaccinia Ankara virus vaccines expressing virus-like particles. Late Breaking Abstract OA09.08. AIDS Vaccine 2012. Boston.
579. Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicenter, randomized, double-blinded, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). *Lancet*. 2018;392:232–243.
580. Fisher W, Perkins S, Theiler J, et al. Polyvalent vaccines for optimal coverage of potential T-cell epitopes in global HIV-1 variants. *Nat Med*. 2007;13:100–106.
581. Barouch DH, O'Brien KL, Simmons NL, et al. Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys. *Nat Med*. 2010;16:319–323.
582. Santra S, Liao H, Zhang R, et al. Mosaic vaccines elicit CD8+ T lymphocyte responses in monkeys that confer enhanced immune coverage of diverse HIV strains. *Nat Med*. 2010;16:324–328.
583. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. *N Engl J Med*. 2012;366:1275–1286.
584. Baden LR, Dolin R. The road to an effective HIV vaccine. *N Engl J Med*. 2012;366:1343–1344.
585. Rolland M, Edlefsen PT, Larsen BB, et al. Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2. *Nature*. 2012;490:417–420.
586. Priddy FH, Brown D, Kublin J, et al. Safety and immunogenicity of a replication-incompetent adenovirus type 5 HIV-1 clade B gag/pol/nef vaccine in healthy adults. *Clin Infect Dis*. 2008;46:1769–1781.
587. Fitzgerald DW, Janes H, Robertson M, et al. An Ad5-vectored HIV-1 vaccine elicits cell-mediated immunity but does not affect disease progression in HIV-1-infected male subjects: results from a randomized placebo-controlled trial (the Step Study). *J Infect Dis*. 2011;203:765–772.
588. Duerr A, Huang Y, Buchbinder S, et al. Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning effect over time among participants in a randomized trial of recombinant adenovirus HIV vaccine (Step Study). *J Infect Dis*. 2012;206:258–266.
589. Rolland M, Tovanabutra S, DeCamp AC, et al. Genetic impact of vaccination on breakthrough HIV-1 sequences from the STEP trial. *Nat Med*. 2011;17:366–371.
590. Janes H, Frahm N, DeCamp A, et al. MRKAd5 HIV-1 gag/pol/nef vaccine-induced T-cell responses inadequately predict distance of breakthrough HIV-1 sequences to the vaccine or viral load. *PLoS ONE*. 2012;7:e43396.
591. Gray GE, Allen M, Moodie Z, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomized, placebo-controlled test-of-concept phase 2b study. *Lancet Infect Dis*. 2011;11:507–515.
592. Hammer SM, Sobieszczyk ME, Janes H, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med*. 2013;369:2083–2092.
593. West AP Jr, Scharf L, Scheid JF, et al. Structural insights on the role of antibodies in HIV-1 vaccine and therapy. *Cell*. 2014;156:633–648.
594. Shingai M, Donau OK, Plishka RJ, et al. Passive transfer of modest titers of potent and broadly neutralizing anti-HIV monoclonal antibodies block SHIV infection in macaques. *J Exp Med*. 2014;211:2061–2074.
595. Barouch DH, Whitney JB, Moldt B, et al. Therapeutic efficacy of potent neutralizing HIV-1 specific monoclonal antibodies in SHIV-infected rhesus monkeys. *Nature*. 2013;503:224–228.
596. Ledgerwood JE, Coates EE, Yamshchikov G, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. *Clin Exp Immunol*. 2015;182:289–301.
597. Lynch RM, Boritz E, Coates EE, et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. *Sci Transl Med*. 2015;7:319ra206.
598. Caskey M, Klein F, Lorenzi JC, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. *Nature*. 2015;522:487–491.
599. HIV Prevention Trials Network. HVTN 704/HPTN 085 - A Phase 2b Study To Evaluate the Safety and Efficacy of VRC01 Broadly Neutralizing Monoclonal Antibody in Reducing Acquisition of HIV-1 Infection Among Men and Transgender Persons Who Have Sex With Men. http://www.hptn.org/web%20documents/HPTN085/HVTN%20704%20HPTN%20085%20Protocol%20Version%201.pdf. Accessed May 13, 2016.
600. Caskey M, Klein F, Lorenzi JCC, et al. Viraemia suppressed in HIV-1 infected humans by broadly neutralizing antibody 3BNC117. *Nature*. 2015;522:487–491.
601. Russell ND, Graham BS, Keefer MC, et al. Phase 2 study of an HIV-1 canarypox vaccine (vCP1452) alone and in combination with rgp120: negative results fail to trigger a phase 3 correlates trial. *J Acquir Immune Defic Syndr*. 2007;44:203–212.

120 Diagnosis of Human Immunodeficiency Virus Infection

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SHORT VIEW SUMMARY

Definition

- Human immunodeficiency virus (HIV) detection is the cornerstone of the medical and public health response to the HIV epidemic. HIV detection is accurate and sensitive, and precise assays have been designed for three general purposes: individual diagnosis, epidemiologic surveillance, and donor screening for blood and tissue products.

Epidemiology

- By the end of 2017 more than 36 million individuals were living with HIV infection throughout the world. New initiatives to eliminate HIV worldwide have adopted a strategy of "90-90-90": 90% of HIV-infected individuals know their diagnosis, 90% of those diagnosed undergo combination antiretroviral therapy (cART), and 90% of those undergoing cART have HIV RNA levels below the limit of detection in commercial assays. The first "90" represents a key landmark and depends on accurate diagnosis. In the Unites States the prevalence of HIV infection is approximately 1.1 to 1.2 million individuals and approximately 85% of individuals know their status. The second "90" also depends on testing; new testing modalities permit diagnosis of HIV in a single visit, which will facilitate engagement in care. Eradication approaches will rely heavily on preexposure prophylaxis (PrEP) regimens, and as a result, many more individuals will require routine testing during PrEP. Testing with robust performance characteristics will be essential to evaluate individuals, potentially in the many millions, undergoing long-term PrEP.

Microbiology

- Worldwide, HIV is highly genetically diverse, and HIV testing modalities are designed to detect all HIV variants. Within an individual the genetic diversity of HIV early in infection is limited but increases with duration of infection, reflecting both the intrinsic mutation rate of HIV and strong selection pressures, including immune responses. At present, useful tools to detect HIV infection include detection of viral components (HIV RNA and p24 antigen) and humoral responses (commonly detected by enzyme-linked immunosorbent assay in various formats or by Western blotting and immunofluorescence-based assays, which are less frequently used).

Diagnosis

- Diagnosis proceeds from history, physical examination, and laboratory studies. Laboratory analysis is a two-step sequential process using a highly sensitive screening test, followed by a highly specific supplemental assay.
- A variety of formats are available, including rapid and home testing, that are approved by the US Food and Drug Administration (see Table 120.1). In many cases it is possible to perform both the screening and the supplemental assays within a single visit.
- The Centers for Disease Control and Prevention recommends all individuals age 18 to 65 years should be tested for HIV infection in an opt-out fashion. Testing has been adopted by the US Preventative Services Task Force, and the cost of opt-out testing is substantially underwritten through current insurance and the Affordable Care Act.
- No test is perfect, and familiarity with assay limitations is essential to ensure accurate identification of HIV infection.

Therapy

- HIV diagnosis is essential to introduce specific ART for treatment of infection.
- Screening assays for HIV infection are essential but not sufficient to initiate ART, and supplemental testing is essential to initiate cART.
- Individuals who have been exposed to HIV can undergo postexposure prophylaxis. Testing after completion of the prophylaxis regimen is essential to determine whether infection has occurred. Continued evaluation and referral for PrEP may be indicated.
- Individuals who are at risk for HIV infection but are not infected should be evaluated for PrEP. Regimens for PrEP are distinct from regimens for therapy for infected individuals, and it is essential to evaluate individuals carefully for HIV infection in such circumstances.
- Specific guidelines are available for testing, treatment, and prophylaxis.

Prevention

- PrEP represents a strategy to treat high-risk individuals with ART to prevent HIV infection. Careful evaluation is needed to rule out HIV infection before initiating PrEP. Expansion of HIV diagnostic approaches beyond clinic settings facilitates early identification of HIV-infected individuals. As individuals with early infection are highly infectious, expansion of testing can improve prevention efforts.

Human immunodeficiency virus (HIV) infection results in a progressive immunodeficiency that has resulted in approximately 35 million deaths worldwide (https://www.who.int/gho/hiv/en). By the end of 2017, more than 36 million individuals were living with HIV infection throughout the world[1] (http://www.unaids.org/en/resources/fact-sheet). Accurate, sensitive, and precise assays have been designed for three general purposes: patient diagnosis and clinical management, epidemiologic surveillance, and donor screening for blood and tissue products. As such, HIV diagnosis has been a fundamental cornerstone to establishing the extent of epidemic spread worldwide (Fig. 120.1)

As the public health response to the HIV epidemic has evolved, several key events have focused even greater attention on HIV diagnostics. The development of affordable combination antiretroviral therapy (cART) combined with the infrastructure for reliable delivery has enabled international public health efforts to propose successive expansion of therapy and, most recently, an ambitious "90-90-90" initiative targets advancing elimination of HIV transmission (90% of HIV-infected individuals know their diagnosis, 90% of those diagnosed undergo cART, and 90% of those undergoing cART have HIV RNA levels below the limit of detection in commercial assays) to eliminate HIV spread. The first critical "90" objective in this initiative is evaluation for HIV infection and has had variable success worldwide[2] but is the basis for subsequent steps in overall elimination of infection. As described, HIV diagnosis has come to rest on critical events surrounding diagnosis: the five Cs (https://www.who.int/hiv/topics/vct/about/en/): "*c*onsent, *c*onfidentiality, *c*ounseling, *c*orrect test results, and *c*onnection/linkage to prevention care and treatment"; diagnosis is therefore critical to eliminating HIV, and ensuring these five goals has become a more compelling imperative.[3] In addition, recent studies demonstrating the benefit to initiating therapy early in the course of HIV infection, as well as expansion of the numbers

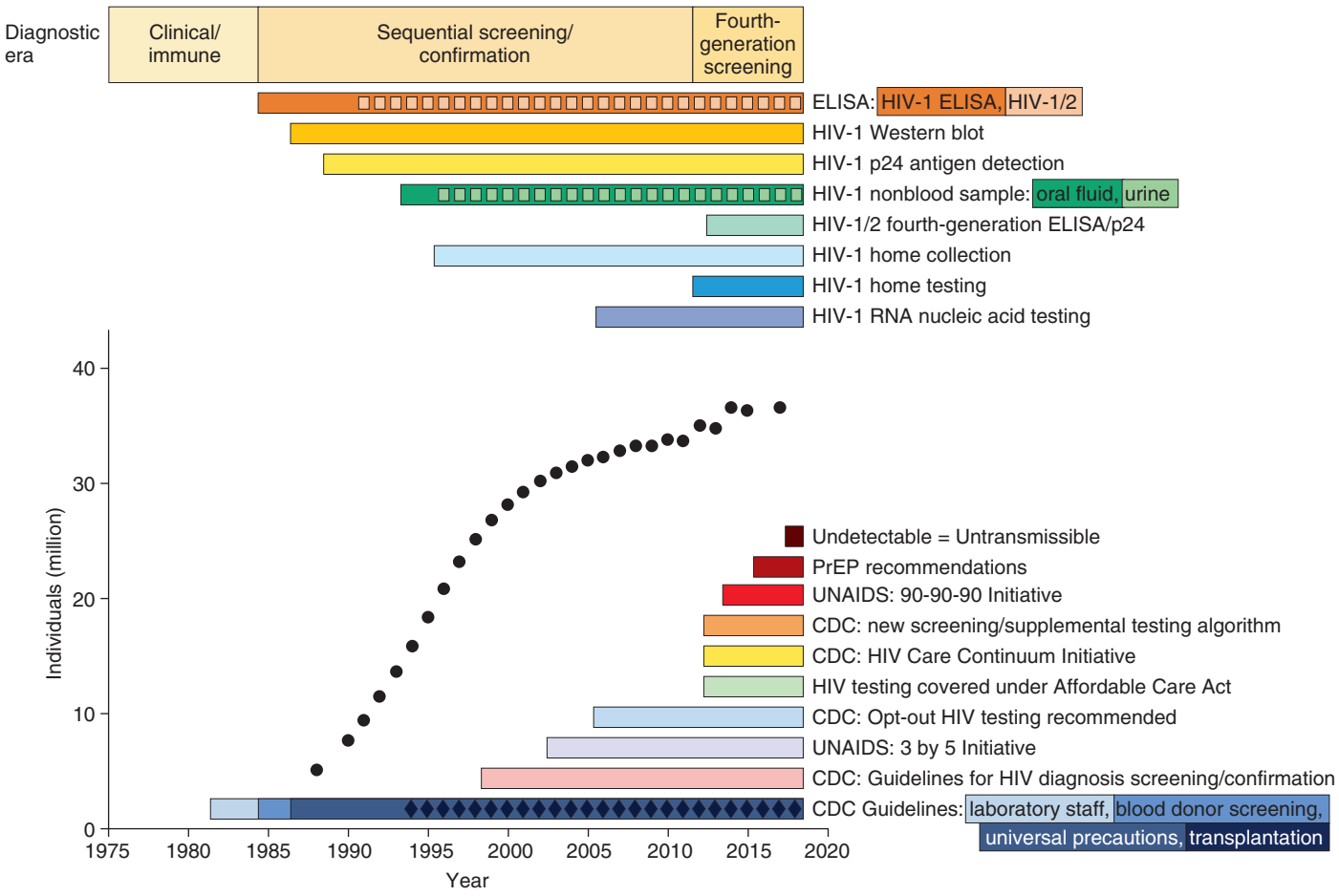

FIG. 120.1 HIV/AIDS diagnosis: three eras of diagnostic approaches. Diagnosis of HIV infection includes clinical and laboratory testing and requires appropriate implementation. Diagnostic approaches have evolved since the first cases of AIDS were recognized in the early 1980s. These eras can be divided chronologically (*x*-axis) and by the phase of the epidemic worldwide (*y*-axis). Above the epidemic curve are depicted laboratory modalities, and below the curve are implementation landmarks and public health initiatives. Initially, AIDS was diagnosed as a clinical syndrome in the setting of specific opportunistic infections or neoplastic diseases; laboratory methods were limited frequently and consisted of studies of immune responses, enumeration of CD4 and CD8 cells, and determining CD4/CD8 ratios in peripheral blood. The development of sequential serologic testing with a variety of techniques to detect HIV antigen and anti-HIV antibody represented the first laboratory techniques to detect HIV and took place as an expanding epidemic was recognized. This period was marked by successive testing modalities that extended the ability of testing to be initiated beyond clinical facilities. In parallel, public health agencies developed guidelines, initiatives, and infrastructure that did not substantially alter the initial trajectory of spread but did contribute to limiting the total disease burden worldwide. A third era of diagnosis emerged with the development of testing modalities that can provide both screening and supplementary diagnostic information in a single visit; advancements coincided with a point where spread remained stable and as wide-ranging changes in recommendations for tests, treatments, and PrEP, and targeted goals ("90-90-90") were implemented. These initiatives, supported by expanded diagnostics, are likely to tip the balance in favor of efforts to eliminate HIV. *CDC,* Centers for Disease Control and Prevention; *ELISA,* enzyme-linked immunosorbent assay; *PrEP,* preexposure prophylaxis; *UNAIDS,* United Nations Programme on HIV/AIDS.

of individuals for whom testing is recommended, has placed an additional burden on optimizing performance characteristics to detect HIV early after infection occurs and to do so in large populations with low incidence of HIV infection. The second "90" relies on the reliable and responsible linkage to care after a positive diagnosis. Diagnostic methodologies have become quite flexible; such capability permits greater opportunity for seamless linkage to care. Adapting the diagnostic approach and setting for diverse risk groups has been a critical development and remains an important responsibility in the public health response to HIV infection. The recent National HIV/AIDS Strategy for the United States[4] reflects the broad shift in emphasis in expanding HIV diagnostics beyond traditional clinical settings.

Advances in diagnostics have been critical to the development of a feasible and scalable response to the epidemic and have often driven the medical and public health response itself. At the same time, limitations of the diagnostics and their appropriate administration can lead to equivocal results at a critical time for potentially infected individuals, Health care professionals represent gatekeepers of diagnosis; no test (or testor) is perfect, and thorough understanding of HIV diagnostic capabilities is an essential responsibility for health care workers at all levels. HIV infection is a life-altering diagnosis with social, medical, and potentially legal consequences. Misdiagnosis of HIV infection has profound consequences for patients and their contacts; liability issues have been justifiably extreme.[5,6]

Diagnosis of HIV infection is not simply the result of interpretation of a laboratory test, but proceeds as for the evaluation of any other illness, from careful history and physical examination to indicated laboratory studies. The present chapter will survey the methods, strategies, and circumstances for diagnosis of HIV infection.

BACKGROUND/PERSPECTIVE

The current state of the art HIV diagnosis is the product of continuous advances in laboratory techniques coordinated with progressive expansion in implementation. HIV detection remains a two-step sequential process consisting of a highly sensitive *screening* test, followed by a highly specific *supplemental* or *confirmatory* assay. In the United States and many developed countries, diagnostics can be conveniently divided into three periods (see Fig. 120.1): (1) An early period (1981–85), before the

identification of the virus, in which diagnosis relied on clinical evaluation with minimal laboratory input; this early approach, although highly specific, was insensitive and identified patients only after a long "window period." (2) A prolonged period (1985–2013), during which serologic diagnostics were used in a strategy of sequential testing and then during which assays for screening and confirmation accurately identified most HIV-infected individuals with successively improved sensitivity and specificity and a progressively shortened window period; however, diagnosis required multiple visits. (3) A recent period (2013 to the present), in which screening includes detection of HIV antibody and antigen in fourth-generation assays and supplemental assays discriminate HIV-1 and HIV-2 infections (see Fig. 120.1). Of importance, this fourth-generation–based approach can be accomplished in many cases within a single visit. These recent developments have coincided with an expansion of use of diagnostics for evaluation of individuals undergoing preexposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) for HIV infection. As the knowledge base expanded, improvements in HIV diagnostic testing improved and drove expansion of testing services and locations. As shown in Fig. 120.1, the combination of improvements in testing modalities, expansion of settings for testing, and increased public health initiatives to engage at-risk populations has strong potential to tip the balance of the epidemic versus prevention struggle in favor of HIV eradication.

Laboratory Advances

In early studies (1981–85) the diagnosis of acquired immunodeficiency syndrome (AIDS) was made by identification of characteristic infections or neoplasms in appropriate risk groups. Before development of molecular techniques for HIV detection, the use of peripheral CD4 cell counts and percentage CD4 cells and, more accurately, use of CD4/CD8 cell ratios was used as a marker of immunodeficiency and used in screening.[7] The recovery of a transmissible agent, in cultures of susceptible cells with reproducible cytopathology associated with virus-like particles containing reverse-transcriptase enzyme activity characteristic of the retrovirus family[8–13] (Fig. 120.2), paved the way for future diagnostics. When virus isolation was reliably positive, this test could be considered a gold standard of infection; virus isolation was, however, cumbersome, time consuming, and was not sufficiently sensitive for routine screening. The discovery that serum from patients with AIDS contained antibodies that recognized viral gene products[8,9,14,15] and that reactivity was lifelong in the majority of infected individuals permitted large-scale investigations of appropriate serologic detection assays.

Several standard laboratory procedures used to detect HIV gene products, including radioimmunoprecipitation, Western blotting (WB), enzyme-linked immunosorbent assays (ELISAs), and immunofluorescence were adapted to form the basis for the earliest HIV detection systems.[16] The first ELISA HIV test kits received US Food and Drug Administration (FDA) approval for use in blood donor screening in the United States in March 1985[17] and ushered in a new era of diagnosis, beginning with HIV blood donor screening. All donations reactive in a single test were discarded, and units with repeat reactivity were considered positive for viral antibodies. Within approximately 3 months, more than 1 million units of donated blood were screened in the United States, with 0.25% reported repeatedly reactive.[17] Two principal technical issues of the first generation of HIV ELISA assays were a high rate of false-positive results arising from a variety of clinical conditions and laboratory artifacts[18] and a small but ominous number of false-negative results resulting from the inability to detect the presence of HIV antibodies early in infection (so-called window period) before full seroconversion.[19,20]

To address false-positive results, highly specific tests, including WB, immunofluorescence, and radioimmunoprecipitation were incorporated as confirmatory assays on all repeat ELISA-reactive samples.[21–23] Although all confirmatory assays are relatively labor intensive, WB procedures proved most useful, efficient, and specific; the WB technique was soon established as a widely used gold standard test for confirmation and was FDA approved for use in the United States in 1987.

Technical advancements in ELISA assays also improved detection of sensitivity early HIV infection during the window period. The development of infectious molecular clones of HIV[24–26] permitted detailed virus characterization of components of the AIDS virus (see Fig. 120.2), facilitating understanding of replication and importantly provided access to cloned HIV genes that could be used to further develop specific diagnostics. A second-generation of ELISA assays decreased false-positive

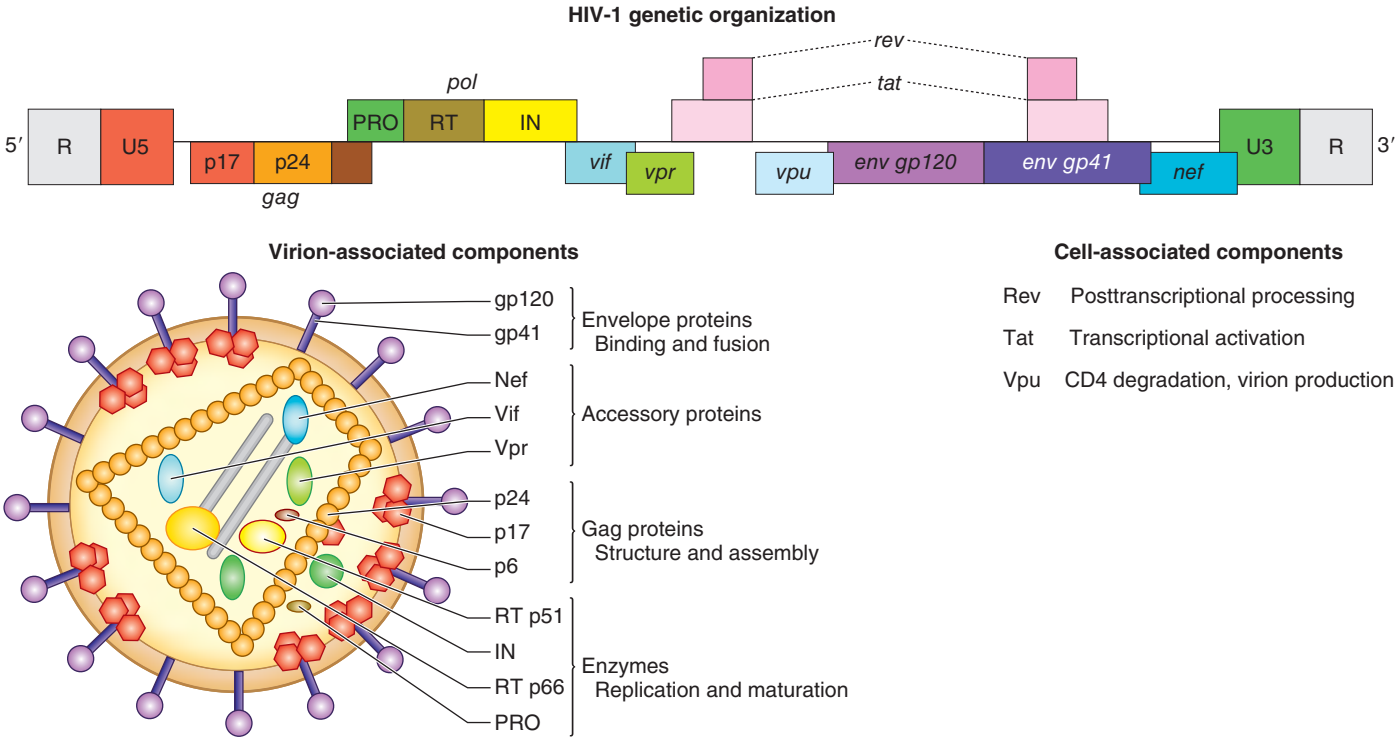

FIG. 120.2 Organization of HIV-1. HIV-1 is an enveloped retrovirus with a positive-stranded genome (two copies/virion) that contains genes for proteins with structural enzymatic and regulatory functions, as indicated.

rates by using recombinant antigens and synthetic peptides instead of infected cell lysates, resulting in greater sensitivity.[27–31] Introduction of an assay to detect the presence of viral antigen (p24) in 1989 to detect HIV was especially useful during early virus infection and improved detection of recent HIV infection[32–36]; p24 antigen detection kits were FDA approved in 1989.

In 1986 a second human immunodeficiency virus, HIV-2, was identified in West African natives by studying individuals with an AIDS-like immunodeficiency who had nonreactive or unusual HIV-1 serologic results,[37,38] and shortly thereafter, cases of HIV-2 were detected in the United States, Canada, and Europe[39–44]; changes in ELISA assays to include HIV-2 antigens ensued, and combination ELISA kits were introduced in 1991 (see Fig. 120.1), which were subsequently adapted into a number of distinct formats to produce flexible, rapid tests that would be useful in resource-limited settings[45] and for use with alternative body fluids, including urine and saliva (see Fig. 120.1).[46–50]

ELISA assays to detect HIV antibody have remained a cornerstone for HIV screening. Confirmatory assays, immunofluorescence and more commonly WB, delivered excellent specificity; WB approaches provided additional information regarding early HIV infection. Progressive emergence of HIV RNA, p24 antigen, and serologic reactivity forms the basis for staging early HIV infection, standardized as six successive "Fiebig stages" (Fig. 120.3). Emergence of serologic reactivity with WB to the HIV integrase protein, p31, is typically delayed after infection occurs, and p31 reactivity distinguishes Fiebig V HIV stage (p31 negative) from Fiebig VI stage (p31 positive). Confirmatory testing with WB techniques had disadvantages as well, including a requirement for specialized equipment and an inability to provide a rapid simple version of the assay, requiring additional visits to arrive at a diagnosis. In addition, a substantial number of blots with indeterminate results required additional evaluation and limited the utility and cost-effectiveness of this modality; in response, alternative approaches using dual ELISA assays were developed within developing countries and World Health Organization (WHO). Ultimately, new strategies were developed that bypassed WB entirely.

Inability to detect HIV during early infection (window period) remains a critical limitation in HIV testing. Methods to detect HIV p24 antigen decreased the window period and became required for blood donor screening in 1996. Improvements in ELISA approaches using "sandwich" antibody techniques resulted in greater specificity in screening and greater sensitivity in detecting antibody during the window period and ushered in a new third generation of HIV ELISA assays.[51,52] Nevertheless, the HIV window period remained unacceptably long, and new approaches to detect HIV nucleic acid, denoted nucleic acid testing (NAT), were developed for diagnosis. NAT is more sensitive than third-generation ELISA assays in detecting window period HIV-1.[53] NAT (for HIV-1 only) was approved for use in screening plasma donors in 2001 and for use in individual blood donors in 2002, and qualitative HIV-1 RNA detection for diagnosis was approved in 2006, which reduced window period, on average, 6 days earlier than p24 assays in seroconversion panels.[54]

In independent efforts to increase detection of window period infections, fourth-generation assays have been developed that use a combination of third-generation ELISA with sensitive p24 antigen detection.[52,55–58] The first antibody-antigen (Ab-Ag) diagnostic assay was FDA approved in 2010 for detection of both HIV-1 and HIV-2; although not as sensitive as NAT, these fourth-generation tests represented marked improvements in detecting early infection, with a median detection time 7 days earlier than that for third-generation ELISAs. Fourth-generation tests that were positive did not distinguish whether the test was positive because of the p24 reactivity or the anti-HIV reactivity. Early infection was therefore inferred, with fourth-generation assays positive and standard ELISAs negative. Newer assays, denoted as fifth-generation assays by some, do distinguish between p24 antigen positivity and serologic reactivity, permitting a more precise diagnosis (see Fig. 120.3). Moreover, these new assays could be performed in a rapid format, permitting diagnosis of HIV infection in a single visit. Together these assays, detecting HIV antigen and antibody and differentiating HIV-1 and HIV-2, have ushered in the current HIV serology + p24 antigen era of HIV diagnosis and serve as supplementary assays in a revised, simplified, and streamlined diagnostic algorithm.

HIV testing was developed to detect HIV-subtype B, the most common subtype in the United States and Europe. The majority of infections worldwide are, however, non–subtype B, and early generation assays had variable sensitivity to detect these non-B subtypes; inclusion of additional antigens and peptides has improved sensitivity such that the current versions of ELISA, WB, and NAT assays will detect B and non-B subtypes with equivalent sensitivity and specificity.

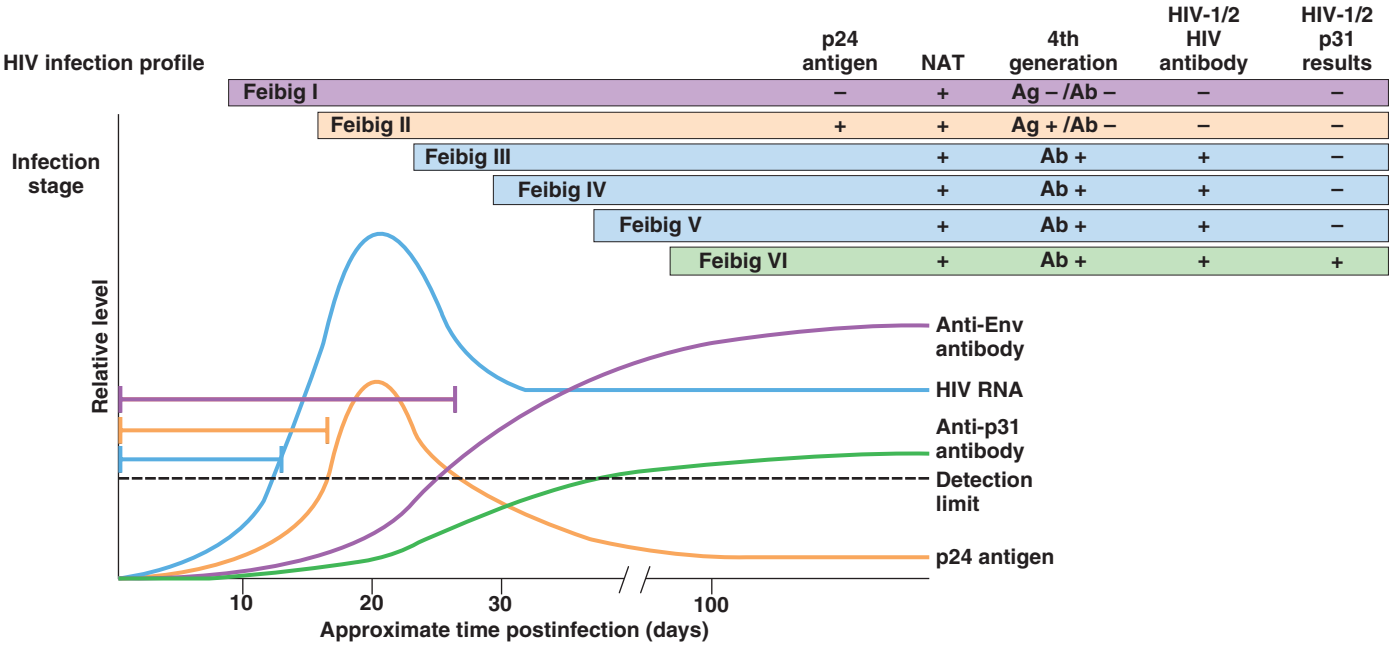

FIG. 120.3 HIV infection profile. After HIV infection, intense viral replication results in high levels of HIV RNA and HIV p24 protein in plasma. Subsequently, increases in anti-HIV antibody are detected, and a variable window period exists between infection and detection by different testing modalities. HIV RNA levels are detected earliest, followed by HIV p24 antigen and antibody production. Antibody to the HIV p31 protein emerges last. Using a combination of testing modalities for detection of HIV RNA, p24 antigen, and anti HIV antibody, individuals with early HIV infection can be categorized into a series of infection stages (Fiebig stages) as indicated. The earliest stage (Fiebig I), with only HIV RNA detectable, and the latest stage (Fiebig VI), in which antibody to HIV proteins, including p31, is present. As indicated, all testing modalities will identify later Fiebig stages, but only HIV nucleic acid testing (NAT) will detect Fiebig I; fourth-generation assays can detect Fiebig II and later.

As testing procedures for blood donation expanded, variations in laboratories carrying out these evaluations were expected, and test kit evaluation procedures were established with the Centers for Disease Control and Prevention (CDC) Model Performance Evaluation Program (MPEP) to evaluate and limit variability[59–61] and worldwide under WHO auspices.[62] MPEP is a voluntary quality assessment program providing well-curated sample sets for testing. Proficiency in HIV testing is of paramount importance, and early surveys of laboratories revealed significant variation and issues with reproducibility.[63] Reporting results of HIV testing was initially haphazard and potentially confusing,[64] leading to uncertainty. Performance rapidly improved, high-quality control measures were documented,[65,66] and guidelines for screening donor organs before transplantation were established by the FDA, with the first interim rule in 1993 requiring donor screening and record keeping. MPEP has been a highly successful CDC initiative and was extended to evaluate proficiency in rapid HIV tests.

Implementation of HIV Diagnostics

Implementation of HIV diagnostic testing has evolved over the last 30 years, although certain goals have remained: Under the majority of circumstances, testing is voluntary and confidential. Identification of so-called "key populations" in the United States, currently including gay, bisexual, and other men who have sex with men (MSM) of all races and ethnicities; black women and men; people who inject drugs; Latino men and women; youth age 13 to 24 years; people in the southern United States; and transgender women.[4] In concert with identifying these key populations, HIV diagnostics were progressively expanded (see Fig. 120.1); in the United States the CDC, FDA, and other governmental authorities provided a series of successive recommendations to broaden testing, which were driven to some degree by the improved performance characteristics and the development of formats that made such expansions feasible, scalable, and reliable. In parallel, programs disseminating information regarding HIV and public service initiatives raised awareness of the need for increasing testing. The first National HIV Testing Day was designated on June 27, 1995, and an important subsequent approach has been administered through HIV.gov to designate a day to focus on specific at-risk communities; beginning in 1999 (National Black HIV/AIDS Awareness Day, February 7) and continuing through 2016 with National Transgender HIV Testing Day (April 18), these events encourage testing using progressively broad approaches, including social media, to engage specific key populations. Similar initiatives have been developed elsewhere and under the auspices of United Nations Programme on HIV/AIDS (UNAIDS) and WHO. Combining these programs with mobile health initiatives and flexible testing modalities has great potential to reach populations who have not routinely engaged health care.[67] As programs for preexposure and PEP expand, rigorous HIV diagnostics will be necessary, and familiarity with the limitations of testing modalities will be essential.

Among the challenges HIV testing encountered early in the epidemic was expanding diagnostics beyond blood donation facilities and implementing a public health measure that was confidential, voluntary, and effective. In the United States and elsewhere, so-called "alternative sites" were established shortly after approval of screening ELISA assays; these alternative sites were independent of blood centers and were permitted to perform voluntary and confidential HIV testing with pretest and posttest counseling procedures.[68] The logistics of screening at alternative sites were often controversial,[69] but mandatory testing of patient populations was rejected. During the screening confirmation period, screening using ELISA assays and confirmation with WB or immunofluorescence was done under defined laboratory conditions only, as simple and rapid testing for HIV were not available. With guidelines for screening and confirmatory studies provided to laboratory staff, blood donor screening was soon followed by development of universal precautions and guidelines for evaluating tissue for transplantation (see Fig. 120.1).

In the United States the introduction of rapid HIV-1 testing procedures, combined with new guidelines in 2001 to recommend screening of all pregnant women and simplification of the consent process, was followed by additional recommendations in 2003 to make testing routine in health care settings and for use of rapid testing during labor and delivery, thus expanding HIV testing beyond traditional health care facilities and permitting support of point-of-care real-time HIV diagnosis. Benchmark results of these advances have been analyzed using a number of statistical approaches. The National Center for Health Statistics surveyed more than 188,000 noninstitutionalized individuals age 18 to 64 years and incorporated questions regarding HIV testing. After an initial increase in individuals tested over the years 1987–95, the total proportion of the population who had ever undergone testing and the rate at which individuals were tested within a year has been calculated (see Fig. 120.2).[70] The total proportion of the population in developed countries who have undergone HIV testing is relatively high (e.g., 40% in the United States [see Fig. 120.2][71] and 50% in France[72]). Of note, the percentage of individuals reporting having been tested in the previous 12 months (10.4%, see Fig. 120.2) has remained unchanged since 2001, despite the promotion of rapid testing modalities and expansion of testing resources, although the proportion of people with HIV aware of their status is about 80% in the United States.[73]

In an effort to reach the substantial proportion of undiagnosed individuals, the CDC revised recommendations in 2006[71] to make HIV testing a part of routine screening for all individuals presenting for care, incorporating an "opt-out" strategy, where patients implicitly agree to testing upon presenting for care; testing is done unless the patient specifically declines. Opt-out testing for HIV infection represents a landmark shift in emphasis for HIV diagnosis; under this recommendation, patients are informed that HIV testing will be performed unless individuals opt out of testing. In this scenario counseling is available and assent is inferred. Although not universally implemented, opt-out testing represents an important change in approach to testing and has been increasingly used.

In an effort to address substantial stigma associated with HIV testing, a number of non–clinic-based and home-based opportunities for HIV testing have been developed. Development of rapid and simple assays for HIV led to true home testing; home testing permits privacy but not readily accessible counseling or interpretation, and availability of health care professionals to provide counseling will be essential.

Opt-out testing includes availability of counseling and the opportunity to refuse testing and is entirely distinct from mandatory testing, which requires testing be performed regardless of consent or degree of counseling. In general, mandatory testing has been repeatedly rejected, based in large measure on concerns for individual dignity.[74,75] Mandatory testing has, however, been supported under states' authority to protect the community interest against epidemic disease (as initially proposed and implemented for smallpox).[76] Testing of inmates in federal corrections facilities was mandated beginning in 1998, and a number of states have mandatory testing in state prisons.[77–79] In certain circumstances, especially sexual offenses, HIV testing has been court ordered; test results are made available to victims and in some cases to prison administrators. HIV testing of infants is mandatory in several states. Testing as a part of military recruitment is required in the United States and in at least 26 other countries.[75] Mandatory testing is required by a number of governments for immigrants entering as a worker, student, temporary or permanent resident; testing performed in US laboratories may or may not be acceptable for this purpose (a list of such countries and whether US testing is accepted is available at www.WHO.int). In the face of involuntary HIV testing, governing bodies, such as WHO, have categorically rejected mandatory HIV testing,[75] and the issue remains debated in the United States[78]; testing practices vary by country and can be influenced by political and unforeseen events.[80] The recent influx of asylum seekers in various countries has prompted some jurisdictions to implement mandatory testing of refugees. The rate of HIV positivity in these groups has been reported, and generally reflects rates from countries from which individuals are fleeing.[81]

Reporting HIV Infection

Initially, reporting of HIV diagnoses for epidemiologic purposes was deemed unnecessary, as the HIV-1 epidemic was tracked using AIDS case definition and mortality statistics. Early identification of key populations focused surveillance efforts on groups such as MSM, intravenous drug users, and commercial sex workers. With the advent of reliable testing modalities and effective ART, resulting in the dramatic

decline in death and in AIDS diagnoses, the presence of HIV infection represents the most useful marker of prevalence. In the United States reporting takes place on the state and federal level.[82] Names reporting and partner notification followed initial recommendations, raising privacy concerns, and partner notification is required in New York State as of 1998[83] and has been considered in others. Names reporting is standard practice in the United States; names of individuals newly diagnosed with HIV infection are reported to state health departments, where data is maintained in confidential databases. Personal identifying information is removed from the dataset when the data are reported to the CDC. Early in the epidemic, WHO endorsed worldwide unlinked anonymous surveys.[84]

Individual states vary in their approach to HIV testing, and specific laws regarding HIV testing, counseling, and reporting have been compiled (https://www.cdc.gov/hiv/policies/law/states/index.html). Even fully implemented, universal testing represents a passive surveillance approach and does not provide sufficient detection for individuals who do not engage health care, and active programs are likely to be required to identify all infected individuals, or even achieve "90-90-90" goals. Pilot programs of active screening are relatively labor intensive but have demonstrated success[85] in identifying HIV infection. Newer surveillance models using mobile, ehealth, and home testing options to enhance surveillance have been reviewed.[86] WHO standards for enhanced testing involves endorsement of home testing and testing through voluntary assisted-partner notification (2017; http://www.who.int/hiv/topics/vct/hts-new-opportunities/en/index2.html).

TERMINOLOGY AND PERFORMANCE CHARACTERISTICS

Laboratory approaches for detecting the presence of HIV infection have been developed, typically with a particular application intended, such as blood safety, patient diagnosis, or epidemiologic surveillance[87]; current assays for patient diagnosis (Table 120.1) have utility for established HIV infection, and some assays have utility for diagnosis of early HIV infection. A number of specific terms have been applied in describing HIV testing, procedures, and results (see Table 120.1). In the United States the FDA has regulatory oversight for testing, and not all modalities have FDA-approved versions. Serologic tests are broadly divided into screening assays and supplemental (formerly popularly described as "confirmatory") tests (see Table 120.1); some assays, such as the qualitative HIV RNA detection assay introduced in 2006, are approved as either a screening or a supplementary assay. No test, however, can be used as both a screening and a supplemental assay for an individual, and all individuals continue to require at least two assays for diagnosis. Serologic screening assays are available in a number of ELISA or p24 antigen assay formats for initial testing. Results of screening tests are considered reactive or nonreactive. In the United States supplemental assays, such as GEENIUS (Bio-Rad, Hercules, CA) or previously WB or immunofluorescence assays, have been used. Home sample collection of dried blood spots includes both a screening and supplementary phase, whereas home testing for HIV testing is for HIV screening only.

No test is perfect, and assay imperfections are quantitated using a number of characteristics: sensitivity, specificity, false-positive rate, and false-negative rate. For assays of HIV infection, both false-negative rate and false-positive rate have profound implications. Sensitivity (Table 120.2) relates to how many infections are missed by testing; inadequate sensitivity has great impact both in blood surveillance and individual diagnosis. In both circumstances inability to detect infection potentially exposes others to infection and misses critical opportunities for counseling and therapy. Specificity (see Table 120.2) describes the proportion of uninfected individuals who test negative for HIV. Decreased specificity results in false-positive findings, prompting profound patient distress and extensive additional evaluation. Decreased specificity compromises HIV testing from a patient diagnosis (fear of positive testing) and public health (inadequate description of the epidemic, unnecessary use of funds) standpoint. In general, the optimization of any test ultimately pits sensitivity at odds with specificity; the greater the sensitivity of a test, the more likely the possibility that false-positives may occur, whereas increasing specificity results in increased numbers of false-negatives (Fig. 120.4). To maximize both specificity and sensitivity for detection of HIV infection, a single test is inadequate. Instead, a sequential strategy has been designed. Testing is initiated with a highly sensitive ELISA screening (>99.5% sensitive); in this phase, false positives may be significant (1%–10%). The screening phase is followed, however, by a highly specific confirmatory test (>99.5% specific), and the initial false positives are excluded. As a result, HIV testing has among the highest level of sensitivity and specificity for any medical diagnostic procedure.

When deciding whether to use HIV testing in individual circumstances, it is essential to know estimates of what the probability is that HIV infection is present if the testing is positive, and what the probability is that HIV is not present if the HIV test is negative. In this regard, knowledge of the positive predictive value (the proportion of all positive results that are actually true positives) and negative predictive value (the proportion of all negative results that are true negatives) of HIV testing is quite useful (see Table 120.2). Even at high specificity and sensitivity, positive predictive values and negative predictive values are dependent upon the disease prevalence (see Fig. 120.3). As a result, no single test for HIV is useful or efficient in low-prevalence populations. The combination of a repeatedly reactive screening assay followed by a highly specific confirmatory assay yields an effective approach for diagnostic purposes, even in low-prevalence populations.

Test characteristics are defined in licensing trials using ideal conditions under which performance characteristics are defined (test efficacy), whereas performance may vary under conditions of actual field use (test effectiveness). Initial trials of kits may use relatively small numbers of samples, and with such small sample sizes, no false positives or negatives may be obtained. In such circumstances, test sensitivity/specificity may be reported as "100%." Reporting of such absolutes of any test may be somewhat misleading because it is more useful to report such findings taking into account the sample size and values, such as "<1 false positive/sample size." This may be more informative, and performance characteristics become even more important as modalities are used for evaluation of individuals undergoing PrEP or PEP.

Numerous screening and supplementary assays have been developed using a variety of patient materials to determine the presence of HIV infection (see Table 120.1); all kit names and manufacturers of the FDA-approved assays are available at www.fda.gov. In addition, WHO has evaluated specificity, sensitivity, negative predictive value, positive predictive value, and cost of all test kits the organization supports for distribution throughout the world. UNAIDS (Report 16, Geneva 2009, http://www.who.int/diagnostics_laboratory/evaluations/hiv/en/).

SPECIFIC LABORATORY METHODS FOR DETECTION OF HIV INFECTION

Immune Responses to HIV

Infection with HIV results in virus replication in a variety of cell types expressing surface markers such as CD4 and a coreceptor such as CXCR4 or CCR5. The genetic diversity of HIV-1 during this early infection period is limited, and it is likely that the majority of individuals are infected with a single variant, with slow, predictable accumulation in genetic diversity reflecting both the intrinsic mutation rate of HIV-1 and strong purifying selection, likely including immune responses.[88,89] Viral replication results in humoral and cellular responses, leading to viral protein processing and display of viral antigen fragments on infected cell surfaces, prompting an immune reaction (see Fig. 120.3). Cellular reactivity represents the earliest detectable immunity to HIV,[90–92] but such responses have not yet been exploited for use in early diagnosis of HIV infection.

Humoral responses represent a reliable method to determine the presence of true HIV infection. Antibody production after HIV infection follows a period of intense virus replication, as demonstrated by relatively high viral RNA levels and p24 antigen production preceding development of antibodies (schematic in Fig. 120.3). The precise kinetics of antibody production to individual HIV proteins is incompletely understood, and significant variability has been detected[93]; in general, however, immune responses to HIV-1 appear similar to other infections, with immunoglobulin M (IgM) followed by appearance of IgG production.[94–98]

The HIV window period (see Fig. 120.3) is the time after infection has occurred but before evidence of HIV infection is detectable. The HIV diagnostic window represents a vulnerable period, particularly

TABLE 120.1 HIV Testing Platforms and Modalities to Detect HIV RNA, p24, and Antibody

TRADENAME	INFECTIOUS AGENT	FORMAT	SPECIMEN	FDA-APPROVED HIV-1/2 SCREENING	HIV-1/2 DIFFERENTIATION OR SUPPLEMENTAL ASSAY	HIV-1 ONLY	HIV-1 ANTIGEN	HIV-1/2 AB	USEFUL FOR ACUTE INFECTION DETECTION	RAPID POINT-OF-CARE TESTING
HIV-1 Nucleic Acid Testing										
APTIMA HIV-1 RNA Qualitative Assay[440]	HIV-1	TMA	Plasma/serum	Yes	Supplemental	Yes			Yes	
HIV-1/2 ELISA/HIV-1 p24										
Elecsys HIV Combi PT[441]	HIV-1, HIV-2	Immunochemiluminescence	Plasma/serum	Yes		Yes	Yes	Yes	Yes	
VITROS HIV-1/HIV-2 Reagent Pack and Calibrator[442]	HIV-1, HIV-2	Immunometric	Serum/ plasma	Yes		Yes	Yes	Yes	Yes	
BioPlex 2200 HIV Ag-Ab Assay[443]	HIV-1 and HIV-2	Multiplex flow immunoassay	Serum, plasma	Yes		Yes	Yes	Yes	Yes	
ADVIA Centaur HIV Ag-Ab Combo (CHIV) Assay[444]	HIV-1, HIV-2	Microparticle chemiluminometric immunoassay	Serum	Yes		Yes	Yes	Yes	Yes	
ARCHITECT HIV Ag-Ab Combo[445]	HIV-1, HIV-2	Chemiluminescent EIA	Plasma/serum	Yes		Yes	Yes	Yes	Yes	
GS HIV Ag-Ab Combo EIA[446]	HIV-1, HIV-2	EIA	Plasma/serum	Yes		Yes	Yes	Yes	Yes	
Alere Determine[447]	HIV-1, HIV-2	Immunoassay	Plasma/serum	Yes		Yes	Yes	Yes	Yes	Yes
Geenius HIV 1/2 Supplemental Assay[448]	HIV-1, HIV-2	HIV detection test	Blood		Supplemental and differentiation		Yes	Yes	Yes	
HIV-1/2 ELISA										
SURE CHECK HIV 1/2 ASSAY[449]	HIV-1, HIV-2	Rapid immunoassay	Fingerstick and venous whole blood, serum, plasma					Yes	Less sensitive	Yes
HIV 1/2 STAT-PAK Assay[450]	HIV-1, HIV-2	Rapid immunoassay	Fingerstick and venous whole blood, serum, plasma	Yes				Yes	Less sensitive	Yes
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test[451]	HIV-1, HIV-2	Rapid immunoassay	Oral fluid, plasma, whole blood (venipuncture and fingerstick)	Yes				Yes	Less sensitive	Yes
Chembio DPP HIV 1/2 Assay[452]	HIV-1, HIV-2	Rapid immunochromatographic assay	Oral fluid, serum, plasma, whole blood	Yes				Yes	Less sensitive	Yes
INSTI HIV-1/HIV-2 Antibody Test[453]	HIV-1 and HIV-2	Rapid immunoassay	Plasma/whole blood (venipuncture and fingerstick)	Yes				Yes	Less sensitive	Yes
Reveal Rapid HIV-1 Antibody Test[454]	HIV-1	Rapid immunoassay	Serum/plasma	Yes		Yes			Less sensitive	Yes
Uni-Gold Recombigen HIV-1/2[455]	HIV-1, HIV-2	Rapid EIA	Whole blood (venipuncture, fingerstick)	Yes				Yes Yes	Less sensitive	Yes
Genetic Systems HIV-1/HIV-2 Plus O EIA[456]	HIV-1, HIV-2	EIA	Serum/plasma/cadaveric serum	Yes				Yes	Less sensitive	

Continued

TABLE 120.1 HIV Testing Platforms and Modalities to Detect HIV RNA, p24, and Antibody—cont'd

TRADENAME	INFECTIOUS AGENT	FORMAT	SPECIMEN	FDA-APPROVED HIV-1/2 SCREENING	HIV-1/2 DIFFERENTIATION OR SUPPLEMENTAL ASSAY	HIV-1 ONLY	HIV-1 ANTIGEN	HIV-1/2 AB	USEFUL FOR ACUTE INFECTION DETECTION	RAPID POINT-OF-CARE TESTING
Uni-GoldRecombigen HIV-1/2[455]	HIV-1, HIV-2	Rapid EIA	Serum, plasma	Yes				Yes	Less sensitive	
Avioq HIV-1 Microelisa System[457]	HIV-1	EIA	Serum, plasma, dried blood spot, oral fluid	Yes		Yes			Less sensitive	
ABBOTT PRISM HIV O Plus Assay[458]	HIV-1, HIV-2	ChLIA	Plasma/serum/cadaveric serum	Yes				Yes	Less sensitive	
VITROS HIV-1/HIV-2 Reagent Pack and Calibrator[442]	HIV-1, HIV-2	Immunometric	Plasma/serum	Yes				Yes	Less sensitive	
ADVIA Centaur HIV 1/O/2 Rapid Test[459]	HIV-1, HIV-2	Microparticle chemiluminometric immunoassay	Plasma/serum	Yes				Yes	Less sensitive	
Home Access/Home Detection										
OraQuick In-Home HIV Test[460]	HIV-1, HIV-2	Immunoassay	Oral fluid	Yes					Not sensitive	
Home Access HIV-1 Test System[461]	HIV-1	Dried blood spot collection device	Dried blood spot		Supplemental	Yes			Less sensitive	
HIV-1 Western Blot[a]										
Cambridge Biotech HIV-1 Western Blot Kit[462]	HIV-1	WB	Serum/plasma		Yes	Yes			Not as sensitive as ELISA	
GS HIV-1 Western Blot[462]	HIV-1	WB	Serum/plasma		Yes	Yes			Not as sensitive as ELISA	
OraSure HIV-1 Western Blot Kit[463]	HIV-1	WB	Oral fluid		Yes	Yes			Not as sensitive as ELISA	
GS HIV-1 Western Blot[462]	HIV-1	WB	Dried blood spot		Yes	Yes			Not as sensitive as ELISA	

[a]No longer in general use.
Ag-Ab, Antigen-antibody; *ChLIA,* chemiluminescent immunoassay; *EIA,* enzyme immunoassay; *ELISA,* enzyme-linked immunosorbent assay; *HIV,* human immunodeficiency virus; *TMA,* transcription-mediated amplification; *WB,* Western blot.

TABLE 120.2 Test Performance Definitions and Derivations

TEST PERFORMANCE CHARACTERISTICS	DEFINITION	FORMULA
True HIV positive	Number of individuals who are actually HIV infected	A
True HIV negative	Number of individuals who are actually HIV uninfected	B
False HIV positive	Number of positive HIV test results/total samples without HIV infection	C
False HIV negative	Number of negative test results/total samples with HIV infection	D
Total number of individuals with HIV infection	HIV-infected population	A + D
Total number of individuals without HIV infection	HIV-free population	B + C
Total number of positive tests	—	A + C
Total number of negative tests	—	B + D
Sensitivity	Number of positive test results/total samples with HIV infection	A/A + D
Specificity	Number of negative test results/total samples without HIV infection	B/B + C
Positive predictive value	Proportion of those with HIV-positive assay who are actually HIV infected	A/A + C
Negative predictive value	Proportion of those with HIV-negative assay who are actually HIV uninfected	B/B + D
Test efficacy	Test performance under ideal conditions	
Test effectiveness	Test performance under practical conditions	
Number of persons with HIV infection who test positive	—	A
Number of persons without HIV infection who test negative	—	B
Number of HIV-positive test results and not infected	—	C
Number of HIV-negative test results with the disease	—	D
Total number of persons	—	A + B

HIV, Human immunodeficiency virus.

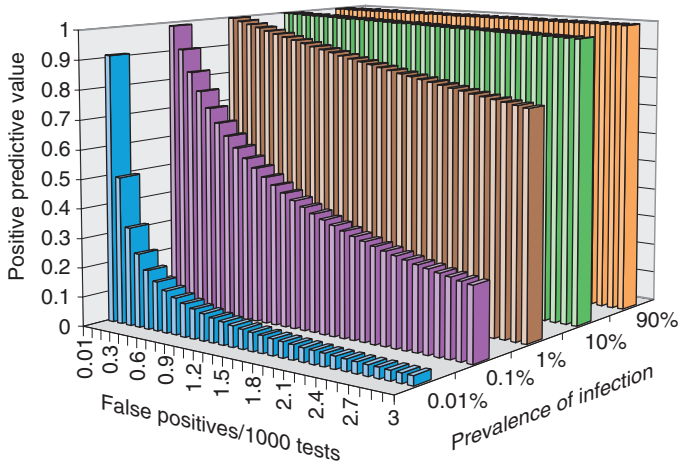

FIG. 120.4 Positive predictive value of HIV supplemental assays is a function of disease prevalence. At very low prevalence of infection in the population (0.01%), the positive predictive value of testing declines sharply with any false-positive testing. As the prevalence of infection in the overall population increases, the positive predictive value improves regardless of a few false-positive results. The HIV screening step eliminates the vast majority of HIV-uninfected individuals; those who screen reactive and are referred for supplemental testing therefore constitute a population with a high prevalence of HIV infection. As such the overall positive predictive value remains high despite relatively few false-positive supplemental results.

from a blood safety standpoint, and several major efforts have been launched to minimize its duration. Initial studies suggested the HIV window period was on the order of 2.1 months,[99] but progressive improvements in ELISA methodology reduced window periods to less than 4 weeks. As shown in Fig. 120.3, HIV p24 antigen or HIV RNA is often detectable before antibody responses, and use of sensitive HIV antigen and nucleic acid have reduced the window period to the current minimum. Limited studies with other HIV antigens have demonstrated early detectable reverse transcriptase after infection.[100] It is important to note, however, that studies of viral and immune kinetics to estimate the duration of the HIV window period use established seroconversion panels consisting of serial samples obtained from patients with known exposure history.[101] The levels of HIV-1 viremia vary in patients, and the rate of change of HIV RNA levels or production of antibodies during acute HIV infection is unpredictable; thus generalizations regarding the timing of seroconversion in such panels (or in newly infected patients) remain imprecise. Instead, analyses describe only average changes in the window period relative to an established comparator method. In general the average window period with third-generation antibody tests is 22 days. Standard antigen testing in fourth-generation assays decreases the window period to approximately 16 days, and NAT further reduces this period an additional 4 to 6 days.[54,102]

Once established, HIV seroreactivity is typically lifelong, although several exceptions have been reported.

1. Late in the course of HIV-1 infection, in the presence of profound immunodeficiency, antibody levels may decline, potentially confusing serodiagnosis. Levels of HIV expression remain relatively high, and detection of HIV RNA is likely to be positive.
2. In rare cases HIV infection may proceed in the absence of detectable serologic markers.[103–113] Typically, such patients have been characterized by rapid disease progression.
3. Early introduction of ART may delay the development of full antibody responses to HIV infection.[114] In addition, introduction of ART may permit humoral immunity so that immunosilent infection may be detected.[115,116] Therapy may decrease the relative levels of anti-HIV antibodies and may affect detection by certain diagnostic platforms.[117,118]

In these unusual circumstances it is typically straightforward to reconstruct the clinical course and establish HIV diagnosis; careful history and dual antigen-antibody (Ag-Ab) and especially NAT assays are useful for clarification.

HIV Screening Assays

Serologic Techniques to Detect Anti-HIV Antibody

Standard ELISA Assays

HIV-1 ELISA assays were the earliest approved serologic tests for HIV infection and remain the most sensitive commercial assays for infection. HIV-1/2 ELISA assays have evolved over a number of generations to

maximize sensitivity and specificity. All assays capture HIV antibody using immobilized HIV antigens. In their earliest iterations, whole-cell lysates of infected cells were used to coat ELISA wells. Incubation with patient sera permitted anti-HIV antibody to bind to the immobilized antigens and the bound antibody was identified using enzyme-conjugated antihuman IgG. The amount of measured enzyme activity is proportional to the amount of bound antibody. Readout for ELISA assays is quantitative (e.g., optical density or fluorescence measurements), and reactivity is defined as enzyme activity exceeding an established threshold. Techniques to produce recombinant HIV-1 antigens[119–121] and chemically synthesized HIV peptides eliminated the use of cell lysates, thereby increasing specificity and sensitivity. Third-generation assays used a sandwich technique with enzyme-coupled HIV antigens and took advantage of the bivalent or multivalent nature of antibodies to improve specificity. Only antibodies bound to ELISA wells that also bind HIV antigens generate a signal; nonspecifically bound antibodies would be less likely to bind HIV antigens.[122] Sandwich technology also expands subtypes of antibodies detected. In direct ELISA assays the conjugate is directed against a specific antibody subtype (e.g., IgG), whereas sandwich technology permits detection of any antibody class, including IgM. Sandwich ELISA thus increased ability to detect HIV antibodies early in HIV infection,[123] and has been adapted in new formats, including immunochromatography, and has been expanded to detect HIV p24 antigen in addition to detecting anti-HIV antibodies (see later); the combination of advances in immunochromatography and sandwich technology to detect p24 antigen forms the basis for the most sensitive HIV screening assays (e.g., Alere Determine; Abbott, Abbott Park, IL; see Table 120.1). Screening tests have also been adapted for epidemiologic use in detecting incident HIV infection.[124]

Efforts to improve HIV detection during HIV-1 seroconversion period have led to combining the standard third-generation ELISA assay with a p24 antigen detection assay with increased sensitivity; microparticles and sandwich strategies are incorporated into microparticle technologies. Monoclonal antibodies to HIV p24 are immobilized onto microparticles, and along with HIV-1 antigens and HIV-2 peptides, the patient sample to be analyzed is added to the well, and any antibody and/or antigen is captured to form a complex. After a wash step, enzyme-labeled anti-p24 antibody and HIV-1 and HIV-2 antigens are added to form antibody-antigen-antibody or antigen-antibody-antigen conjugate complexes; finally, a substrate is added to provide a detectable signal proportional to the amount of bound enzyme.

Particle Agglutination Assays

HIV antigen antibody reactions have been used to develop relatively rapid, simple assays that do not require colorimetric readout. Such assays, denoted particle agglutination (PA), are based on the ability of sera containing HIV antibodies to cross link small particles containing HIV antigens on the surface (Fig. 120.5). PA has advantages of sensitivity and relatively high inherent specificity because the presence of bivalent or multivalent reactions is necessary for agglutination to occur. PA assays are relatively easy to perform and require little equipment and as such have important advantages for resource-poor areas.[125–130] Assays based on particle agglutination have been FDA approved[45]; PA are subject to reader interpretation, are time sensitive, and have no permanent records of agglutination reactions.[45,131] Nevertheless, in large field trials and hospital-based studies, PA platforms are quite robust, performed well for HIV screening,[132–134] and have reported utility with dried blood spots.[135] Moreover, advances in particle research with miniaturization and use of paramagnetic particles has been useful in development of new detection methodologies, including new fourth-generation tests.

Alternative ELISA Formats: Simple/Rapid Tests

Despite excellent performance characteristics, there are significant drawbacks of current HIV screening assays, including delays from the time of sample collection to reporting and the complexity of assay procedure. In the United States, publicly funded programs perform approximately 2.1 million HIV tests; in 2000, 30% of patients with positive results and 39% with negative results did not return to obtain test findings. The need for simple HIV detection assays for point-of-care sites and resource-poor circumstances has spurred development of a class of more user friendly kits known as "rapid" and "simple/rapid." Simple and rapid tests are manufactured in a variety of formats, and WHO and the CDC differ in details of definition (storage requirements, time required to obtain results). In general, these assays use lateral or capillary flow of sample along a solid support to permit interaction with an embedded antigen; controls are included to identify nonspecific reactivity. Simple tests react with antigen in variable storage requirements at ambient temperature using whole blood as substrate and require little or no equipment. Rapid tests are completed in less than 15 minutes (WHO) or in 30 minutes or less (CDC). Simple/rapid tests require confirmation but have been used in circumstances of emergency detection (e.g., pregnant women at time of delivery).

Sensitivity of rapid testing methods is sufficiently high with non-B HIV subtypes and with group O viruses,[136,137] and several kits include detection of HIV-2. In seroconversion panels, however, rapid testing may be less sensitive than conventional assays; Makuwa and coworkers[136] found rapid tests were positive 2 to 8 days after a conventional third-generation ELISA using a seroconversion panel including subtypes A, B, and C. Similarly, WHO surveys noted that in some panels, p24 antigenemia was detectable before simple/rapid assay–positive results. Brauer and colleagues[138] recently evaluated the only currently available fourth-generation rapid assay, finding a detrimental low sensitivity for p24 (10%) in seroconversion panels, implying that most of acute infections would be missed with this assay.

Nevertheless, strategies have been evaluated to use sequential independent rapid testing assays exclusively for HIV screening and confirmation.[139,140] Dual ELISA formats may yield higher false-positive results.[140]

Use of rapid HIV testing has resulted in increases in frequency of patient populations receiving test results, including pregnant women,[141] individuals attending sexually transmitted disease (STD) and outpatient clinics,[142] and patients presenting in emergency departments.[143] Modeling studies using the performance characteristics of the Single Use Diagnostic System (Abbott) rapid test kit suggested significant increases in numbers of individuals who would have learned their serostatus.[144] Rapid HIV testing permits early counseling and discussion of risk reduction and therapy but is challenged by the consequences of immediately discussing unexpected test results. For example, in a randomized study of rapid versus conventional testing in pregnant women, more women in the rapid testing arm were likely to obtain their serostatus results but were *less* likely to return for ART compared with women who received their results in a traditional follow-up appointment.[145]

Development of rapid and simple assays and worldwide experience with ELISA formats as supplemental assays led to new studies of the potential for alternative strategies. In domestic US settings this was rigorously analyzed[146] in the context of FDA sensitivity/specificity requirements, and it was concluded that some dual formats excluding WB may provide appropriate performance characteristics and may have fewer indeterminate or discordant results. These initial studies fueled new initiatives to develop supplemental assays that aid in the diagnosis of HIV infection. In parallel, advances in immunochromatographic applications for serologic detection offered new and useful modalities to detect HIV.

Saliva as Source of Patient Material for ELISA Assay

The difficulty, expense, and risk involved in obtaining blood for HIV detection has led to investigation of alternative sources for diagnosis. Several investigators noted the presence of anti-HIV antibodies in saliva, which contains little, if any, infectious virus[47,48,147] and can be obtained safely without the risk of needlestick injury.[148,149] Oral fluid consists of saliva, bacteria, mucus, debris, and a crevicular transudate containing significant and detectable levels of anti-HIV antibodies in infected individuals.[49,150] The presence of anti-HIV antibody appears to be transudative in origin and generally, although not exclusively, is the result of local synthesis.[151,152] Both IgA[48] and IgG classes are present, but anti–HIV-1 IgG is present in greater abundance; even so, anti–HIV-1 antibodies in saliva are nearly 1000 times lower in concentration than

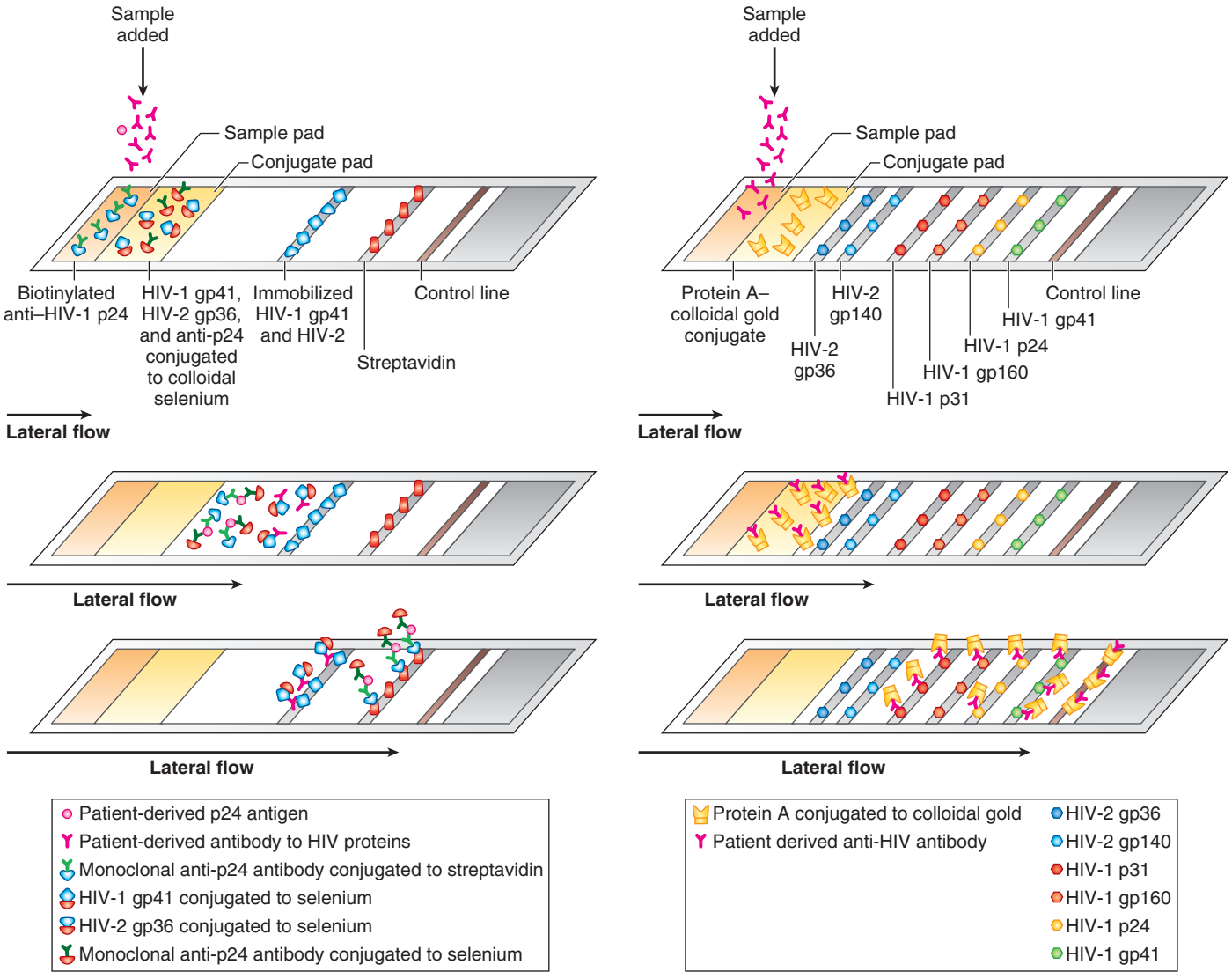

FIG. 120.5 Current ELISA strategies for HIV detection. (A) Fourth-generation detection of HIV antigen and antibody by immunochromatography. Sample is applied to the sample pad impregnated with monoclonal anti-p24 antibody conjugated to biotin. If HIV p24 is present in the sample, it binds to anti–p24-biotin conjugate; sample is carried through the conjugate pad containing HIV-1 gp41 and HIV-2 gp36, each conjugated to selenium, as well as monoclonal anti-p24 conjugated to selenium. If p24 antigen–anti-p24–biotin is present, it is bound by anti-p24 conjugated to selenium. The p24-antibody sandwich continues to travel along the strip by lateral flow until the complex reaches a line of immobilized streptavidin, which captures the complex via binding to avidin; as these complexes accumulate they generate a pink-red precipitate. In parallel, patient-derived anti–HIV-1 gp41 or HIV-2 anti-gp36 binds gp41-selenium or gp36-selenium, respectively, and those conjugates travel by lateral flow along the strip until they are captured by a line of immobilized gp41 or gp36, creating a pink-red precipitate as they accumulate. These sandwiched antibody or antigen precipitates are then visualized by the operator. A final line, which will react with any antibody serves as a positive control. (B) Immunochromatographic supplemental assay to detect HIV. Sample containing antibodies to HIV-1 (p24, p31, gp160, gp41) or HIV-2 (gp140, gp36) is applied and travels by lateral flow. The sample first encounters protein A conjugated to colloidal gold; protein A will bind antibody molecules regardless of antigen specificity, and HIV antibody–protein A conjugate continues to travel along the strip until it encounters corresponding immobilized proteins, where the complex accumulates and gradually creates a pinkish-red color, which is visualized by the operator. A final line binding all antibodies represents a positive control that the sample was applied and lateral flow took place. *Ag-Ab,* Antigen-antibody; *ELISA,* enzyme-linked immunosorbent assay.

in serum.[153] Nevertheless, IgG levels remain sufficiently high for measurement by both ELISA and WB techniques.[46,154,155]

Oral fluid detection of HIV-1 has excellent performance characteristics, comparable to that detected using serum.[46,154,155] Recently, O'Connell and coworkers[118] reported several false-negative results using oral fluid testing in patients with HIV infection who have undergone ART early in the course of HIV infection. It is possible that partial resolution of polyclonal gammopathy reduced transudative IgG levels, thereby reducing sensitivity. Obviously, patients on ART will be identified as HIV infected, but there are circumstances where such patients may be unwilling to disclose their status. Such false-negative results may have an impact on new HIV testing development, as new assays will likely be tested in positive, control, HIV-infected patients who may be undergoing therapy.[118] Instances of false-positive oral HIV testing have been reported.[156] The etiology of such occurrences remains uncertain, although recent data suggest an increasing false-positive rate as test kits reach expiration dates.[157]

Although little, if any, infectious HIV is present in saliva, HIV DNA was detected in crevicular fluid samples from patients with gingivitis or periodontitis, even in the absence of local bleeding.[158,159] The source

of HIV nucleic acid in these circumstances is unclear, although oropharyngeal shedding may contribute.[160]

Saliva IgA has been investigated as source material to diagnose HIV infection in newborns. Early studies in newborns and infants suggested that determining anti-HIV IgA might represent a useful assay to specifically identify HIV infected infants[161]; more recently, several studies have suggested lower sensitivity and greater nonspecific reactivity for saliva IgA detection.[162,163]

Although use of nonbloody oral fluid reduces possibilities for exposure to HIV, there remain concerns for potential exposure to other infectious agents, particularly tuberculosis.[164]

Urine as Source of Patient Material for ELISA

Urine as a source of patient material for HIV detection offers relative ease of collection and high sensitivity.[165] As levels of HIV IgG in urine are relatively low (estimated in the range of 1 mg/L), sensitive techniques are required for detection; ELISA assays were developed and were approved in 1996, followed by WB assays in 1998. There are no FDA-approved simple/rapid tests for urine approved as of 2009. False-positive results have been identified with urine,[166] although performance characteristics are generally excellent. One potential advantage of urine is that a single sample can be used to investigate the presence of chlamydia and gonorrhea in addition to HIV-1.[167]

SEROLOGIC TECHNIQUES TO SCREEN FOR HIV ANTIGENS

Acute HIV-1 infection is characterized by relatively high levels of viremia compared with the levels of various anti-HIV antibodies[168] (see Fig. 120.4). As a result, there is a short but significant period in early infection during which p24 antigen is present in the absence of specific anti-p24 antibody. ELISA techniques have been developed to specifically detect p24 using polyclonal patient-derived IgG preparations or monoclonal antibodies to coat ELISA wells. Wells are incubated with dilutions of patient sera, washed, and bound p24 is detected using a second anti-HIV antibody conjugated to a colorimetric detection system. HIV antigen capture assays detect as little as 5 to 20 pg of p24. Assuming all p24 in blood is from intact virions and that there are approximately 3000 p24 molecules per virion, the limit of p24 detection is in the range of approximately 40,000 to 200,000 virion particles.

Clinical application of p24 antigens revealed that newly infected patients had transient p24 detectable levels,[33,35] and that p24 antigenemia in established disease suggested a poor prognosis.[34] As antibody to p24 develops, complexes of p24 with endogenous antibody interfere with laboratory detection, and p24 sensitivity is reduced.[36] Methods incorporating pH adjustment or heat treatment to dissociate p24 Ag-Ab complexes have resulted in increased p24 detection sensitivity, and immune complex dissociation results in more frequent detection of antigenemia late in disease.[169,170] The combination of heat denaturation and signal amplification using biotinylated tyramide has extended the lower limit of signal detection to 0.5 pg p24 (≈4000 virion particles) has been reported,[171–173] suggesting this assay may be particularly attractive in resource-limited areas without the capability to perform quantitative HIV-1 RNA levels. Gag p24 protein is a relatively well-conserved protein among HIV-1 variants, and commercially available kits have performed consistently well even with diverse HIV-1 subtypes, but new p24 panels have been developed to represent the wide diversity of subtypes for sensitive detection.[174]

FOURTH-GENERATION HIV ANTIGEN-ANTIBODY ASSAYS

Improvements in sensitivity in p24 detection, combined with improvements in sandwich antibody testing, which could both be adapted to immunochromatographic formats, permitted development of rapid fourth-generation testing modalities, which have become the standard for initial evaluation of HIV-infected individuals. Fourth-generation testing (see Fig. 120.5A) involves application of the test sample into a lateral flow immunochromatographic device, in which patient sera or plasma is applied to a sample pad, where it first encounters anti-p24 antibody conjugated to biotin p24 Ag-Ab conjugates, and HIV antibodies travel by lateral flow to a conjugate pad containing HIV detection reagents conjugated to selenium, including a second anti-p24 antibody and peptides from HIV-1 (gp41) and from HIV-2 (gp36). Ag-Ab complexes continue to migrate by lateral flow and are captured by gp41 peptide, gp36 peptide, and streptavidin immobilized in lines perpendicular to the lateral flow. Note that lines are visualized only by accumulation of selenium conjugate; as a result, only "sandwiched" Ag-Ab conjugates will yield a visual result. This strategy takes advantage of the increases in sensitivity and specificity afforded by the sandwich approach; the lateral flow adaptation permits simultaneous detection of both antigen and antibody (see Fig. 120.5A).

In a second immunochromatographic application, supplementary assays were developed to detect and discriminate antibodies to HIV-1 and HIV-2 (see Fig. 120.5B) and detect antibodies to specific viral antigens. These rapid assays now provide supplemental assays to detect HIV infection in individuals with reactive fourth-generation assays and to discriminate between HIV-1 and HIV-2 (see Fig. 120.5B). In addition, these lateral flow devices were built after long experience with WB and included detection of HIV-1 p31 so that these new rapid assays could also provide information regarding early HIV infection (p31 negative corresponds to Fiebig V infection). The success of these newer assays has enabled whole-scale replacement of the WB or other prior confirmatory assays and permitted completion of HIV diagnostics in a single visit in many cases, facilitating linkage to care.

FALSE-POSITIVE AND FALSE-NEGATIVE RESULTS IN SCREENING TESTS FOR HIV ANTIBODY

HIV screening assays are designed for highest available sensitivity and specificity; sensitivity is a more paramount requirement for screening because the consequences of a false-negative screening test, which permits HIV infection to proceed undiagnosed, are more profound than a false positive, which will be further evaluated with a confirmatory test. Currently, the false-positive rate in a low-risk population remains low (0.06%–0.12% in the blood donor population),[175] suggesting practical test effectiveness is consistent with performance efficacy. Despite high specificity and sensitivity of HIV screening assays, false-negative and false-positive results may occur. Technical difficulties in assay execution may represent a cause for either false-negative reaction or false-positive results and may represent the most common cause of a false-positive or -negative test result.

False-negative results from ELISA methodology are rare but may arise from the lack of antibodies of sufficient avidity to generate a colorimetric signal above the assay background threshold. Early HIV infection, as described earlier, represents a common cause of low-level antibody production; rare immunosilent HIV infection, without development of antibody response despite HIV replication, and other underlying conditions, such as neoplasms/chemotherapy and common variable immunodeficiency (CVI), represent potential causes of false-negative HIV screening assays; patients with CVI have had detectable seroconversions.[176] Unusual circumstances, such as extensive transfusion, may sufficiently dilute endogenous antibody in infected individuals to yield false-negative HIV results[177]; robust antibody reactivity is not universally present.[178] In the past, technical difficulties, especially in early second-generation assays containing limited numbers of synthetic antigens, represented significant sources of false-negative results[179–181]; currently, such artifacts are highly unlikely sources of false-negative results.

False-positive screening results are more common than false-negative results and may arise from a number of reasons, generally classified as technical artifacts, chronic medical conditions, multiparity, and unusual circumstances. Reports of false-positive ELISA assays are frequent and often occur in the setting of testing patients with low pretest probability for HIV infection; as a result, it is not always certain whether the false-positive result was associated with a particular medical condition or was the result of the false-positive rate of the test itself.

Several medical conditions may contribute to falsely reactive HIV ELISA tests, including chronic alcohol use, rheumatic disease, congenital bleeding disorders, syphilis, and neurocysticercosis. In certain rheumatic diseases, polyclonal antibody production has been a persistent source

of false-positive HIV ELISA results. Specific reactivity for gp41 has been identified in some cases, and p24 reactivity is responsible for false positives in Sjögren syndrome; reactivity is generally of low avidity and has been eliminated by thiocyanate washing.[182] Recent vaccination with hepatitis B[183] or rabies[184,185] has been reported to result in false-positive HIV screening results, although the frequency of these events is likely to be quite low.[186] In 1992 influenza vaccination was reported to be associated with increased false-positive HIV testing; an extensive analysis traced increases in false positives to certain ELISA kit lots, and frequent false reactivity after routine influenza vaccination has not been reported. Multiparous women also have a higher rate of false-positive screening tests for HIV, although the etiology remains uncertain. Fourth-generation assays also have false-positive results; recently, the presence of heterophile antibodies has been reported to result in false-positive assay results.[187]

Acute infections may yield false-positive HIV screening assays; recent infection with dengue, malaria, and hepatitis B has been reported to yield false reactivity. False-positive results have been reported in patients with leprosy using early ELISA assays,[188,189] with antibodies to lipoarabinomannan of *Mycobacterium leprae* implicated as potential cross-reacting antibody,[190] although a study using double-sandwich ELISA did not reproduce the high rate of false-positive results in this population.[191] As primary HIV infection may present as an acute viral syndrome with fever, rash, and numerous constitutional symptoms, thoughtful interpretation of any screening assay in patients with such symptoms is warranted. Recent survey of patients with documented acute mononucleosis did not identify a positive HIV screening assay result.[192] However, several patients with primary HIV infection have been reported with false-positive serologic tests for Epstein-Barr virus infection noted during evaluation.

The presence of HIV infection may affect serologic detection of other infections: False-positive results for syphilis, Ebola, Marburg, and Lassa fever have been reported in patients with HIV infection; HIV infection has been reported to result in occasional false-negative results in human T-cell lymphotropic virus (HTLV)-1/2 assays.[193]

With time and widespread application it is possible that new sources of false-positive results may occur. In needlestick circumstances, samples for HIV testing from inpatients may be obtained from indwelling catheters; samples drawn in such a fashion may become contaminated with vehicles for drugs administered through the catheter. One diluent, propylene glycol, has been reported to give a false-positive result with HIV ELISA assays.[194]

NONSEROLOGIC TECHNIQUES TO SCREEN FOR HIV

Hybridization and Amplification Assays to Detect HIV Nucleic Acids

Use of nucleic acid testing (NAT) represents an adjunct to, but not a replacement for, serologic methods for HIV detection. Various formats can detect HIV-1 RNA with great sensitivity, and new real-time polymerase chain reaction (PCR) methods have been developed capable of detecting a single copy of HIV-1 RNA.[195] Clinical methods for HIV nucleic acid detection for use in monitoring HIV infection have included nucleic acid sequence-based amplification (NASBA), branched DNA (bDNA), and PCR amplification; NASBA formats have detected as low as 22 to 31 copies/mL.[196,197] The first of these methods to be FDA approved for donor screening or diagnosis is a "TMA/HPA" system (Fig. 120.6) consisting of a transcription-mediated amplification (TMA) and hybridization protection assay (HPA), named Aptima, developed by Gen-Probe (San Diego, CA).[54] This modality has been approved *both* for screening and confirmation of infection and only detects HIV-1.

The principle of the TMA/HPA assay is to generate large numbers of HIV RNA copies from HIV-1 for detection by specific hybridization to chemiluminescent probes (see Fig. 120.6). Plasma samples are extracted, and HIV-1 RNA is reverse transcribed to complementary DNA (cDNA) using exogenous murine leukemia virus reverse transcriptase. The primer for the cDNA reaction contains the promoter sequence for the T7 bacteriophage RNA polymerase, followed by sequences complementary to HIV-1. The resulting cDNA product contains T7 promoter sequences linked to HIV-1 sequences, which are used as a template for added T7 RNA polymerase, a high-efficiency enzyme that rapidly transcribes

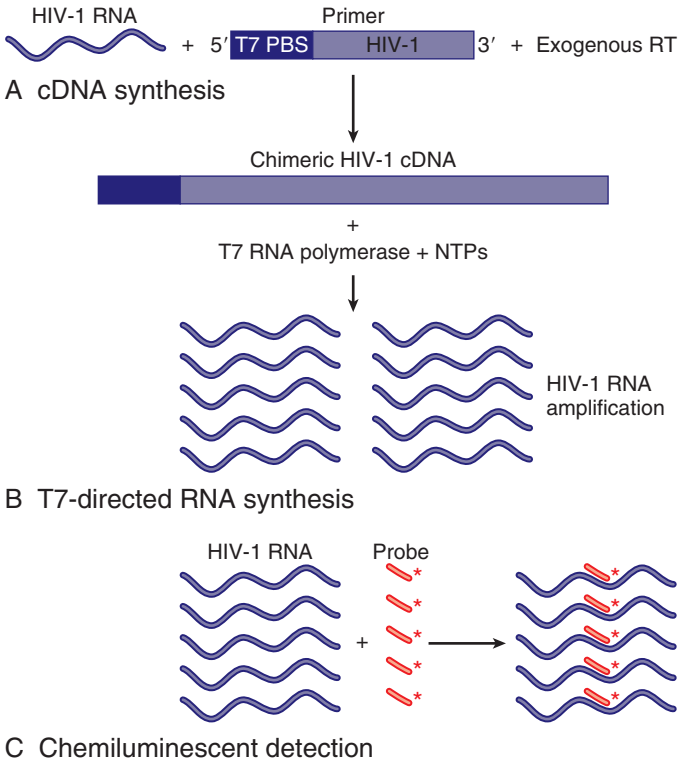

FIG. 120.6 Detection of HIV nucleic acid. Detection of HIV nucleic acid by transcription mediated amplification/hybridization protection assay. (A) Complementary deoxyribonucleic acid *(cDNA)* synthesis. (B) T7-directed ribonucleic acid *(RNA)* synthesis. (C) chemiluminescent detection. *NTPs,* Nucleotide triphosphates; *PBS,* phosphate-buffered saline; *RT,* reverse transcriptase.

multiple copies from the chimeric T7-HIV cDNA. The RNA copies are visualized by addition of chemiluminescent probes, which hybridize to HIV-1 sequences; excess probe is quenched; and the luminescence from the RNA-probe hybrid is quantitated (see Fig. 120.6). The assay is qualitative only and does not yield specific copy number; sensitivity of the assay is in the range of 13 copies/mL plasma.[54] TMA/HPA detected a limited panel of non-B subtypes of HIV-1 equally well. The TMA/HPA assay was sufficiently sensitive to detect HIV RNA 12 days earlier than standard third-generation ELISA and 6 days earlier than p24 assays. Thus one primary application of TMA/HPA is in diagnosis of early HIV-1 infection; the Aptima system was approved for screening and confirmation of HIV-1 in 2006 and should supplant use of bDNA or PCR assays for diagnosis.

Similarly, TMA/HPA technology was developed for blood donor screening. In the United States trials for blood donor screening by NAT screened more than 20 million donations and found seven HIV-infected samples that scored negative for HIV antibody.[102] NAT systems detected a number of HIV-1 infections that would have been missed by previously licensed test methods, confirming the increased sensitivity of these systems.[198] Similarly, trials in Europe, South Africa, and Japan[199–202] and in case reports[203–207] have documented, either in real time or retrospectively, identification of patients in seroconversion windows, using NAT, who had scored negative using p24 antigen detection. By contrast, there are also reports of undetected HIV-1 in the setting of relatively low HIV-1 RNA levels, especially in minipools of 16 or 24 plasma samples,[102] Retrospective analysis of a blood transmission case (before NAT) revealed a relatively low viral RNA level (estimated 40 copies/mL)[208]; the benefit of NAT over traditional testing has been estimated to reduce the window period by 2 to 6 days. Using NAT technology, the risk of HIV infection through transfusion was estimated as 1 per 1,576,000[209]; four cases of p24 antigen negative blood component were identified in more than 19,000,000 screened units.[210] In consequence, the risk of HIV-1

transmission via blood components is reduced, but not completely eliminated, by incorporating NAT into screening procedures; the residual risk of HIV infection in United States is estimated at 1 per 2,135,000.[210] Similar or lower risks have been estimated from other reporting countries,[211,212] and although there are concerns regarding subtype sensitivity and sample preparation, many blood centers throughout the world have incorporated NAT as a component of HIV screening. The relative cost-effectiveness of NAT remains a concern.[199,201,213] NAT is approved in the United States for blood-donor screening using plasma, and assays must be able to detect 100 copies 95% of the time; several assays exceed this limit.[197] Standard subtype B virus preparations have been established as quantitative controls.[214] Testing can be performed on single samples or minipools of plasma and may be combined with testing for hepatitis C and B.

TMA/HPA requires trained personnel and is more expensive than traditional HIV testing or routine HIV RNA quantitation assays, and routine assays have been used for diagnosis in resource-limited settings. NAT has, however, reported both false-positive and false-negative results in plasma.[215,216] A value of 10,000 copies/mL has been proposed as a cutoff for the HIV-1 RNA level above which is suggestive of HIV infection in the nondonor population. NAT has not been extensively used for cadaveric specimens; RNA is chemically labile, and delays in sample processing may present particular challenges in detection by this method. NAT is effective in detecting HIV in serum or dried blood spots,[217] so plasma (nonheparinized) is a more ideal starting material, especially for low copy-number detection.

In unusual circumstances HIV-infected individuals may have TMA/HPA-negative results. As described in Chapter 121, the spectrum of HIV infection includes long-term nonprogressors (LTNPs) with persistently high CD4 cell numbers and relatively low HIV-1 RNA levels.[218] Although LTNPs are HIV-1 ELISA reactive and WB positive, screening with current NATs could not be expected to reliably identify such individuals as HIV infected. As reported by Migueles and coworkers,[219] the HIV-1 RNA levels in LTNPs with naturally suppressed viremia are approximately two copies/mL plasma, below the limit of reported detection for TMA/HPA.[219] At present, NAT systems for patient analysis only detect HIV-1; currently, there are no FDA-approved HIV-2 NAT kits. In the United States, NAT blood bank screening procedures do not evaluate the presence of HIV-2 infections, although assays for HIV-2 RNA have been developed to monitor known infections and have been useful in characterizing samples identified from blood donors.[220]

NAT performance characteristics have been established largely with subtype B virus. HIV-1 RNA detection assays used to monitor HIV infection have been adapted for use with alternative HIV subtypes. A collaborative study of 28 laboratories from 16 countries evaluated an HIV-1 RNA Genotype Reference Panel for use with NAT[221] that contained six pure subtypes plus two recombinants (CRF01_AE and URF A/G) from group M and two isolates from group N and O, respectively. Despite some interassay differences, subtypes A to D and AE were detected consistently, but some assays had difficulty with the detection and quantification with subtypes F and G and the representative of group N; most assays failed to detect group O. More recent NAT assays have been designed to overcome the impact of HIV diversity on HIV detection, but some peculiar strains can still affect NAT efficiency. In a case report Foglieni and coworkers[222] described a repeat blood donor seroconverting to anti-HIV antibodies but showing undetectable HIV RNA at diagnosis and 2- to 3-log lower viral load during follow-up when compared with other NATs targeting different regions; genome sequencing revealed a B/F recombinant with mutations affecting primers and probe annealing. Genetic variation in HIV subtypes have prompted WHO to standardize strategies for testing for HIV and other NATs.[223]

HIV SUPPLEMENTAL AND CONFIRMATORY ASSAYS

HIV-1/2 ELISA for Confirmation of HIV Infection

In the United States and many western countries the requirements for optimum sensitivity and specificity in HIV testing have generally been supplied by sequential ELISA-WB formats. ELISA assays have been used to provide confirmation of HIV infection, especially in developing countries with limited resources to support WB or immunofluorescence assays. As described later, WHO has established several strategies incorporating dual ELISA formats with distinct design formats for diagnosis algorithms. In 2013 the FDA expanded the approval for the HIV MultiSpot ELISA screening test to include confirmation as part of a new CDC-proposed algorithm. MultiSpot uses sample concentrated onto a solid-phase membrane to overcome relatively slow, diffusion-mediated interactions between immobilized ligands and free analytes in solution.[224] The initial HIV-1/2 discriminatory assay, MultiSpot, consisted of immobilized ligands, including recombinant gp41, an immunodominant gp41 peptide, and a gp36 immunodominant peptide representative of HIV-2 isolates, as well as a procedural control consisting of goat antihuman IgG. Patient samples are added to a cartridge, which is then concentrated onto the membrane, and antibodies reacting with immobilized ligands are detected with goat antihuman antisera. In a series of studies the sequential use of a third-generation HIV ELISA, followed by MultiSpot, was equivalent to the standard ELISA-WB algorithm.[225–228] The MultiSpot approach also detected HIV antibodies in individuals with decreases in anti-gp41 antibodies as the result of ART. A newer discriminatory assay (see Fig. 120.5B) distinguishes HIV-1 and HIV-2 in an straightforward immunochromatographic approach with equivalent performance characteristics that have supplanted the prior MultiSpot assay.

WESTERN BLOTTING

HIV WB represents a specific method to detect the presence of serologic reactivity to individual viral antigens. WB has a specificity of greater than 99% and was the practical gold standard confirmatory test for HIV infection in the United States for many years (see Fig. 120.1). New supplementary assays have replaced WB as a confirmatory or supplemental assay; detailed description of this technique can be found in Chapter 122 of the eighth edition of *Principles and Practice of Infectious Diseases*.

IMMUNOFLUORESCENCE

Indirect immunofluorescence assay (IFA) is a standard virologic technique to identify the presence of antibodies by their specific ability to react with viral antigens expressed in infected cells; bound antibodies are visualized by incubation with fluorescently labeled antihuman antibody.[229,230] A requirement for antibodies to demonstrate reactivity with characteristic staining patterns provides additional specificity to the interpretation. Indirect immune fluorescence had been used extensively as a confirmatory assay in HIV diagnosis,[230,231] and continues to be used in laboratories with extensive experience with the assay. The presence of HIV antibodies is demonstrated by intense cytoplasmic immunofluorescence in cells observed in multiple fields as determined by an experienced examiner. Negative results consist of no significant difference in background fluorescence staining in positive and negative cells; results that are neither positive or negative (denoted "other" or "indeterminate") may be obtained as well when intense fluorescence is present in uninfected cells and infected cells. Conditions interfering with immunofluorescence include severe lipemia, hyperbilirubinemia, paraproteinemia, and autoimmune diseases. IFA for HIV-2 has been described,[232] but no FDA-approved kits for this purpose are available in the United States.

Performance characteristics for IFA remain excellent and in good agreement with other supplemental/confirmatory tests such as WB results.[233] In a MPEP survey no false positives were detected, and 14.3% of 215 results were indeterminate. Commercial IFA assays are relatively rapid, straightforward, and inexpensive[234] but require special equipment and expertise; nevertheless they may be particularly suited for programs with limited resources.[235] In the United States IFA has largely been replaced by fourth-generation testing. The Home Access system, approved in 1996, however, continues to use IFA as confirmatory testing.[236]

Radioimmunoprecipitation assay (RIPA) is a standard technique to identify the presence of antibodies by their ability to react with

radiolabeled antigens.[237–239] Antigens may be labeled by iodination or metabolic labeling, in which HIV-infected cells are grown in the presence of radioactive amino acids, resulting in the incorporation of label into HIV proteins. Lysates of radiolabeled cells are incubated with dilutions of patient serum; complexes of radiolabeled antigen-HIV antibody are harvested using reagents such as Sepharose-bound protein A. Radioimmunoprecipitations are highly specific and were used as early confirmatory assays.[238] In some circumstances, RIPA may be more sensitive than WB reactivity. Huisman and coworkers[237] detected early Gag p24 reactivity before ELISA reactivity, and Saah and coworkers[240] noted the utility of radioimmunoprecipitation in resolving indeterminate WB early in infection. RIPA is still likely less sensitive than p24 assay or NAT, as described in case reports of analyses of serial specimens from seroconversions.[241] Techniques to distinguish HIV-1 and HIV-2 have been reported.[242] Radioimmunoprecipitation assays are relatively labor intensive, have specific equipment and laboratory requirements, and do not have commercial versions approved by the FDA.

VIROLOGIC TECHNIQUES TO DETECT HIV INFECTION

Isolation of HIV by in vitro cultivation techniques remains a useful method for establishing HIV infection. Although the levels of HIV in plasma may be relatively high, the proportion of circulating viremia that is capable of transmitting infection is relatively low; thus use of serum or plasma for HIV cultivation is relatively insensitive. Use of peripheral blood mononuclear cells (PBMCs) from HIV-infected individuals as a source of HIV has a much higher rate of positive isolation, especially if PBMCs are CD8 depleted. PBMCs may be cocultivated with uninfected donor PBMCs, activated with phytohemagglutinin, and cultivated with interleukin-2 to increase detection. To increase detection of HIV with CCR5 specificity, monocyte-derived macrophages may be used for cocultivation.

DIAGNOSTIC ALGORITHMS AND PRACTICAL APPLICATION OF HIV DETECTION ASSAYS

Several algorithms for HIV detection have been devised, depending upon the purpose of the detection. In the United States the diagnostic algorithm underwent major revision as new fourth-generation assays were approved for confirmation of HIV infection; in that setting the CDC recommended new diagnostic approaches, which are now universally accepted in the United States (Fig. 120.7). In the new algorithm fourth-generation testing represents the first stage in testing; samples reactive by either Ag or Ab reactivity are subjected to HIV-1/2 differentiation assay as a supplemental assay (see Fig. 120.7). In the cases of discordant results (differentiation assay is negative), early HIV infection may be suspected, and HIV-1 NAT is recommended (see Fig. 120.7). In any case of uncertainty, repeat testing is typically quite useful, as the repeat samples will typically be from a later time point in the HIV infection profile, permitting a more mature serologic response to develop.

HIV-1/2 Screening Phase

Screening for HIV begins during the patient interview. As described earlier, HIV testing is imperfect, with a significant false-positive rate in low-prevalence populations. For patient diagnostic purposes, efficient application of HIV testing should be implemented after some risk assessment and with serious consideration of scientific and ethical consequences.[243]

In the United States the CDC revised guidelines describe populations recommended for HIV testing.[71] New guidelines recommend routine screening for HIV infection in all persons 13 to 64 years of age presenting in all health care settings, unless HIV prevalence is <0.1%. Testing is recommended for any patient presenting with an STD, viral hepatitis, or tuberculosis. Repeat screening is indicated for persons with elevated risk for HIV infection, for persons engaging in sex with a new partner, and in persons with occupational HIV infection.

All screening ELISA tests with reactive results are automatically repeated in duplicate; repeatedly reactive samples are referred for confirmation. In cases of discordant results an independent blood sample should be obtained, and a screening HIV-1/2 ELISA should be repeated; use of an independent approved HIV-1/2 ELISA kit using a different detection strategy may be considered. Nonreactive results identify patients who are at elevated risk but do not have detectable infection. Such individuals represent a critical population that requires continued care and counseling.

Acute HIV Infection

Individuals in whom acute HIV infection is strongly suggested represent a potentially difficult but important group to diagnose correctly and quickly, especially if early ART is under consideration. In general, a fourth-generation Ab-Ag ELISA and appropriate HIV-1 RNA detection provide essential information in a timely fashion. In contrast, other

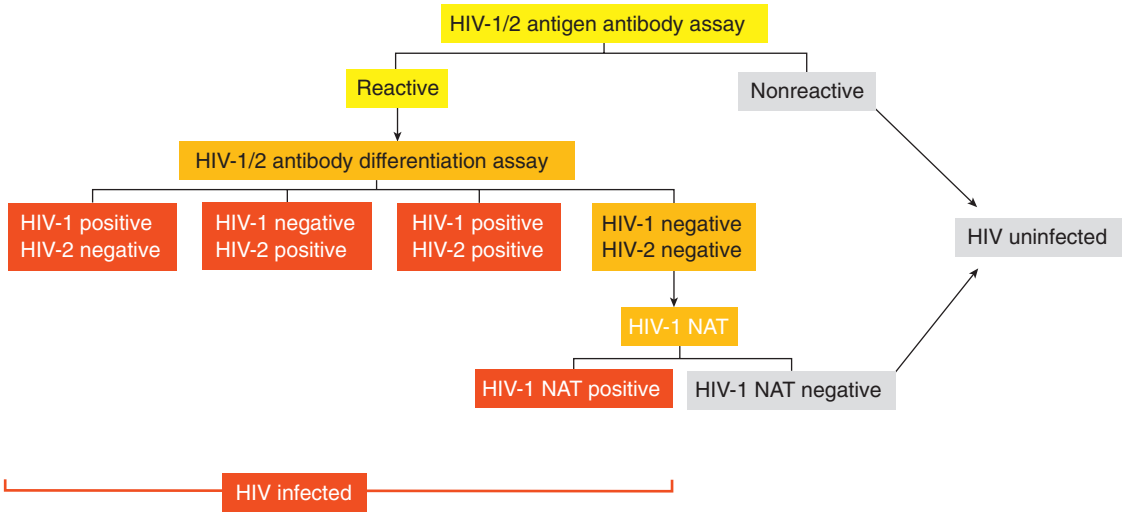

FIG. 120.7 HIV testing algorithm. Initial testing is performed with HIV-1/2 antigen antibody assay (see Table 120.1; HIV-1/2/HIV-1 p24 platform; assay depicted in Fig. 120.5A). Samples that are reactive for either antigen or antibody are referred for supplemental testing with HIV-1/2 antibody differentiation assay (see Table 120.1 for assays, strategy depicted in Fig. 120.5B). Where HIV antibody is present, the differentiation assay confirms the presence of HIV antibody and distinguishes HIV-1 from HIV-2; if antibody is not detected, the sample may be from an early HIV infection, and the sample is referred for HIV-1 NAT. If the NAT is negative, then the patient is not infected, and the initial HIV-1/2 antigen-antibody assay was a false-positive result. *NAT,* Nucleic acid testing.

rapid testing modalities, especially oral, urine, and home testing modalities, have decreased sensitivity during the acute infection period.

Repeated reactivity with HIV-1/2 ELISA, positive qualitative NAT assay, or positive p24 antigen represents a positive screening test for HIV infection; the presence of positive NAT or p24 is strongly suggestive of early HIV infection. TMA/HPA qualitative NAT is approved as a screening *and* a supplemental assay (but not both in a single individual). Thus, in the acute HIV infection before seroreactivity by ELISA-WB, a positive p24 and positive NAT represents HIV infection. In circumstances of discordant results a repeat specimen should be obtained. Even where p24 and NAT are positive, repeated serologic testing is advisable, especially if early ART is considered. Serologic reactivity evolves in a relatively reproducible fashion. Fiebig and colleagues[243a] proposed an early HIV infection staging system based on NAT, p24, and serologic reactivity patterns (Fig. 120.3): Fiebig I–positive HIV RNA, negative p24 antigen, negative third-generation enzyme immunoassay (EIA); Fiebig II–positive HIV RNA, positive p24 antigen, negative third-generation EIA; Fiebig III–positive HIV RNA, positive p24 antigen, positive third-generation EIA, negative WB; and Fiebig IV–positive HIV RNA, positive or negative p24 antigen, positive third-generation EIA, and indeterminate WB. All subjects had to have a nonreactive EIA by non–IgM-sensitive EIA. The corresponding mean cumulative durations from onset of HIV infection, according to Fiebig and coworkers, are 5 (Fiebig I), 10.3 (Fiebig II), 13.5 (Fiebig III), and 19.1 (Fiebig IV) days.

HIV-1/2 Supplemental Analysis

Samples repeatedly reactive in screening assays are referred for supplemental testing (see Fig. 120.7). These supplemental/confirmatory tests approved by FDA include HIV differentiation assays (e.g., GEENIUS), WB, IFA, and qualitative NAT. In current practice ELISA differentiation assays are now most commonly used, replacing long-standing use of WB assays. New assays are flexible and can be performed in a rapid fashion, permitting more effective linkage to care.

Test Counseling

Pretest and posttest counseling sessions represent critical opportunities for health care professionals to impact HIV transmission and are an integral part of the HIV testing process. Patient counseling is a paramount concern in patient diagnosis, and use of specially trained counselors should be considered. In general, typical pretest counseling includes a discussion of the importance and limitations of the assays; a discussion of behaviors to reduce risk of contracting HIV; implications of positive results, including effects on employment; and insurance. Consent for HIV testing, including implied opt-out testing, should be explicitly documented as part of clinical evaluation, and in some circumstances this may require written signed consent from patients. Posttest counseling involves a discussion of the results and their accuracy, the implications of negative and positive results, and consideration of behaviors that may prevent transmission or acquisition. When testing is performed outside the health care circumstances, opportunities for pretest and posttest counseling remain essential.

Notification strategies are traditionally carried out in a face-to-face manner, to permit broad discussion and to address patient concerns. Telephone counseling was found to be surprisingly effective in home collection strategies,[244] and alternatives to face-to-face discussions may be advantageous in certain circumstances. Tsu[245] compared direct (face-to-face) and telephone notification (patients called to obtain results) in a randomized trial of 351 at-risk and homeless youth; a significantly higher proportion of individuals in the telephone notification group received testing results and posttest counseling compared with those who returned to receive information face to face. Counseling has always been a component of home collection services and has been incorporated into new home testing, including web-based information, 24-hour telephone contacts, and referral services.

Alternative Strategies for Screening/Confirmation HIV Detection

Although the sequential screening and supplementary assays is a sensitive and specific approach for HIV detection and has been useful in United States and developed countries, it is relatively expensive, labor intensive, and requires special equipment; alternative strategies are essential for detection of HIV antibodies in resource-poor circumstances. Initially, dual ELISA strategies, using assays with different principles or antigens, have demonstrated >99% sensitivity and specificity in field tests using HIV subtypes appropriate for resource poor areas.[246–254] Poor-quality testing remains an infrequent but preventable error; improving both test quality and implementation of test algorithms will be essential in widespread expansion of initiatives and procedures for HIV testing.[255]

WHO and UNAIDS[137,256,257] initially developed three alternative strategies for detection of HIV infection: designed for surveillance of blood supply (strategy I), surveillance and diagnosis (strategy II), and diagnosis (strategy III). Subsequently, diagnosis recommendations have been clarified,[258] and current recommendations include ELISA strategies: two sequential reactive ELISA results for HIV diagnosis in high-prevalence areas (>5% HIV infection) and three sequential ELISA reactive results in low-prevalence (≤5% HIV infection) areas.

SPECIFIC CIRCUMSTANCES AND SPECIAL POPULATIONS

HIV Diagnosis in Individuals Undergoing Preexposure Prophylaxis

Several studies have directly addressed the use of ART either as PrEP or as early treatment to prevent HIV transmission and have shown these approaches to have great promise as tools for HIV prevention[259] (see Chapter 119). Testing that gives accurate HIV infection status is important so that only uninfected individuals are given PrEP. Detection of acute infection is important as demonstrated by results from the PrEP study. In this study two individuals with undetected acute HIV infection were randomized to the PrEP arm of the study and developed drug resistance, highlighting the importance of accurate diagnoses when implementing PrEP; guidance for the use of PrEP[260] recommends HIV testing before PrEP. Since the development of HIV testing, more than 40 million individuals have been identified with HIV infection. The success of PrEP and PEP requires that many more individuals will need to be followed and sequentially tested for HIV infection, placing an enormous burden on testing modalities in correctly detecting HIV in low-prevalence and early infection populations. The approach to evaluation of all PrEP and PEP circumstances should have three components: at the initial visit, a careful history establishing the time line of all potential exposure events; second, relevant physical examination and laboratory tests should be performed to determine whether HIV infection is already present at the time of the visit, which may predate the presenting history; and finally, the timeline of ongoing visits to track the effect of PrEP or PEP interventions must be established, which will include additional testing. Clinicians should strongly consider that individuals presenting for either PrEP or PEP may already have early or acute HIV infection, and HIV screening modalities should be chosen accordingly. Similarly, repeat testing is essential during the course of PrEP and PEP and after discontinuation to exclude a window period infection that was suppressed and not detectable by routine testing during PEP.

Widespread implementation of PrEP strategies will have a profound effect on HIV spread, but successful programs require rigorous diagnostic accuracy. PrEP consists of a two–antiretroviral drug combination and is inadequate as therapy for established HIV infection. Incident infections during PrEP are commonly due to nonadherence with PrEP regimens, less frequently to initiation of PrEP during the occult window period infection,[261] and rarely due to true PrEP regimen failure.[262] Laboratory assays for HIV infection should use assays with the highest sensitivity. Fourth-generation Ag-Ab combination assays are likely to become the standard for routine evaluation; oral screening assays are likely to be inadequate because of decreased sensitivity.[263–266] Ongoing evaluation should be individualized. Some individuals undergoing PrEP may use self-testing or other testing modalities that are less sensitive to detect early HIV infection; an accurate history and precise understanding of the performance characteristics of testing is essential for comprehensive patient evaluation; and there may be circumstances requiring more frequent monitoring and NAT evaluation.