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Modeling interventions to assess HIV epidemic impact in Africa

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Mid-2011 marks the 30th anniversary of the first reports of the AIDS.[1–3] Many scientists who engaged the field of HIV/AIDS in the 1980s did so because their professional disciplines were copacetic with the challenges faced in HIV discovery, as with T-cell immunologists, retrovirologists,[4] oncologists, behavioral scientists, infectious disease clinicians, and epidemiologists. Others were moved to study HIV disease because of their clinical and/or personal experiences with the disease.[5] Many of us who cared for dying patients in the pre-antiretroviral era still felt empowered by the epidemiological insights of the day, that we might be able to prevent infection through behavior change and scientific discovery.[6]

Behavioral and structural changes based on the "ABC" principles of delayed sexual debut among, the young ("**a**bstinence"), reduced numbers of sexual partners ("**b**e faithful"), and use of barriers to viral infection ("**c**ondoms") have reduced viral transmission in such nations as Uganda and Thailand.[7,8] Distribution and use of clean syringes and needles have reduced markedly the spread of HIV among persons who inject drugs in North America, Europe, and elsewhere.[9] Three stellar randomized clinical trials in South Africa, Kenya, and Uganda have shown that adult men undergoing medical circumcision are half as likely to acquire HIV infection as are uncircumcised men.[10–12] We know that exclusive breastfeeding by an HIV-infected mother will reduce risk of transmission to an infant compared to mixed feeding (both breast and replacement "bottle" feeding), though complete replacement feeding is safest of all if clean water and adequate infant formula can be assured.[13] The blood supply is no longer a menace in most of the world, thanks to HIV screening of donations and blood products like factor VIII.[14] And there is more.

The herculean efforts of our research colleagues in the field of HIV drug discovery and development that have saved so many lives since the advent of combination antiretroviral therapy (cART) have borne fruit in reducing HIV transmission. The first "ART for Prevention" success was in the prevention of mother to child transmission of HIV (PMTCT). In 1994, the AIDS Clinical Trials Group 076 protocol confirmed that zidovudine monotherapy in the pregnant woman and her infant reduced MTCT by two-thirds, albeit with costly oral and intravenous dosing regimens.[15] In 1999, the another NIH-sponsored network (the antecedent to today's HIV Prevention Trials Network [HPTN]) reported the HIVNET 012 study with a simpler single-dose oral monotherapy with nevirapine given to the women pre-partum and the infant post-partum; its impact was almost as good as the ACTG 076 trial, cutting transmission by half but using a cheaper, easier regimen suitable for resource limited settings with underdeveloped health care infrastructures.[16,17] And subsequent trials have used both drugs or cART to drive transmission down to <2–5% of

exposed infants), reducing viral resistance in the process.[18–20] Treatment of the breastfeeding mother or ART prophylaxis in her infant both work to drop breastfeeding transmission rates markedly.[21] This progress in efficacy, however, is belied by the challenges the global health community faces in fully rolling out PMTCT programs. Years of quality improvement research, health human and systems infrastructure improvement, and community education and mobilization will be needed to overcome issues ranging from community stigma to systems underperformance in order to succeed in full coverage of the mothers and infants who need the testing and treatment for prevention.[22–26]

In 2010 and 2011, investigators presented long-awaited results of studies conceived up to a decade earlier when the correlation of viral load and transmission risk was noted in observational studies.[27–38] A “chemical condom” was developed, taking advantage of features of tenofovir (long half-life and good tissue concentrations) to develop and test a microbicide, also known as topical pre-exposure prophylaxis (PrEP). South African investigators confirmed in a rigorous randomized and placebo-controlled trial (Centre for AIDS Prevention Research in South Africa [CAPRISA] protocol 004) that topical tenofovir 1% gel worked well in women using the product before and after coitus, reducing risk of HIV acquisition by 39%.[39] Furthermore, suggestions in post-hoc analyses that women were even more protected when they were highly adherent to the topical tenofovir gel use, linking the essential behavioral work needed for any biomedical intervention (combination prevention).

Also in 2010, the iPrEx investigators from North and South America reported that among men who have sex with men, oral PrEP (tenofovir disoproxil fumarate [TDF, 300 mg] and emtricitabine [FTC, 200 mg]) worked to prevent infection 44% of the time.[40] As with the CAPRISA 004 results, iPrEx post-hoc analyses suggested strongly that higher protection was seen in persons with higher adherence to the daily oral regimen. The CDC has issued public health guidance on use of PrEP among MSM on this basis of these findings.[41] An analogous PrEP trial in women was stopped early; FEM-PrEP did not confirm oral TDF/FTC PrEP efficacy in women.[42] This finding generated the question as to whether the two-log higher genital tract tissue doses seen with topical gel in women might work for prevention of sexual transmission, while the lower cervicovaginal levels from oral dosing may not.

Most recently, sexual partners who are infected with HIV who go on cART at higher CD4+ cell counts than would qualify them for cART in their home countries (that generally follow WHO guidelines) are 96% less likely to transmit infection to their partners than persons who do not take cART at this earlier timeframe (the HPTN 052 protocol).[43] Thus the circle is complete; antiretroviral drugs can help the infected person delay disease progression and can also provide the benefits to sexual partners and newborn infants alike of markedly reduced infection. And ARVs can even be used for prophylaxis uninfected persons who are especially vulnerable to HIV acquisition.

The study by Williams et al in the current issue of JAIDS[44] continues the useful investigative tradition of mathematical modeling the putative impact of an innovative prevention methodology, in this case the CAPRISA 004 topical tenofovir trial results. Use of a microbicide at a “high” level of 90% of all sexual encounters over a 20 year span in South Africa would reduce transmissions markedly, preventing 2 million infections. Use of the products at a “low” level of 25% of sexual encounters would still reduce transmissions markedly, preventing half a million infections over the 20 year span modeled. The investigators begin their model in 2011, when they would have done well to start in 2015 when it is more likely the product will actually be licensed and in use. The modeling is presented clearly and the mathematics are sound insofar as one can conclude from the

summary methods. The optimistic conclusions are inspiring and suggest the urgency of confirmatory trials to ensure the validity of the single positive CAPRISA 004 trial. We likely have a new tool to combat HIV that can save lives; scientists, pharmaceutical manufacturers, and government policy makers alike must work tirelessly to make tenofovir gel microbicides available expeditiously.

There is a caveat that one must acknowledge, however. The difficulty with transmission models is not so much that the challenges in the mathematic methods are insurmountable, but rather that the parameter estimations are too often indefensible. Let's take the high end coverage for a moment and ask whether it is plausible, under any foreseeable scenario, that 90% of South African women (or any other women) would succeed in using topical tenofovir gel for 90% of their sexual encounters for the next 20 years. Whether adherence data are extrapolated from analogous preventive medicine behaviors such as adherence to male or female condom use, hormonal contraception, or daily medications for tuberculosis, one would not posit 90% adherence to gel use before and after every coital event over 20 years to be plausible.[45–53] Similarly fanciful assumptions in other models lead to such conclusions that if every HIV-infected person in the world were diagnosed and then took ART daily with 100% adherence for the rest of their lives, the epidemic would go away, or if seronegative sexually active persons took PrEP, the incidence would plummet.[54–56] Models of HIV control strategies need more plausible assumptions of uptake and adherence to guide real-world policies; in turn, unrealistic assumptions will drive fanciful modeling assumptions that may well mislead policymakers.

As for the lower coverage rate, even 25% use of a product for each and every sexual encounter for the modeled 20 year period will be challenging given adherence levels reported in prior microbicide studies. A substantial increase in preventive resources would be needed to achieve even the “low” coverage estimate over 20 years for dual use of tenofovir 1% gel for 25% of coital episodes. And time will tell the extent to which the global donor community and the government of South Africa will increase investment in HIV prevention in that comparatively prosperous nation, compared to its poorer southern African neighbors struggling with similar epidemic profiles.

Modeling single interventions with challenging population coverage rates for product use with the millions of coital episodes per month is still a useful exercise. Even more helpful are those models that tackle combination prevention approaches including identifying persons with HIV early in their disease, effectively linking diagnosed persons to care, placing infected persons on cART as best we can, and maximizing adherence to the cART regimen for many years to come (ART for Prevention). At the same time, we must roll out ARV PrEP to the vulnerable HIV uninfected persons who are willing and able to access and take regularly the oral (for men) or topical (for women) ARVs that can reduce their risk. “ABC” interventions and community education and mobilization are vital adjuncts to any biomedical intervention. Medical male circumcision programs must be expanded for willing adult men and for male infants whose parents are supportive. Imagine if a panoply of prevention tools were made available in communities at the same time, even with imperfect coverage.[57–67] Modeling the levels and combinations of coverage that will be plausibly achieved can be done using realistic assumptions given varying epidemic circumstances and community receptivity to the components of prevention offered. This is meaningful and reflects the real world, building on the insights of such unitary intervention models such as that of Williams et al.[44]

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References

1. Centers for Disease Control (CDC). Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep. 1981; 30:250–2. [PubMed: 6265753]
2. Centers for Disease Control (CDC). Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. MMWR Morb Mortal Wkly Rep. 1981; 30:305–8. [PubMed: 6789108]
3. Centers for Disease Control (CDC). Follow-up on Kaposi's sarcoma and Pneumocystis pneumonia. MMWR Morb Mortal Wkly Rep. 1981; 30:409–10. [PubMed: 6792480]
4. Vahlne A. A historical reflection on the discovery of human retroviruses. Retrovirology. 2009; 6:40. [PubMed: 19409074]
5. Bayer, R.; Oppenheimer, GM. AIDS doctors: Voices from the epidemic. Oxford University Press; New York: 2000. p. 1-310.
6. Jaffe HW, Choi K, Thomas PA, et al. National case-control study of Kaposi's sarcoma and Pneumocystis carinii pneumonia in homosexual men: Part 1. Epidemiologic results. Ann Intern Med. 1983; 99:145–51. [PubMed: 6603806]
7. Stoneburner RL, Low-Beer D. Population-level HIV declines and behavioral risk avoidance in Uganda. Science. 2004; 304:714–8. [PubMed: 15118157]
8. Park LS, Siraprapasiri T, Peerapatanapokin W, et al. HIV transmission rates in Thailand: evidence of HIV prevention and transmission decline. J Acquir Immune Defic Syndr. 2010; 54:430–6. [PubMed: 20418773]
9. Palmateer N, Kimber J, Hickman M, et al. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. Addiction. 2010; 105:844–59. [PubMed: 20219055]
10. 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. [PubMed: 16231970]
11. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007; 369:657–66. [PubMed: 17321311]
12. 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; 369:643–56. [PubMed: 17321310]
13. Kuhn L, Aldrovandi GM, Sinkala M, et al. Effects of early, abrupt weaning on HIV-free survival of children in Zambia. N Engl J Med. 2008; 359:130–41. [PubMed: 18525036]
14. Takei T, Amin NA, Schmid G, et al. Progress in global blood safety for HIV. J Acquir Immune Defic Syndr. 2009; 52(Suppl 2):S127–31. [PubMed: 19901625]
15. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994; 331:1173–80. [PubMed: 7935654]
16. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet. 1999; 354:795–802. [PubMed: 10485720]
17. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. Lancet. 2003; 362:859–68. [PubMed: 13678973]
18. Mofenson LM. Prevention in neglected subpopulations: prevention of mother-to-child transmission of HIV infection. Clin Infect Dis. 2010; 50(Suppl 3):S130–48. [PubMed: 20397941]

19. Dabis F, Bequet L, Ekouevi DK, et al. Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission. AIDS. 2005; 19:309–18. [PubMed: 15718842]
20. Palombi L, Marazzi MC, Voetberg A, et al. Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of HIV. AIDS. 2007; 21(Suppl 4):S65–71. [PubMed: 17620755]
21. Mofenson LM. Antiretroviral drugs to prevent breastfeeding HIV transmission. Antivir Ther. 2010; 15:537–53. [PubMed: 20587847]
22. Stringer EM, Ekouevi DK, Coetzee D, et al. Coverage of nevirapine-based services to prevent mother-to-child HIV transmission in 4 African countries. JAMA. 2010; 304:293–302. [PubMed: 20639563]
23. Megazzini KM, Sinkala M, Vermund SH, et al. A cluster-randomized trial of enhanced labor ward-based PMTCT services to increase nevirapine coverage in Lusaka, Zambia. AIDS. 2010; 24:447–55. [PubMed: 19926959]
24. Potter D, Goldenberg RL, Chao A, et al. Do targeted HIV programs improve overall care for pregnant women?: Antenatal syphilis management in Zambia before and after implementation of prevention of mother-to-child HIV transmission programs. J Acquir Immune Defic Syndr. 2008; 47:79–85. [PubMed: 17984757]
25. Reithinger R, Megazzini K, Durako SJ, et al. Monitoring and evaluation of programmes to prevent mother-to-child transmission of HIV in Africa. BMJ. 2007; 334:1143–6. [PubMed: 17540943]
26. Stringer JS, Sinkala M, Maclean CC, et al. Effectiveness of a city-wide program to prevent mother-to-child HIV transmission in Lusaka, Zambia. AIDS. 2005; 19:1309–15. [PubMed: 16052086]
27. Fideli US, Allen SA, Musonda R, et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. AIDS Res Hum Retroviruses. 2001; 17:901–10. [PubMed: 11461676]
28. 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; 342:921–9. [PubMed: 10738050]
29. Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. Clin Infect Dis. 2010; 50(Suppl 3):S85–95. [PubMed: 20397961]
30. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. J Acquir Immune Defic Syndr. 2002; 29:275–83. [PubMed: 11873077]
31. Ragni MV, Faruki H, Kingsley LA. Heterosexual HIV-1 transmission and viral load in hemophilic patients. J Acquir Immune Defic Syndr Hum Retrovirol. 1998; 17:42–5. [PubMed: 9436757]
32. Thea DM, Steketee RW, Pliner V, et al. The effect of maternal viral load on the risk of perinatal transmission of HIV-1. New York City Perinatal HIV Transmission Collaborative Study Group. AIDS. 1997; 11:437–44. [PubMed: 9084790]
33. Weiser B, Nachman S, Tropper P, et al. Quantitation of human immunodeficiency virus type 1 during pregnancy: relationship of viral titer to mother-to-child transmission and stability of viral load. Proc Natl Acad Sci U S A. 1994; 91:8037–41. [PubMed: 8058753]
34. Hisada M, O'Brien TR, Rosenberg PS, et al. Virus load and risk of heterosexual transmission of human immunodeficiency virus and hepatitis C virus by men with hemophilia. The Multicenter Hemophilia Cohort Study. J Infect Dis. 2000; 181:1475–8. [PubMed: 10753732]
35. Pedraza MA, del Romero J, Roldán F, et al. Heterosexual transmission of HIV-1 is associated with high plasma viral load levels and a positive viral isolation in the infected partner. J Acquir Immune Defic Syndr. 1999; 21:120–5. [PubMed: 10360803]
36. Modjarrad K, Chamot E, Vermund SH. Impact of small reductions in plasma HIV RNA levels on the risk of heterosexual transmission and disease progression. AIDS. 2008; 22:2179–85. [PubMed: 18832881]
37. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet. 2010; 375:2092–8. [PubMed: 20537376]

38. Lingappa JR, Hughes JP, Wang RS, et al. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. PLoS One. 2010; 5:e12598. [PubMed: 20856886]
39. 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; 329:1168–74. [PubMed: 20643915]
40. 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; 363:2587–99. [PubMed: 21091279]
41. Centers for Disease Control and Prevention (CDC). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011; 60:65–8. [PubMed: 21270743]
42. Family Health International. [accessed July 8, 2011] FEM-PrEP June 2011 Update. Available from: http://www.fhi.org/NR/rdonlyres/erj6hevouwvddigjldvcca6tvtybfolh4nedyfeo4yz2i7la53jknim6ex42 bme2rvyq6zfzovyrkb/FEMPrEPFactSheetJune2011.pdf
43. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 Infection with Antiretroviral Therapy. N Engl J Med. July 19.2011 in press.
44. Williams BG, Abdool Karim SS, Karim QA, et al. Epidemiological impact of tenofovir gel on the HIV epidemic in South Africa. J Acquir Immune Defic Syndr. Jun 7.2011 Epub ahead of print.
45. Halpern V, Lopez LM, Grimes DA, et al. Strategies to improve adherence and acceptability of hormonal methods of contraception. Cochrane Database Syst Rev. 2011; (4):CD004317. [PubMed: 21491389]
46. Kalichman SC, Cherry C, Amaral CM, et al. Adherence to antiretroviral therapy and HIV transmission risks: implications for test-and-treat approaches to HIV prevention. AIDS Patient Care STDS. 2010; 24:271–7. [PubMed: 20438373]
47. Desgrées-Du-Loû A, Msellati P, Viho I, et al. Contraceptive use, protected sexual intercourse and incidence of pregnancies among African HIV-infected women. DITRAME ANRS 049 Project, Abidjan 1995–2000. Int J STD AIDS. 2002; 13:462–8. [PubMed: 12171665]
48. Volmink J, Garner P. Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment. BMJ. 1997; 315:1403–6. [PubMed: 9418086]
49. Mills EJ, Nachega JB, Bangsberg DR, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med. 2006; 3:e438. [PubMed: 17121449]
50. Munro SA, Lewin SA, Smith HJ, et al. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 2007; 4:e238. [PubMed: 17676945]
51. Mensch BS, Hewett PC, Abbott S, et al. Assessing the reporting of adherence and sexual activity in a simulated microbicide trial in South Africa: an interview mode experiment using a placebo gel. AIDS Behav. 2011; 15:407–21. [PubMed: 20886278]
52. Turner AN, De Kock AE, Meehan-Ritter A, et al. Many vaginal microbicide trial participants acknowledged they had misreported sensitive sexual behavior in face-to-face interviews. J Clin Epidemiol. 2009; 62:759–65. [PubMed: 19013762]
53. Minnis AM, Steiner MJ, Gallo MF, et al. Biomarker validation of reports of recent sexual activity: results of a randomized controlled study in Zimbabwe. Am J Epidemiol. 2009; 170:918–24. [PubMed: 19741042]
54. Pretorius C, Stover J, Bollinger L, et al. Evaluating the cost-effectiveness of pre-exposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa. PLoS One. 2010; 5:e13646. [PubMed: 21079767]
55. Vissers DC, Voeten HA, Nagelkerke NJ, et al. The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. PLoS One. 2008; 3:e2077. [PubMed: 18461185]
56. 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. [PubMed: 19038438]

57. Kurth AE, Celum C, Baeten JM, et al. Combination HIV prevention: significance, challenges, and opportunities. Curr HIV/AIDS Rep. 2011; 8:62–72. [PubMed: 20941553]
58. Vermund SH, Allen KL, Karim QA. HIV-prevention science at a crossroads: advances in reducing sexual risk. Curr Opin HIV AIDS. 2009; 4:266–73. [PubMed: 19532063]
59. Burns DN, Dieffenbach CW, Vermund SH. Rethinking prevention of HIV type 1 infection. Clin Infect Dis. 2010; 51:725–31. [PubMed: 20707698]
60. Kalichman SC, Cherry C, Kalichman MO, et al. Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission. Am J Public Health. 2011; 101:531–8. [PubMed: 21233431]
61. DeGruttola V, Smith DM, Little SJ, et al. Developing and evaluating comprehensive HIV infection control strategies: issues and challenges. Clin Infect Dis. 2010; 50(Suppl 3):S102–7. [PubMed: 20397937]
62. Beyrer C. Global prevention of HIV infection for neglected populations: men who have sex with men. Clin Infect Dis. 2010; 50(Suppl 3):S108–13. [PubMed: 20397938]
63. Vlahov D, Robertson AM, Strathdee SA. Prevention of HIV infection among injection drug users in resource-limited settings. Clin Infect Dis. 2010; 50(Suppl 3):S114–21. [PubMed: 20397939]
64. Mofenson LM. Prevention in neglected subpopulations: prevention of mother-to-child transmission of HIV infection. Clin Infect Dis. 2010; 50(Suppl 3):S130–48. [PubMed: 20397941]
65. Vermund SH, Hodder SL, Justman JE, et al. Addressing research priorities for prevention of HIV infection in the United States. Clin Infect Dis. 2010; 50(Suppl 3):S149–55. [PubMed: 20397942]
66. Bassett IV, Walensky RP. Integrating HIV screening into routine health care in resource-limited settings. Clin Infect Dis. 2010; 50(Suppl 3):S77–84. [PubMed: 20397960]
67. Moore RD. Epidemiology of HIV infection in the United States: implications for linkage to care. Clin Infect Dis. 2011; 52(Suppl 2):S208–13. [PubMed: 21342909]