Published in final edited form as:

Curr HIV/AIDS Rep. 2014 June ; 11(2): 93–98. doi:10.1007/s11904-014-0208-x.

Global HIV Epidemiology: A Guide for Strategies in Prevention and Care

Sten H. Vermund, MD, PhD

Vanderbilt Institute for Global Health and Department of Pediatrics, Vanderbilt University School of Medicine, Nashville TN USA

Abstract

Global trends in HIV incidence are estimated typically by serial prevalence surveys in selected sentinel populations or less often in representative population samples. Incidence estimates are often modeled since cohorts are costly to maintain and are rarely representative of larger populations. From global trends, we can see reason for cautious optimism. Downward trends in generalized epidemics in Africa, concentrated epidemics in persons who inject drugs (PWID), some female sex worker cohorts, and among older men who have sex with men (MSM) have been noted. However, younger MSM and those from minority populations, as with black MSM in the United States, show continued transmission at high rates. Among the many HIV prevention strategies, current efforts to expand testing, linkage to effective care, and adherence to antiretroviral therapy are known as “treatment as prevention” (TasP). A concept first forged for the prevention of mother to child transmission, TasP generates high hopes that persons treated early will derive considerable clinical benefits and that lower infectiousness will reduce transmission in communities. With the global successes of risk reduction for PWID, we have learned that reducing marginalization of drug users, implementation of non-judgmental and pragmatic sterile needle and syringe exchange programs, and offering of opiate substitution therapy to help persons eschew needle use altogether can work to reduce the HIV epidemic. Never has the urgency of stigma reduction and guarantees of human rights been more urgent; a public health approach to at-risk populations requires that to avail themselves of prevention services, they must feel welcomed.

Keywords

HIV; global epidemic; surveillance; global; prevention; epidemiology; barriers; human rights; HIV prevention strategies; men who have sex with men (MSM); persons who inject drugs (PWID)

Address for correspondence: Sten H. Vermund Vanderbilt Institute for Global Health 2525 West End Ave., Suite 750 Nashville, TN 37203 USA sten.vermund@vanderbilt.edu phone: 615-322-9015.

Compliance with Ethics Guidelines Conflict of Interest Sten H. Vermund reports that he serves as a consultant for the World Bank, the WHO, and UNAIDS.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

This *Current HIV/AIDS Reports* issue brings timely, helpful updates on the global epidemiology of HIV/AIDS, within the limitations of currently available surveillance data. It is worth presenting these contributions in the context of successes and challenges in HIV prevention, limitations of global estimations, and present a few caveats about current HIV/AIDS trends.

GLOBAL TRENDS

There is little doubt that HIV prevalence is dropping worldwide, but declines are dramatic only where prevention strategies have been highly implemented and taken up by the target population. In Africa, we have concrete evidence of a decline in prevalence among young women, for example, but the reasons for this are not yet well understood [1••]. Despite salutary trends, the most highly prevalent nations of southern Africa (Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Zambia, Zimbabwe) remain the continental and global epicenter for the generalized epidemic. There is no indication of a transmission breakpoint, i.e., a basic reproduction rate for transmission that has dropped below the level that can sustain a cycle of transmission, in these highest prevalence nations [2].

An additional challenge in Africa is among the key populations that would be likely to continue transmission even if incidence in the general population were to continue to wane [3,4]. Among these are men who have sex with men (MSM), long neglected in Africa, persons who inject drugs (PWID) in certain regions such as Zanzibar, and more familiar groups like female sex workers (FSWs) and migrant men in the trucking and mining industries whose multiple and often concurrent partnerships may provide a disproportionate impact on local transmission network dynamics [5,6].

In Asia, tremendous progress has been noted in rolling out effective prevention programs among PWID with consequent reductions in prevalence in India, China, Thailand, and elsewhere, though hepatitis C rates have risen markedly [7••,8•]. Yet success in some venues is matched with failure in others, such as Pakistan, where policy has been indolent and programs underdeveloped [9]. FSWs have been engaged in highly successful prevention programs in Cambodia, Thailand, Vietnam, and elsewhere with promising HIV trends as a consequent [10]. Trends among MSM are not salutary and it is apparent that the epidemic is rising or stable at a high level in Asian MSM [11].

In South America and the Caribbean, key populations are drivers of transmission, and except for Haiti, general populations have been spared the extent of epidemic penetration seen elsewhere [12••, 13••]. Considerable sexual transmission continues among MSM and high risk heterosexuals; the dominant circulating B subtype is the same as the major subtype circulating in high income nations.

High and high middle income nations continue to vary in their background prevalences [14••,15]. Australia's pragmatic approach has yielded benefits in every risk group [16]. Europe and North America continue to struggle to make progress among MSM but see

marked declines in both incidence and prevalence among PWID. Eastern Europe and Central Asia have had spotty results with risk reduction among PWID, with the worst trends noted where opiate substitution therapy and sterile needle/syringe exchange programs are illegal and/or underfunded, as in Russia [17••]. With PWID overrepresenting prison populations, tuberculosis (and likely HIV, hepatitis B, and hepatitis C) spread remains common decades after this phenomenon was first reported [18].

Aspirational goals of an “AIDS-free generation”, “zero transmission” from mother-to-infant, and the like are inspirational rallying slogans within popular and political audiences. However, considerable innovation will be needed to change the surveillance-based realities. Innovation in programmatic efforts for women and children are proposed in this issue of *Current HIV/AIDS Reports* [19•,20•].

PREVENTION—Prevention strategies are more numerous and promising today than ever before. For example, there is now a wide array of biomedical approaches using agents or devices that block virus spread either physically, chemically, or immunologically. These may focus on protecting the uninfected (acquisition) or reducing infectiousness (transmission). The advent of more and more products and strategies has emerged from a prevention developmental pathway epitomized by research networks that promulgate developmental science, clinical trials, and combination prevention strategies (Figure).

Barriers to reduce acquisition: Barriers to acquisition of HIV include physical blocks such as condoms, both male and female. Their major challenges are five “A’s”: awareness, availability, acceptability, affordability, and adherence [21]. Male condoms have made a huge impact on the Thai epidemic, alongside policy changes in brothels and in the national consciousness. Low HIV prevalence among FSWs and clients in such nations as Japan may be due to very high condom use. Australian MSM use condoms more than counterparts elsewhere and also have lower prevalence rates. Female condoms have had niche utilities but do not seem to have made a major global impact. Chemical barriers include topic and systemic antiretroviral drugs to kill virus near the time of exposure or early infection [22]. Pre-exposure prophylaxis (PrEP) has been shown to work both systemically (most notably, tenofovir/emtricitabine) and topically (tenofovir vaginal gel). However, large efficacy trials suggest that adherence is very challenging and that low utilization dooms the approach to ineffectivity [23]. Current efforts seek to overcome challenges of poor adherence to oral and topical PrEP by testing depot long-acting injections for systemic administration and antiretroviral microbicide via a dapivirine vaginal ring (monthly changes) to the target cervicovaginal tissues. Immediate post-exposure treatment of infants born to infected mothers with high viral loads shows promise to block transmission, even when pre- and intrapartum prophylaxis opportunities have been missed [24,25].

Immunological barriers are in development and may be available in the future. These include HIV vaccines and passive immune barriers such as monoclonal antibodies [26]. We do not know the extent to which they will be protective against circulating strains, applicable across diverse sub-types, or will generate durable protective immunity. In any case, they will not be commercially available until 2025 or later.

Barriers to reduce transmission: One can think about barriers in the seropositive person analogous to how they are presented to avoid acquisition. Condoms interrupt transmission from condom wearer to uninfected sexual partner. Therapeutic vaccines could reduce infectiousness someday, if they could be engineered successfully to enhance human immune responses beyond what natural infection provides. But the principal innovation in recent years has been the documentation that treatment can reduce viral load and serve to protect others from infection. Treatment as prevention has been proposed since studies in the late 1990s demonstrated that lower viral loads were associated with lower transmission rates to sexual partners [27,28]. The observational and clinical trials evidence was even more dramatic than had been hoped, suggesting massive protective benefit of a seropositive partner taking combination antiretroviral therapy (cART) assiduously [29]. Of course, the implementation challenges of rolling out universal testing and near-universal treatment are daunting [30-32], and are the topic of intensive pragmatic investigation [33-40].

Male circumcision to reduce the vulnerability of male genital tissues to HIV infection has proven to be hugely successful in generalized heterosexual contexts [41-43]. There is even promise that male circumcision will help reduce MSM risk [44]. Lessons of how to bring circumcision programs to the large scale needed to truly impact the HIV pandemic are being applied in real field conditions [45,46].

Prevention of mother to child transmission programs are well established, but continuing health systems constraints and, in many venues, continued stigma and fear inhibit full program implementation and success [19,20,47,48]. Quality improvement programs are needed for the further reduction of pediatric HIV infections, as well as for the improved therapy of already infected children, elusive goals to date [49,50].

Behavioral change: The prospects of widespread behavior change to reduce sexual risk exposure are not promising [23,51,52]. Since the HIV pandemic began in the 1970s, changes in sexual behaviors have been dramatic following catastrophic viral spread in communities, as with reduced sexual risk taking among MSM in the USA in the mid 1980s, but so many men were infected by that point that the benefits of risk reduction were less dramatic [53]. In Thailand and Uganda, dramatic declines in HIV rates in the 1990s were noted, with commensurate behavioral data suggesting a decline in partner numbers and high risk partners [54,55]. Yet the global community has not yet seen a widespread effective replication of the dramatic Ugandan and Thai experiences.

PWID have had marked reductions in HIV incidence in venues where effective community outreach for needle and syringe exchange have increased clean needle usage [56,57]. Similarly, opiate substitution therapy has reduced injection behaviors altogether among subsets of PWID [58,59]. One example of many of a behavioral support strategy is the information, motivation, behavioral (IMB) skills model of care to improve uptake of biomedical interventions and reduce HIV risk behaviors, for example [60,61]. While behavior change must be a part of any successful combination prevention approach, it is not likely to be successful in isolation from biomedical approaches. However, all behavioral adherence strategies require client assent and adherence [62], even for user-friendly monthly changes of a microbicidal ring, a depot PrEP injection, or a vaccine series. For the decision

to get circumcised, for daily adherence to antiretroviral drugs, or for coital compliance with condom use, it is obvious how essential behavioral intervention is to support complex or long-term decisions.

A combination of strategies is more likely to achieve success in global HIV control than single approaches, given the synergism of different approaches, the need for behavioral change just to implement biomedical tools, and the diversity of at-risk populations [63-70]. Historic initiatives to reduce HIV morbidity, to prevent transmission, and to stop deaths from AIDS have achieved unprecedented gains through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria [71-73]. With resources never before marshalled for global disease control and prevention, millions of persons are on life-saving antiretroviral drugs and are less infectious to others [74,75].

We face daunting challenges in preserving the political will in donor countries to continue supporting these programs, nurturing indigenous support and expertise for long term program maintenance and expansion, and building health systems capacities to prevent stock-outs, to ensure respect for patients, and to maximize successful client empowerment [76,77]. We also have an opportunity to expand new HIV service infrastructures to provide care for other chronic diseases whose management has been neglected by poor medication supply chains, poor clinical infrastructures, or a lack of trained health workforce [78-82]. Adolescents and young adults continue to get infected and our tools for this population are limited [83]. Expanding HIV clinical services to others with chronic medical conditions like tuberculosis (as is being done now), diabetes, hypertension, malignancies, rheumatic and collagen vascular conditions, and sickle cell disease, to name but a few, can improve the political base of support to continue this historic global health initiative [84]. The Pink Ribbon Red Ribbon campaign to integrate HIV care with cervical and breast cancer screening for women is an example of such expansive inspiration [85,86]. While concerns are raised that changing the focus of HIV programs to more chronic disease conditions will compromise their effectiveness, one might also argue that such programs are doomed to shrinkage if they maintain their one-dimensional focus and fail to build wider constituencies [87,88-92].

Acknowledgments

Supported in part by NIH grant #UM1 AI068619, the HIV Prevention Trials Network (HPTN) Leadership Group.

Supported in part by NIH grant #UM1 AI068619, the HIV Prevention Trials Network (HPTN) Leadership Group.

REFERENCES

1. Delva W, Abdool Karim Q. The HIV epidemic in Southern Africa – Is an AIDS-free generation possible? *Current HIV/AIDS Reports*. 2014 in press. The authors present an epidemiologic update and prospects for progress in the world's HIV epicenter of southern Africa.
2. Leclerc PM, Matthews AP, Garenne ML. Fitting the HIV epidemic in Zambia: a two-sex micro-simulation model. *PLOS ONE*. 2009; 4(5):e5439. [PubMed: 19415113]
3. Okal J, Geibel S, Muraguri N, et al. Estimates of the size of key populations at risk for HIV infection: men who have sex with men, female sex workers and injecting drug users in Nairobi, Kenya. *Sex Transm Infect*. 2013; 89(5):366–71. [PubMed: 23761166]

4. Beyrer C, Abdool Karim Q. The changing epidemiology of HIV in 2013. *Curr Opin HIV AIDS*. 2013; 8(4):306–10. [PubMed: 23743721]
5. Epstein H, Morris M. Concurrent partnerships and HIV: an inconvenient truth. *J Int AIDS Soc*. 2011; 14:13. [PubMed: 21406080]
6. Sawers L. Measuring and modelling concurrency. *J Int AIDS Soc*. 2013; 16:17431. [PubMed: 23406964]
- 7••. Suguimoto SP, Techasrivichien T, Musumari PM, et al. Changing patterns of HIV epidemic in 30 years in East Asia. *Current HIV/AIDS Reports*. 2014 in press. The authors present both recent trends and challenges of HIV amidst the vast population of East Asia.
- 8•. Ye S, Pang L, Wang X. Epidemiological implications of HIV-hepatitis C co-infection in South and Southeast Asia. *Current HIV/AIDS Reports*. 2014 in press. A brief review of HIV-HCV co-infection focused on south and southeast Asia indicates the challenge facing Asia.
9. Samo RN, Altaf A, Agha A, et al. High HIV incidence among persons who inject drugs in Pakistan: Greater risk with needle sharing and injecting frequently among the homeless. *PLOS ONE*. 2013; 8(12):e81715. [PubMed: 24358123]
10. Steen R, Zhao P, Wi TE, Punchihewa N, Abeyewickreme I, Lo YR. Halting and reversing HIV epidemics in Asia by interrupting transmission in sex work: Experience and outcomes from ten countries. *Expert Rev Anti Infect Ther*. 2013; 11(10):999–1015. [PubMed: 24124797]
11. van Griensven F, Thienkrua W, McNicholl J, et al. Evidence of an explosive epidemic of HIV infection in a cohort of men who have sex with men in Thailand. *AIDS*. 2013; 27(5):825–32. [PubMed: 23169330]
- 12••. Garcia PJ, Bayer A, Cárcamo CP. The changing face of HIV in Latin America and the Caribbean. *Current HIV/AIDS Reports*. 2014 in press. The authors present a comprehensive assessment of the multifaceted epidemic in the Americas south of the USA/Canada.
- 13••. Figueroa JP. Review of HIV in the Caribbean: Significant progress and outstanding challenges. *Current HIV/AIDS Reports*. 2014 in press. The author describes the complex epidemiology of different island HIV transmission patterns.
- 14••. Nakagawa F, Phillips AN, Lundgren JD. HIV in Western Europe. *Current HIV/AIDS Reports*. 2014 in press. The authors present a current and historic perspective on Western Europe's struggle with HIV/AIDS.
15. Vermund SH, Leigh-Brown AJ. The HIV epidemic: High-income countries. *Cold Spring Harb Perspect Med*. 2012; 2(5):a007195. [PubMed: 22553497]
16. Plummer D, Irwin L. Grassroots activities, national initiatives and HIV prevention: clues to explain Australia's dramatic early success in controlling the HIV epidemic. *Int J STD AIDS*. 2006; 17(12): 787–93. [PubMed: 17212850]
- 17••. DeHovitz J, Uusküla A, El-Bassel N. The HIV epidemic in Eastern Europe and Central Asia. *Current HIV/AIDS Reports*. 2014 in press. The authors review epidemiological trends and prevention challenges for the epidemic in Eastern Europe and Central Asia, largely driven by injection drug use.
18. Vagenas P, Azbel L, Polonsky M, et al. A review of medical and substance use comorbidities in Central Asian prisons: Implications for HIV prevention and treatment. *Drug Alcohol Depend*. 2013; 132(Suppl 1):S25–31. [PubMed: 23932844]
- 19•. Dunlap J, Foderingham N, Bussell S, Wester CW, Audet CM, Aliyu MH. Male involvement for the prevention of mother-to-child HIV transmission: A brief review of initiatives in East, West and Central Africa. *Current HIV/AIDS Reports*. 2014 in press. Concentrating on sub-Saharan Africa exclusive of the 10 nations in southern Africa, the authors highlight an innovative approach to improving PMTCT coverage, namely the engagement of men in antenatal, intra-partum, and post-partum care.
- 20•. Roxby AC, Unger JA, Slyker JA, et al. A lifecycle approach to HIV prevention in African women and children. *Current HIV/AIDS Reports*. 2014 in press. The authors put HIV care in the broader context of overall health and prevention needs, describing a lifecycle approach for sustained epidemic response.
21. Crosby RA. State of condom use in HIV prevention science and practice. *Curr HIV/AIDS Rep*. 2013; 10(1):59–64. [PubMed: 23224425]

22. Baeten JM, Haberer JE, Liu AY, Sista N. Preexposure prophylaxis for HIV prevention: where have we been and where are we going? *J Acquir Immune Defic Syndr*. Jul; 2013 63(Suppl 2):S122–9. [PubMed: 23764623]
23. Amico KR, Mansoor LE, Corneli A, Torjesen K, van der Straten A. Adherence support approaches in biomedical HIV prevention trials: experiences, insights and future directions from four multisite prevention trials. *AIDS Behav*. 2013; 17(6):2143–55. [PubMed: 23435697]
24. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013; 369(19):1828–35. [PubMed: 24152233]
25. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012; 366(25):2368–79. [PubMed: 22716975]
26. Tieu HV, Rolland M, Hammer SM, Sobieszczyk ME. Translational research insights from completed HIV vaccine efficacy trials. *J Acquir Immune Defic Syndr*. 2013; 63(Suppl 2):S150–4. [PubMed: 23764628]
27. Fideli US, Allen SA, Musonda R, et al. Virologic and immunologic determinants of heterosexual transmission of HIV-type 1 (HIV-1) in Africa. *AIDS Res Hum Retrovir*. 2001; 17(10):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(13):921–9. [PubMed: 10738050]
29. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011; 365(6):493–505. [PubMed: 21767103]
30. Shelton JD. HIV/AIDS. ARVs as HIV prevention: a tough road to wide impact. *Science*. 2011; 334(6063):1645–6. [PubMed: 22194560]
31. Wilson DP. HIV treatment as prevention: natural experiments highlight limits of antiretroviral treatment as HIV prevention. *PLoS Med*. 2012; 9(7):e1001231. [PubMed: 22807656]
32. HIV Modelling Consortium Treatment as Prevention Editorial Writing Group. HIV treatment as prevention: models, data, and questions--towards evidence-based decision-making. *PLoS Med*. 2012; 9(7):e1001259. [PubMed: 22802739]
33. Granich R, Gupta S, Suthar AB, et al. Antiretroviral therapy in prevention of HIV and TB: update on current research efforts. *Curr HIV Res*. 2011; 9(6):446–69. [PubMed: 21999779]
34. Iwuji CC, Orne-Gliemann J, Tanser F, et al. Evaluation of the impact of immediate versus WHO recommendations-guided antiretroviral therapy initiation on HIV incidence: the ANRS 12249 TasP(Treatment as Prevention) trial in Hlabisa sub-district, KwaZulu-Natal, South Africa: study protocol for a cluster randomised controlled trial. *Trials*. 2013; 14:230. [PubMed: 23880306]
35. Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. *Science*. 2013; 339(6122):966–71. [PubMed: 23430656]
36. Jain V, Byonanebye DM, Liegler T, et al. Changes in Population HIV RNA Levels in Mbarara, Uganda, During Scale-up of HIV Antiretroviral Therapy Access. *J Acquir Immune Defic Syndr*. Mar 1; 2014 65(3):327–32. [PubMed: 24146022]
37. Chamie G, Kwarisiima D, Clark TD, et al. Uptake of community-based HIV testing during a multi-disease health campaign in rural Uganda. *PLoS One*. Jan 2.2014 9(1):e84317. [PubMed: 24392124]
38. Vermund SH, Fidler SJ, Ayles H, Beyers N, Hayes RJ. Can combination prevention strategies reduce HIV transmission in generalized epidemic settings in Africa? The HPTN 071 (PopART) study plan in South Africa and Zambia. *J Acquir Immune Defic Syndr*. 2013; 63(Suppl 2):S221–7. [PubMed: 23764639]
39. Cori A, Ayles H, Beyers N, et al. HPTN 071 (PopART): A cluster-randomized trial of the population impact of an HIV combination prevention intervention including universal testing and treatment: Mathematical model. *PLOS ONE*. 2014; 9(1):e84511. [PubMed: 24454728]
40. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, Bock P, Griffith S, Moore A, Watson-Jones D, Fraser C, Vermund SH, Fidler S. HPTN 071 (PopART): Rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention

- including universal testing and treatment - a study protocol for a cluster randomised trial. *Trials*. 2014; 15(1):57. [PubMed: 24524229]
41. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet*. 2007; 369(9562):657–66. [PubMed: 17321311]
 42. 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(9562):643–56. [PubMed: 17321310]
 43. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med*. 2005; 2(11):e298. [PubMed: 16231970]
 44. Qian, HZ.; Ruan, Y.; Liu, Y., et al. Lower odds of HIV among circumcised MSM in China and interaction with anal sexual role. Conference on Retroviruses and Opportunistic Infections (CROI); Boston, MA. 2014. p. 83abstract 963
 45. Gray RH, Wawer MJ, Kigozi G. Programme science research on medical male circumcision scale-up in sub-Saharan Africa. *Sex Transm Infect*. 2013; 89(5):345–9. [PubMed: 23698513]
 46. Mehta SD, Moses S, Agot K, et al. The long term efficacy of medical male circumcision against HIV acquisition. *AIDS*. 2013; 27(18):2899–2909.
 47. Stringer JS, Stinson K, Tih PM, et al. Measuring coverage in MNCH: population HIV-free survival among children under two years of age in four African countries. *PLoS Med*. 2013; 10(5):e1001424. [PubMed: 23667341]
 48. 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(3):293–302. [PubMed: 20639563]
 49. Ciampa PJ, Tique JA, Jumá N, et al. Addressing poor retention of infants exposed to HIV: a quality improvement study in rural Mozambique. *J Acquir Immune Defic Syndr*. 2012; 60(2):e46–52. [PubMed: 22622077]
 50. Geelhoed D, Lafort Y, Chissale É, Candrinho B, Degomme O. Integrated maternal and child health services in Mozambique: structural health system limitations overshadow its effect on follow-up of HIV-exposed infants. *BMC Health Serv Res*. 2013; 13:207. [PubMed: 23758816]
 51. Smith LR, Fisher JD, Cunningham CO, Amico KR. Understanding the behavioral determinants of retention in HIV care: a qualitative evaluation of a situated information, motivation, behavioral skills model of care initiation and maintenance. *AIDS Patient Care STDS*. 2012; 26(6):344–55. [PubMed: 22612447]
 52. Laisaar KT, Uusküla A, Sharma A, DeHovitz JA, Amico KR. Developing an adherence support intervention for patients on antiretroviral therapy in the context of the recent IDU-driven HIV/AIDS epidemic in Estonia. *AIDS Care*. 2013; 25(7):863–73. [PubMed: 23391132]
 53. Beyrer C, Baral SD, van Griensven F, et al. Global epidemiology of HIV infection in men who have sex with men. *Lancet*. 2012; 380(9839):367–77. [PubMed: 22819660]
 54. Park LS, Siraprapasiri T, Peerapatanapokin W, Manne J, Niccolai L, Kunanusont C. HIV transmission rates in Thailand: evidence of HIV prevention and transmission decline. *J Acquir Immune Defic Syndr*. 2010; 54(4):430–6. [PubMed: 20418773]
 55. 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):i1–8. [PubMed: 16581753]
 56. Petersen Z, Myers B, van Hout MC, Plüddemann A, Parry C. Availability of HIV prevention and treatment services for people who inject drugs: findings from 21 countries. *Harm Reduct J*. 2013; 10:13. [PubMed: 23957896]
 57. Mathers BM, Degenhardt 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(9719):1014–28. [PubMed: 20189638]
 58. Gowing LR, Hickman M, Degenhardt L. Mitigating the risk of HIV infection with opioid substitution treatment. *Bull World Health Organ*. 2013; 91(2):148–9. [PubMed: 23554530]

59. MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *BMJ*. 2012; 345:e5945. [PubMed: 23038795]
60. Naar-King S, Parsons JT, Johnson AM. Motivational interviewing targeting risk reduction for people with HIV: a systematic review. *Curr HIV/AIDS Rep*. 2012; 9(4):335–43. [PubMed: 22890780]
61. Lorimer K, Kidd L, Lawrence M, McPherson K, Cayless S, Cornish F. Systematic review of reviews of behavioural HIV prevention interventions among men who have sex with men. *AIDS Care*. 2013; 25(2):133–50. [PubMed: 22774763]
62. Gurman TA, Rubin SE, Roess AA. Effectiveness of mHealth behavior change communication interventions in developing countries: a systematic review of the literature. *J Health Commun*. 2012; 17(Suppl 1):82–104. [PubMed: 22548603]
63. Parkhurst JO. HIV prevention, structural change and social values: the need for an explicit normative approach. *J Int AIDS Soc*. 2012; 15(Suppl 1):1–10. [PubMed: 22713355]
64. Vermund SH, Tique JA, Cassell HM, Pask ME, Ciampa PJ, Audet CM. Translation of biomedical prevention strategies for HIV: prospects and pitfalls. *J Acquir Immune Defic Syndr*. 2013; 63(Suppl 1):S12–25. [PubMed: 23673881]
65. Vermund SH, Hayes RJ. Combination prevention: new hope for stopping the epidemic. *Curr HIV/AIDS Rep*. 2013; 10(2):169–86. [PubMed: 23456730]
66. Chang LW, Serwadda D, Quinn TC, Wawer MJ, Gray RH, Reynolds SJ. Combination implementation for HIV prevention: moving from clinical trial evidence to population-level effects. *Lancet Infect Dis*. 2013; 13(1):65–76. [PubMed: 23257232]
67. Hayes R, Sabapathy K, Fidler S. Universal testing and treatment as an HIV prevention strategy: research questions and methods. *Curr HIV Res*. 2011; 9(6):429–45. [PubMed: 21999778]
68. Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. *Curr HIV/AIDS Rep*. 2011; 8(1):62–72. [PubMed: 20941553]
69. Smith K, Powers KA, Kashuba AD, Cohen MS. HIV-1 treatment as prevention: the good, the bad, and the challenges. *Curr Opin HIV AIDS*. 2011; 6(4):315–25. [PubMed: 21646878]
70. Burns DN, Dieffenbach CW, Vermund SH. Rethinking prevention of HIV type 1 infection. *Clin Infect Dis*. 2010; 51(6):725–31. [PubMed: 20707698]
71. Bowser D, Sparkes SP, Mitchell A, et al. Global Fund investments in human resources for health: innovation and missed opportunities for health systems strengthening. *Health Policy Plan*. Nov 22, 2013 [Epub ahead of print]. doi:10.1093/heapol/czt080. PubMed PMID: 24197405.
72. Goosby E, Dybul M, Fauci AS, et al. The United States President's Emergency Plan for AIDS Relief: a story of partnerships and smart investments to turn the tide of the global AIDS pandemic. *J Acquir Immune Defic Syndr*. 2012; 60(Suppl 3):S51–6. [PubMed: 22797740]
73. El-Sadr WM, Holmes CB, Mugenyi P, et al. Scale-up of HIV treatment through PEPFAR: a historic public health achievement. *J Acquir Immune Defic Syndr*. 2012; 60(Suppl 3):S96–104. [PubMed: 22797746]
74. April MD, Wood R, Berkowitz BK, et al. The survival benefits of antiretroviral therapy in South Africa. *J Infect Dis*. 2014; 209(4):491–9. [PubMed: 24307741]
75. Vermund SH. Massive benefits of antiretroviral therapy in Africa. *J Infect Dis*. 2014; 209(4):483–5. [PubMed: 24307740]
76. Vermund SH, Sidat M, Weil LF, Tique JA, Moon TD, Ciampa PJ. Transitioning HIV care and treatment programs in southern Africa to full local management. *AIDS*. 2012; 26(10):1303–10. [PubMed: 22706012]
77. Hull MW, Wu Z, Montaner JS. Optimizing the engagement of care cascade: a critical step to maximize the impact of HIV treatment as prevention. *Curr Opin HIV AIDS*. 2012; 7(6):579–86. [PubMed: 23076123]
78. Schouten EJ, Jahn A, Ben-Smith A, et al. Antiretroviral drug supply challenges in the era of scaling up ART in Malawi. *J Int AIDS Soc*. 2011; 14(Suppl 1):S4. [PubMed: 21967844]
79. Boyer S, Clerc I, Bonono CR, Marcellin F, Bilé PC, Ventelou B. Non-adherence to antiretroviral treatment and unplanned treatment interruption among people living with HIV/AIDS in

- Cameroon: Individual and healthcare supply-related factors. *Soc Sci Med*. 2011; 72(8):1383–92. [PubMed: 21470734]
80. Pasquet A, Messou E, Gabillard D, et al. Impact of drug stock-outs on death and retention to care among HIV-infected patients on combination antiretroviral therapy in Abidjan, Côte d'Ivoire. *PLOS ONE*. 2010; 5(10):e13414. [PubMed: 20976211]
 81. Muhamadi L, Nsabagasani X, Tumwesigye MN, et al. Inadequate pre-antiretroviral care, stock-out of antiretroviral drugs and stigma: policy challenges/bottlenecks to the new WHO recommendations for earlier initiation of antiretroviral therapy (CD<350 cells/microL) in eastern Uganda. *Health Policy*. 2010; 97(2-3):187–94. [PubMed: 20615573]
 82. Tankwanchi ABS, Özden C, Vermund SH. Physician emigration from sub-Saharan Africa to the United States: Analysis of the 2011 AMA Physician Masterfile. *PLoS Med*. 2013; 10(9):e1001513. [PubMed: 24068894]
 83. Pettifor A, Bekker LG, Hosek S, et al. Preventing HIV among young people: research priorities for the future. *J Acquir Immune Defic Syndr*. Jul; 2013 63(Suppl 2):S155–60. [PubMed: 23764629]
 84. Vermund SH, Narayan KMV, Glass RI. Non-communicable Diseases in HIV Survivors. *Sci Transl Med*. 2014 in press.
 85. Oluwole D, Kraemer J. Innovative public-private partnership: a diagonal approach to combating women's cancers in Africa. *Bull World Health Organ*. 2013; 91(9):691–6. Pink Ribbon Red Ribbon. [PubMed: 24101785]
 86. Sahasrabudde VV, Parham GP, Mwanahamuntu MH, Vermund SH. Cervical cancer prevention in low- and middle-income countries: feasible, affordable, essential. *Cancer Prev Res (Phila)*. 2012; 5(1):11–7. [PubMed: 22158053]
 87. Dionne KY, Gerland P, Watkins S. AIDS exceptionalism: another constituency heard from. *AIDS Behav*. 2013; 17(3):825–31. [PubMed: 22120880] The authors' qualitative research suggests Malawians value many other issues ahead of HIV care.
 88. Emanuel EJ. PEPFAR and maximizing the effects of global health assistance. *JAMA*. 2012; 307(19):2097–100. [PubMed: 22665111]
 89. Leach-Kemon K, Chou DP, Schneider MT, Tardif A, Dieleman JL, Brooks BP, Hanlon M, Murray CJ. The global financial crisis has led to a slowdown in growth of funding to improve health in many developing countries. *Health Aff (Millwood)*. 2012; 31(1):228–35. [PubMed: 22174301]
 90. Schneider K, Garrett L. The end of the era of generosity? Global health amid economic crisis. *Philos Ethics Humanit Med*. 2009; 4:1. [PubMed: 19134211]
 91. Holmes CB, Blandford JM, Sangrue N, et al. PEPFAR's past and future efforts to cut costs, improve efficiency, and increase the impact of global HIV programs. *Health Aff (Millwood)*. 2012; 31(7):1553–60. [PubMed: 22778345]
 92. Grépin KA. HIV donor funding has both boosted and curbed the delivery of different non-HIV health services in sub-Saharan Africa. *Health Aff (Millwood)*. 2012; 31(7):1406–14. [PubMed: 22778329]

Figure 1.
Developmental pathway for HIV prevention science: discovery to trials to combination interventions that control the pandemic