Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)

ATN Expert Panel Meeting Summary

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ATN Expert Panel

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Introduction

ATN Background and Purpose of the ATN Expert Panel

The ATN is the only national, multicenter research network devoted to the health and well-being of HIV-infected and at-risk adolescents and young adults. The need for the ATN is driven by the fact that, since 2006 in the United States, the number of people newly diagnosed with HIV has substantially increased among adolescents and young adults ages 13 to 24 (see Appendix 1). ATN activities encompass the full spectrum of research needs for youth. This includes primary prevention for HIV at-risk youth in the community, such as HIV preventive vaccine, microbicide, and pre-exposure prophylaxis (PrEP) trials. It also includes secondary and tertiary prevention with clinical management of HIV infection among youth along the entire HIV care continuum.

The ATN has extensive experience in recruiting and retaining understudied youth populations in the United States. The ATN's research has resulted in 128 abstracts and 155 publications. The ATN has collaborated with the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), the AIDS Clinical Trials Group (ACTG), the HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), the International Maternal Pediatric Adolescent AIDS Clinical Trial Network (IMPAACT), and the Microbicide Trials Network (MTN).

The ATN was started in 2001 through a cooperative agreement mechanism. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is the primary funding agency, with co-funding from the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH). The second and third funding cycles began in 2006 and 2011, respectively. The current, third funding cycle will end in 2016.

The The Maternal and Pediatric Infectious Disease Branch (MPIDB) asked the panel to consider the work of the ATN and the current needs of the adolescent population with respect to HIV/AIDS, including:

- The most important public health needs and scientific opportunities related to HIV/AIDS research in adolescents and whether the ATN is addressing them
- Whether the ATN is effectively prioritizing work on therapeutics, behavior, and community-based prevention
- How the ATN addresses the special challenges of at-risk and HIV-infected adolescents
- How the ATN collaborates with programs funded by other NIH institutes and Department of Health and Human Services agencies like CDC and HRSA
- The impact of the ATN's work on clinical practice and guidelines for HIV prevention and treatment
- The structure of the ATN and whether it is effective

The expert panel heard presentations by NICHD, NIMH, and NIDA program staff; the scientific leadership of the ATN; and representatives of the ATN Data Coordinating Center.

Comments

The expert panel discussed the work of the ATN. The panel congratulated the ATN and NIH leaders of the network for their extraordinary contributions and insights to date and discussed the following areas in light of the current state of the HIV epidemic among adolescents:

- ATN mission
- Research priorities
- ATN structure

ATN Mission

1. **To bend the curve of new infections among adolescents.**

   The ATN is not a public health control program and therefore is unlikely to halt the HIV epidemic among adolescents in the 5 years of the upcoming funding cycle, but interventions should be considered with that mission in mind. Every protocol should be developed and focused on addressing this aim by identifying at-risk youth for enrollment into prevention or treatment interventions or by designing the interventions themselves to reach this goal.

2. **To use phase II and phase III studies, including research on implementation science and comparative effectiveness using large-scale epidemiological studies, to achieve the goal of bending the curve of new infections.**

   The panel noted that the ATN is uniquely positioned to carry out trials that demonstrate the efficacy of interventions. The network should focus on trials with a potential for wide impact and changes in public health and clinical practice that address big-picture research questions with innovative hypothesis-testing. For example, there are many studies on different ways of providing PrEP, but there is a dearth of knowledge on how to persuade young men who have sex with men (YMSM) to stay on PrEP, including YMSM from minority racial/ethnic groups. Likewise, studies of innovative interventions that identify HIV infected young men who have sex with men and women (MSMW), engage them in care, initiate treatment and adherence to combination antiretroviral therapy (cART), and retain them in care are urgently needed.

   The ATN has carried out a large number of qualitative, developmental pilot/feasibility, and acceptability studies that could have been done outside of the network. Part of the evaluation process of a study on a new approach to primary prevention and treatment interventions should be whether it needs to be done in a network or whether it could be more efficiently executed outside of the network structure. Pilot studies, feasibility studies, and developmental studies may not need to be done inside the network. The decision to use the network should be driven by the need to assemble the large numbers of potential subjects needed to answer the primary question, keeping in mind the overall goal to “bend” the HIV incidence curve among U.S. adolescents and young adults.

3. **To increase collaboration with outside researchers throughout the ATN developmental process by including more outside investigators in phase II and III and large-scale epidemiological studies.**

   Outside investigators need to be engaged more. Eliciting protocols from outside members will help ensure that the ATN is conducting the best science, rather than the best science from its members. One weakness noted during the meeting is that the ATN, like many long-standing networks, is perceived as insular. It can be difficult for outsiders to find out how to work with the ATN or even to know that collaboration is welcome. There is little systematic attention to making the ATN data and samples available, for example.

4. **To issue a request for applications (RFA) for phase I development of interventions.**

   The panel suggests that the NICHD and its NIH partners (such as NIMH, NIDA, the National Institute for Allergy and Infectious Diseases [NIAID], and the National Institute on Alcohol Abuse and Alcoholism) consider releasing an RFA to focus on phase I development of interventions via an "incubator fund." This would be part of a strategy for providing opportunities for outside researchers to work with the ATN. The most promising ideas studies would eventually be brought into the ATN if they merited large-scale evaluation, led by outside investigators in partnership with ATN investigators.

   This RFA would help connect the network with outside investigators while freeing the network from carrying out the developmental studies that might distract from high-impact science. The RFA might also invite researchers to use existing data and specimens and would allow more support for principal investigators (PIs) and their research groups, such as research assistants. The PIs whose pilot studies show the most promise would also play a leadership role within the ATN. Another advantage of an ATN linked RFA incubator fund is that it would allow for competitive peer review.

   An example is available from the experience of the NIAID and its IC partners (e.g., NIMH, NIDA, NIAAA), which developed the Methods for Prevention Packages Program (MP3) as a way to fund developmental research that could come into the HPTN, if warranted at a later date. The developmental work within the MP3 award in San Francisco and Peru has led directly to the large scale HPTN 080 protocol, for example. Scientists were able to apply to the MP3 program to develop HIV prevention packages for populations and to do feasibility and acceptability studies on the proposed packages.

Research Priorities

1. **Improving the continuum of care by expanding testing and linkage for MSM and MSMW and improving retention, ART uptake, and adherence for MSM and MSMW.**

   The continuum of care can be divided naturally into two sections based on where the potential participants are found and their HIV status. The earlier part of the continuum, including HIV testing and linkage to care, involves connecting with people who are in the community and are

by definition not linked with care for HIV. The later section, involving ART uptake and adherence, is more naturally addressed in a clinical setting.

MSM have proven to be the population of participants that the ATN has had the most success in reaching. Because the epidemic is most active among these men, it makes sense to focus effort on them. Observations from the PHACS network suggest that controlling the epidemic among MSMW will help control the spread of HIV among young women (see appendix). We note that the current leading ATN investigators are very sensitive and committed to this agenda.

2. **Trials of potential treatments for both men and women.**

   The ATN has a unique capability to find adolescents who may enroll in treatment trials. The ATN can do important work in both adolescent-specific trials and in finding an adolescent population as part of a larger trial. This may include oral PrEP, microbicides and vaccines, with the HPTN, MTN, and HVTN, respectively. Again, we acknowledge current ATN leadership efforts in this direction.

3. **Trials on primary prevention among Adolescent MSM and MSMW.**

   Phase II and phase III trials with primary prevention as an endpoint are more appropriate work for the network. It is difficult to find at-risk individuals to enroll in large-scale primary prevention trials. However, the effort of seeking out those people would help achieve the goal of expanded testing and linkage. For new ideas on prevention, the panel suggests using the R01 or R21 mechanisms to fund phase I studies via the "incubator RFA."

4. **Trials on primary prevention for at-risk Adolescent women and retention, ART uptake, and adherence for Adolescent women.**

   Women cannot be ignored; for drugs and other interventions to be licensed in women, there must be enough data on women, including adolescent women, from clinical trials and comparative effectiveness/safety studies. At-risk women have proven extremely difficult to reach. Mandatory HIV testing of pregnant women has been an essential tool for identifying HIV-infected pregnant young women and engaging them in care and prevention of mother-to-child transmission, but this also reflects a missed prevention opportunity. More formative work will be needed, utilizing the "incubator fund" to develop innovative interventions to reduce young women's risk of infection by addressing the role of stigma within the populations at risk. Reaching MSMW may be an important part of reducing new infections among young women.

5. **Possible expansion to international populations.**

   In some cases, results from trials in one setting may be applicable or generalizable in international situations, but in many cases they are not. For example, working in sub-Saharan Africa requires a completely different approach that is much more centered on young women.

Because the domestic epidemic is the top priority for ATN, domestic trials should be a priority. However, entirely neglecting the global epidemic would be a mistake. There may be some opportunities to provide adolescent-specific ancillary studies, taking advantage of high research investment from non-NICHD sources into international trials; a good example would be the HPTN 071/PopART Study, a treatment-as-prevention trial in Zambia and South Africa. An adolescent sub-study has been planned for that study, but funding is unavailable.

ATN Structure

1. **The scientific leadership groups shouldalign with the mission.**

   The leadership groups (behavioral, community prevention, and therapeutic) do not align clearly with the mission as suggested by ATN leaders and redefined by the expert panel. The ATN may need to be restructured to suit the mission, creating an interdisciplinary Continuum of Care group may be needed, for example.

2. **Consider finding sites in geographical centers of the epidemic.**

   The choice of sites is complex and depends on proposals received and site performance. The sites in the ATN may not be the right sites in the right locations to fulfill the network's mission. If possible, the network should have sites that represent all regions, particularly locations where the epidemic is most active, such as the San Francisco Bay area and the Deep South, now underrepresented. There is precedent for including geographic considerations in awarding sites within an RFA; NIAID issued an RFA specifically for new sites in the Southeast US for the Women's Interagency HIV Study.

3. **Use research needs to select the coordinating center, the data/operations center, and the analysis center.**

   The coordinating center, the data/operations center, and the analysis center are three separate functions. The current arrangement has the coordinating center at one location and the data/operations and analysis center at another. The panel's impression was that, given the ATN's number of protocols and the quantity of data collected over the years, there is a disproportionately low number of publications. For example, the number and quality of publications on the Connect to Protect program do not seem to reflect the amount of effort and resources associated with that program. While investigators who work with the network should be familiar with the literature in their area, they should not be expected to be experts in cutting-edge data analysis. This is not a problem unique to the ATN, but has become more apparent and acute as population science has become more complex. Teaming with an experience epidemiological and biostatistical design and analysis center, with a clear leadership role, could be helpful in addressing this challenge in productivity. A future data analysis center to be competed within the new RFA must offer a wider spectrum of innovation required to extract publishable narratives from the data.

The decisions about the mission of the ATN in the funding cycle should drive the RFA for analytic and scientific leadership. If the mission is refocused on phase II and phase III trials, for example, the analysis center may be able to refocus on supporting trials, as well as needing to have the depth to be able to do translational research, including comparative effectiveness/safety research. In any approach, a strong data analysis methods core will be needed moving forward.

The panel discussed several possibilities for possibly dividing these roles to ensure that the very best groups are occupying each function. One possibility is to offer three RFAs, one for each function. A second option is to issue one RFA, inviting responses for any or all of the three functions, i.e., a center could be chosen for one, two, or all three functions. This would require centers to be skilled at collaborative work. A third approach would be to keep the current structure (coordinating center and data/operations center) but to specify the skill sets needed in the RFA.

4. **Expand research portfolio to include social determinants of HIV infection among youth in the US.**

   The ATN should focus more on research related to social determinants of HIV risk, which are of fundamental importance in driving the US HIV epidemic – especially among racial/ethnic minorities. Such research would fill a critical gap in the NIH's HIV research portfolio by adding social scientists to address questions related to mass incarceration, poverty, inequality, and other issues that impact prevention and care among youth.

Other Topics Discussed

Other points of consideration by the ATN expert panel were as follows:

1. It was suggested that the staffing model for sites should change in the next funding cycle to decrease the number of core staff at each site and to consider site performance data when selecting sites. There may also be different ways of managing how the sites are funded, such as the model used by the PHACS study.

2. The panel discussed the necessity of continuing to study young women, using outcomes related to HIV risk for uninfected adolescent girls and young women. Since a lower incidence of HIV is to be expected compared to YMSM, HIV endpoint studies may not be feasible. However, much vital research on risk and prevention is needed with non-HIV endpoints (e.g., sexually transmitted infections and behavior change) that can help both find and study at-risk young women.

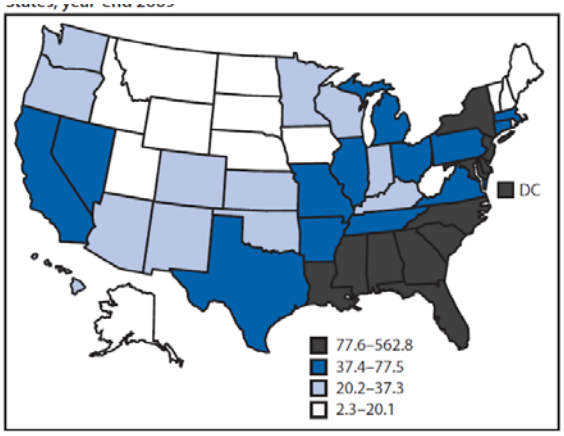
Conclusion

The expert panel commends ATN's work on the HIV epidemic in adolescents and looks forward to its refocused efforts toward high-impact science on evidence-based approaches to bringing the epidemic under control.

Appendix

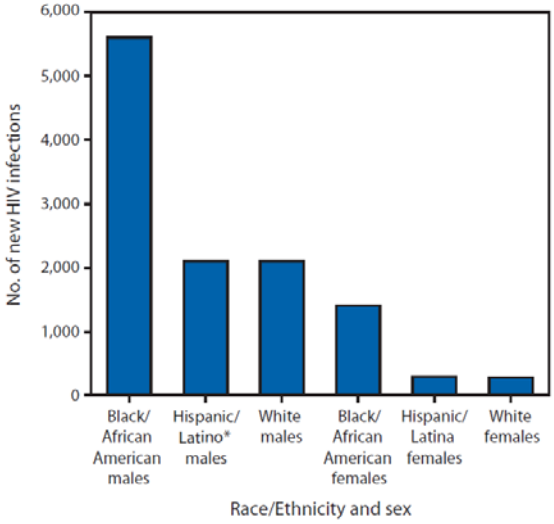
Since 2006 in the United States, the number of people newly diagnosed with HIV has substantially increased among adolescents and young adults aged 13 to 24. In particular, the number of new HIV infections has risen most dramatically among young men (aged 13 to 24) who have sex with men (YMSM), with the largest increase among African-American YMSM (see figure 1 and 2).

Figure 1. Prevalence rates of persons aged 13-24 years living with a diagnosis of HIV infection* — National HIV Surveillance System, United States, year-end 2009



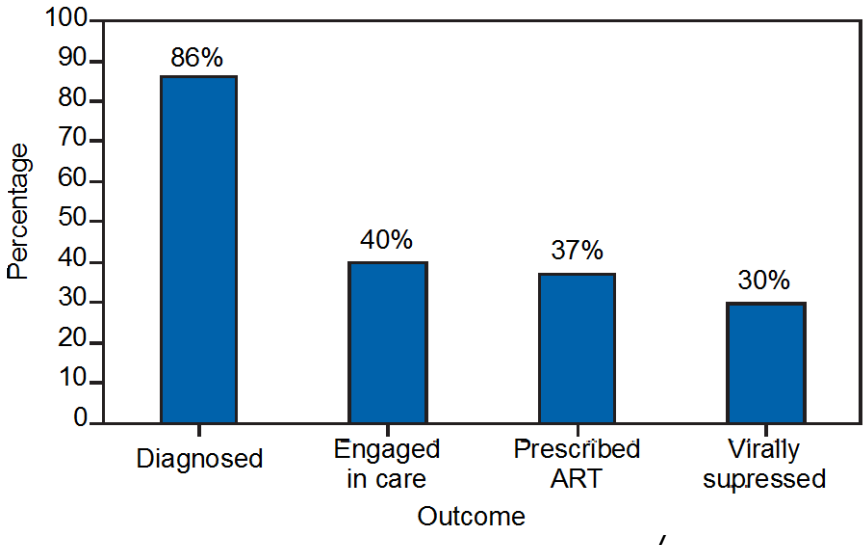
Abbreviation: HIV = human immunodeficiency virus.
* Prevalence rates are per 100,000 population and are not adjusted for reporting delays. Prevalences are categorized into quartiles. Overall prevalence rate: 69.5 per 100,000.

Figure 2. Number of new HIV infections among youths aged 13-24 years, by sex and race/ethnicity – United States, 2010



The highest prevalence of HIV infections among YMSM are observed in New York, New Jersey, Maryland, Washington, D.C., and the Deep South (see Figure 1, above).

Figure 3. Estimated percentage of persons living with HIV infection,* by outcome along the HIV care continuum ----United States States, 2011 (1).

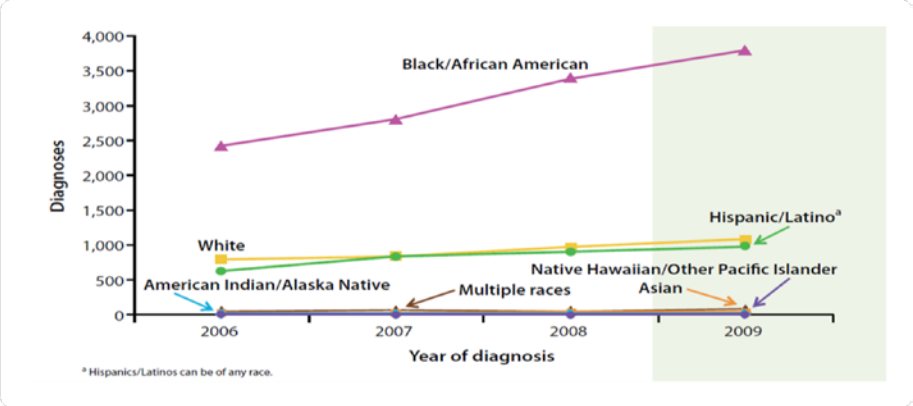


At the end of 2011, an estimated 1.2 million people were living with HIV in the United States, of whom 14 percent were unaware of their HIV status, 40 percent were engaged in care, and only 30 percent were virally suppressed, as seen in Figure 3.[1]

Of particular concern is that the number, and proportion, of new

infections among men who have sex with men (MSM) has increased, from 59 percent of all reported cases of HIV in 2008 to 64 percent in 2012.[2] In 2012, 30,695 HIV infections were reported among MSM, with 39 percent among black/African-American men, and 23 percent reported among Hispanic/Latino men.[2] This shift, from a largely white MSM epidemic to an epidemic among MSM of color, poses new challenges in HIV prevention, identification, and treatment (Figure 4).

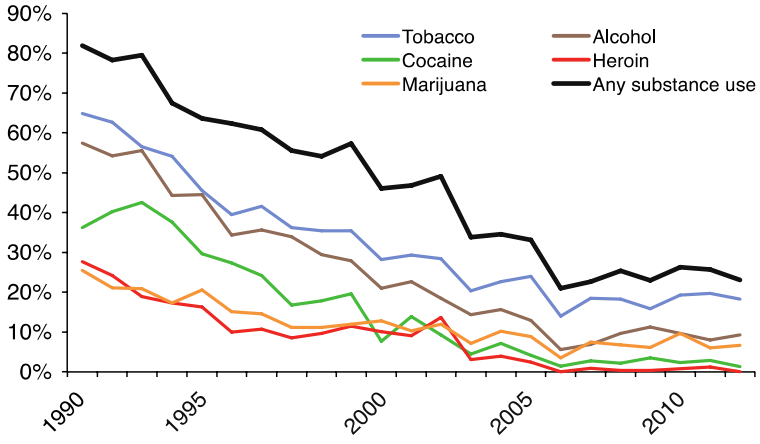
Figure 4. HIV Infection Diagnoses Among YMSM Aged 13-24 Years by Race/Ethnicity, 2006-2009—40 States and 5 US territories.



These challenges include the impact of racism, stigma, poverty, and access to health care on HIV testing and subsequent access to treatment and prevention, as can be seen in Figure 3. Despite treatment guidelines recommending that MSM be tested every 3 to 6 months,[3,4] only 20 percent of MSM reported having been tested in the past 6 months and 67 percent in the past 12 months.[5–7] Forty-seven percent of MSM and men who have sex with men and women (MSMW) have never discussed their sexual orientation with their doctors, and 56 percent have never been advised by a doctor to be tested for HIV.[7]

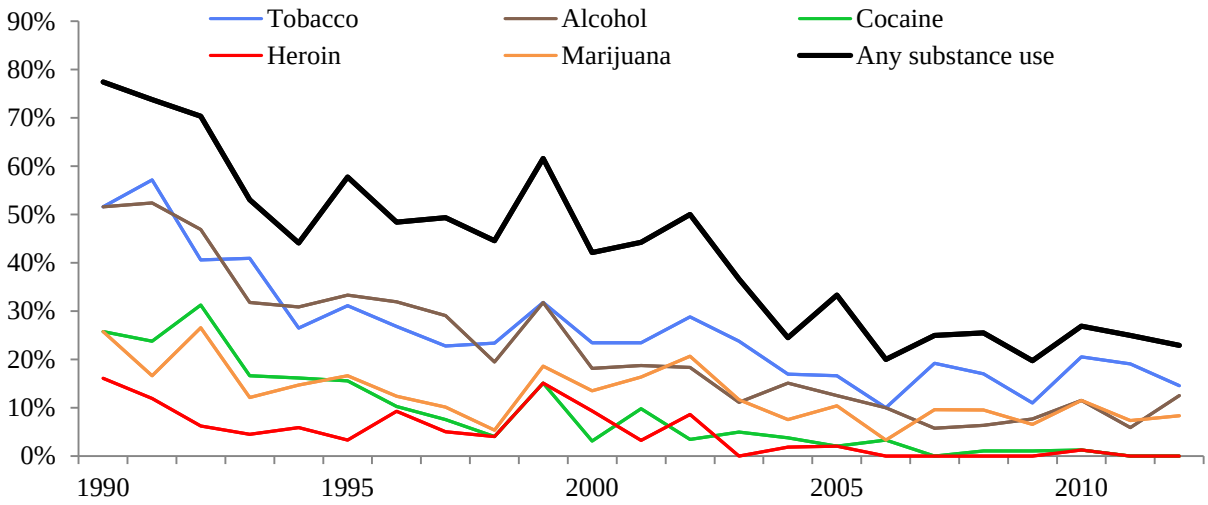
While the number of *reported* new infections among adolescents continues to increase, they represent only a fraction of the number of people 24 or younger with HIV infection in the United States. Based on estimates of how many people are infected, only 49 percent of HIV-infected adolescents are thought to have been diagnosed, compared to 88 percent of HIV-positive adults 25 and older (see figure 3).[1] Even when identified and diagnosed, the changing demographics of the HIV epidemic in the United

Figure 5. Proportion of HIV-infected women using substances during pregnancy, by delivery year (n = 5,451)).[8]



States are not only among men. Of the 9,586 HIV infections reported among women in 2012, 85 percent reported heterosexual contact as their major risk, with 13.5 percent of infections attributed to injection drug use.[2] These trends represent a "flipping" of the HIV epidemic among women in the past 25 years, as recently reported by Rough et al. (Figure 5).[8] In the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring for Antiretroviral Treatment Toxicities, more than 85 percent of the more than 3,000 women reported heterosexual sex as their primary risk for HIV, and substance use during pregnancy has reached the same level as HIV uninfected women in the U.S. population.[8] In a subset of women 24 and younger, the same dramatic decrease in substance use has been observed in the same cohort over the past 25 years (Personal Communication, K. Rough, 2015, Figure 6).

Figure 6. Substance use during pregnancy in Women and Infants Transmission Study/Surveillance Monitoring for Antiretroviral Therapy Toxicities Study, by year of delivery (24 and younger only, n = 1,550).



MSMW may contribute to this changing trend. MSMW have dense sexual networks, which include more male partners and higher rates of concurrency than MSM (32 percent versus 27 percent).[9,10] Furthermore, black MSMW have denser sexual networks than white MSMW, with 63 percent of black MSMW reporting concurrent partners in their sexual network and 38 percent having unprotected sexual intercourse with male and female concurrent sexual partners.[11,12] Sexuality and HIV-related stigma is common in black communities and a significant barrier to disclosure of HIV status to sexual partners.[13,14] Hampton et al. found that non-gay identified black MSM were more likely to engage in unprotected sexual behaviors with women.[15] Hypermasculine ideals contribute to an increase in numbers of both male and female partners among black MSMW.[16] The prevalence of other high-risk behaviors, such as substance use and exchange or transactional sex, is high among MSMW.[17] The role of MSMW in heterosexual HIV transmission is important to explore as MSMW are more likely to engage in anal intercourse with women than heterosexual men, and 43 percent to 56 percent of MSMW report unprotected vaginal or anal intercourse with female sexual partners.[18–22]

To control the HIV epidemic, each person with HIV must progress through the HIV continuum of care. This occurs when people with HIV are diagnosed, engage in care, adhere to combination antiretroviral therapy (cART), and achieve viral suppression. Suppressing the virus in people who are HIV-positive substantially lowers the risk of viral transmission. Thus, nearly 20 years after the introduction of cART, which has proven to reduce mortality, increase survival, and reduce HIV transmission, we have fallen short of our goal to eliminate HIV infection and now have an ever increasing HIV epidemic curve among individuals younger than 25[23]. A focused effort will be needed to "bend" the HIV incidence curve among people younger than 25 in the United States.

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