



## HIV/AIDS AT 35 YEARS

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### A BRIEF HISTORY OF THE EPIDEMIC

This June marked the 35th anniversary of the first five cases of “AIDS” in the United States that were reported in 1981 in the CDC publication, *Morbidity and Mortality Weekly Review (MMWR)*.<sup>1</sup> By the end of that year, more than 300 gay men with severe immune deficiency had been reported and almost half had died. This experience was soon followed by several thousand cases over the next three to four years in both the U.S. and other parts of the world.<sup>2</sup> The mode of disease transmission beyond men who had sex with men (MSM) was unknown, which created a great deal of fear and stigma among both the lay and medical communities. Along with male sexual transmission, it soon became apparent that HIV could be transmitted from mother to child, to the female partners of HIV-infected men, and also via the transfusion of blood and blood products.<sup>3</sup> Many health care workers, including physicians, refused to take care of “AIDS patients” out of fear of contracting the virus.<sup>4</sup> The first decade of the pandemic was associated with significant and increasing morbidity and mortality as HIV/AIDS became a leading cause of death among men and women worldwide.

The causative agent of AIDS, later named Human Immunodeficiency Virus (HIV), was first identified in 1983 by Dr. Luc Montagnier and colleagues at the Pasteur institute in France, for which he would later receive the Noble Prize in Medicine.<sup>5</sup> A group led by Dr. Robert Gallo and colleagues in the United States concurrently reported discovery of the same virus.<sup>6</sup> HIV is transmitted as a single-stranded RNA-virus (lentivirus), which is characterized by its mechanism of replication via reverse transcription and integration of viral DNA into the host cell genome. This mechanism allows the virus to remain latent and escape normal immune surveillance. Untreated patients experience a state of chronic infection and progressive immune depletion, specifically of CD4+ T lymphocytes. The mechanisms of immune activation and immunologic deterioration are quite complex and involve multiple

mechanisms beyond destruction of CD4+ T cells.<sup>7</sup>

The first HIV antibody (EIA) test was developed in 1985, specifically to screen the blood supply, but the availability of this test also allowed those infected with the virus to be diagnosed, which raised many ethical and moral issues. Since there were no effective treatments, did those infected with HIV want to be identified as having a terminal illness that would also lead to loss of jobs, housing, and abandonment by families and friends?<sup>8</sup> It was not until more than 10 years later, when we finally had effective treatments for the virus, that HIV testing was more readily accepted.

### HIV EPIDEMIOLOGY

According to the Centers for Disease Control and Prevention (CDC), which reports annually on the prevalence and incidence of HIV and AIDS, in 2014 an estimated 1.2 million people age 13 years and older were living in the U.S. with a diagnosis of HIV/AIDS.<sup>9</sup> Since 1981 more than 650,000 people in the United States have died from AIDS. For the past 15 years the number has been stable at about 14,000 annually. More remarkably, the historic number of global AIDS deaths is approximately 40 million with 37 million living with HIV. Due to increased access to testing, treatment, and prevention, the global number, especially from Sub-Saharan Africa where 70% of those with HIV live, has been declining over the past ten years.<sup>10,11</sup>

Despite the widespread availability of testing, and recommendations for routine HIV screening by the CDC, American College of Physicians, U.S. Preventive Services Task Force, and most other major medical organizations, about 13% of adults in the United States are unaware of their HIV status.<sup>9</sup> This number is considerably higher among adults aged 18-29. The epidemic continues to be primarily driven by diagnoses among gay and bisexual men (67%), and that incidence has outweighed decreases in other susceptible populations, including those who inject drugs (6%). As a result of HIV prevention methods (see section below) this number has been stable but has not yet

significantly declined - which some see as a failure in public health management.<sup>12</sup>

In 2014 there were an estimated 44,073 people diagnosed with HIV in the United States. More than 50% of new infections occurred in people less than 35 years of age,<sup>9</sup> and about 10% of new infections were in those 55 and older. These data illustrate that age or gender bias should not preclude health care providers from offering HIV screening for their respective patient population or area of medical or surgical practice. The goal of the CDC and others is to reduce the number of new infections by 50% by the year 2020. This goal will only be reached if health care providers are willing to encourage patients to undergo one-time HIV screening, while also remaining focused on more frequent testing (at least yearly) of high-risk groups including men who have sex with men, individuals who inject drugs or are diagnosed with any sexually transmitted infection, and the partners of those known to be infected with HIV.

#### TREATMENT OF HIV

The treatment of HIV has undergone a remarkable transition since 1987 when the first antiretroviral, zidovudine (AZT), was approved by the FDA.<sup>13</sup> Zidovudine was actually a chemotherapy agent taken off the shelf at the National Institutes of Health and found to have antiviral activity. This drug was followed by the development and approval of several other nucleoside reverse transcriptase inhibitors (NRTIs), including stavudine and lamivudine. Although these drugs were effective against HIV for a short while when they were used singly or in two-drug combinations, drug-resistance ultimately developed due to viral mutations, and patients then experienced progression of their disease and ultimately death.

In 1995, the presentation of data about the first protease inhibitor (PI) at the International AIDS Society meeting in Vancouver ushered in a new era of disease-changing therapy.<sup>14</sup> This was the “AIDS cocktail” - a three-drug combination of 2 NRTIs and a PI that resulted in dramatic clinical improvement, including in patients with very advanced disease, AIDS-related complications, and opportunistic infections. This combination of therapy (initially known as “HAART” - now ART [Antiretroviral Therapy]) began transforming HIV/AIDS in most patients into a chronic, manageable disease.

In subsequent years, other classes of antiviral drugs have been developed, including non-nucleoside reverse

transcriptase inhibitors (NNRTIs), a fusion inhibitor, a CCR-5 receptor antagonist, and most recently a class of drugs known as integrase strand transfer inhibitors (INSTIs). The INSTIs inhibit integrase, the viral enzyme that allows insertion of the HIV genome into host cell DNA. The newer antiretroviral drugs that are more potent, have a higher genetic barrier to resistance and longer half-lives than the older agents. Moreover, the newer agents are better tolerated and less toxic than the older drugs.

With the progressive development and approval of single-tablet regimens (STRs) that contain three or four drugs, the majority of patients with HIV in the United States now take just one pill a day to treat their infection. The current drugs are highly effective in fully suppressing HIV replication and allowing for immune recovery and clinical stability for most patients. Life expectancy for individuals living with HIV is estimated to be approaching that of uninfected adults - provided they remain on ART.<sup>15,16</sup> As a way to further simplify ART, current clinical trials are looking at two-drug regimens including an integrase inhibitor with one NRTI, an INSTI and NNRTI, or a PI with one NRTI. This approach could further reduce pill burden and toxicity, but could substantially decrease the cost of long-term treatment. The currently available single-tablet regimens cost approximately \$3,000 per month. Also on the horizon are long-acting injectable antiretroviral drugs that likely will be available for clinical use in the next two to three years.

#### AIDS-RELATED OPPORTUNISTIC INFECTIONS

Opportunistic infections (OIs) were historically the point of entry into the health care system for most people diagnosed with AIDS and were also a common cause of mortality. An HIV diagnosis was often first made when patients presented with an “AIDS-defining” condition such as *Pneumocystis jirovecii* pneumonia, esophageal candidiasis, or Kaposi’s sarcoma. For patients with significant immune suppression (CD4+ count < 200 cells/mm<sup>3</sup>), primary prophylaxis with trimethoprim-sulfamethoxazole and other antimicrobial agents is effective in preventing several of these conditions, and it remains part of standard medical care for these patients. However, with the advent of effective ART and subsequent immune recovery, especially in patients diagnosed early, the incidence of all OIs has significantly declined. When conditions such as CMV disease, mycobacterium avium complex (MAC), cryptococcal meningitis, and toxoplasmosis are now seen,

it is invariably in people who have not been diagnosed with HIV, or – if they have been – are not taking ART. Survival among HIV-infected individuals with OIs has markedly improved, and for most patients diagnosed with these infections, appropriate antimicrobial treatment and prompt institution of ART is recommended.<sup>17</sup> The majority of patients clinically do very well, and following effective immune recovery from ART (e.g. a significant increase in CD4-Tcell lymphocytes), which may take months to years, primary prophylaxis and/or maintenance therapy against OIs can be safely discontinued.

### AIDS-RELATED MALIGNANCIES

Malignancies were one of the earliest manifestations of the AIDS epidemic. In the pre-ART era, Kaposi's sarcoma and Central Nervous System lymphoma were two of the most common AIDS-defining cancers (ADCs) and were a main cause of AIDS mortality. These cancers are virally mediated and developed in the presence of severe immune deficiency. In the post-ART era, cancer continues to be a significant source of morbidity and mortality, but there has been a shift to "non-AIDS-defining cancers" (NADCs) including – but not limited to – colorectal, anal, and lung cancers.<sup>18</sup> The incidence of Hodgkin's lymphoma also remains very high in individuals who are HIV-infected.

Among the factors that account for a significant increase in the incidence of NADCs are continued immune deficiency and dysregulation despite ART. Other contributing factors include cigarette smoking, longer survival time, and increased screening for cancers in the HIV population. Compared with the non-HIV population with NADCs, patients with HIV present at a younger age and often at a later stage. Though treatments are essentially the same as in patients without HIV disease (surgery, chemotherapy, radiation therapy), patients with HIV and an NADC have a higher mortality than the general population with the same malignancies.<sup>19</sup> More studies are needed to determine if alternative or more aggressive cancer screening methods, apart from those currently used for the general population, are indicated for people living long-term with HIV disease.

### HIV PREVENTION METHODS

1. Despite numerous clinical trials over the past 15 years we are still not close to having an effective "AIDS vaccine." Only one vaccine trial thus far (RV 144),

done in Thailand, has shown any efficacy in preventing HIV infections, and it was only effective in 31% of patients.<sup>20</sup> The HIV Vaccine Trials Network (<http://www.hvtn.org/en.html>) continues to pursue this goal at its nine sites in the United States and 10 others globally. At the recent 21st International AIDS Conference in Durban, interim results from the HVTN 100 study were presented. This study, conducted by the HIV Vaccine Trials Network, tested the immune responses of study volunteers in Africa to a modified version of the RV144 regimen, specifically against clade C subtype of HIV. After just 6½ months, the study met four pre-specified immunogenic criteria including the development of IgG-binding Antibody to  $\geq 2$  of 3 vaccine antigens. This trial will now move ahead to phase IIb efficacy studies that, hopefully, will continue to show promising results.<sup>21,22</sup>

2. The use of *condoms* has been promoted for many years and continues to be 70 to 80 percent effective in preventing transmission of the virus, depending on the sexual practices and the specific population studied.<sup>23</sup>

3. *Screening of the U.S. blood supply* since 1985 has made transfusion an extremely rare cause of HIV. Since 1999, donations have also been pooled and tested for HIV-1 ribonucleic acid (RNA). There was one case of HIV transmitted by transfusions in 2002 and two cases in 2008.<sup>24</sup> Currently the estimated risk of acquiring HIV via blood transfusion is about one in 1.5 million.

4. Three large randomized trials done in sub-Saharan Africa demonstrated that *voluntary circumcision* of HIV-uninfected men led to a 50% reduction of risk for HIV from heterosexual relations.<sup>25</sup> However, this benefit did not appear to extend to the female partners of circumcised but HIV-infected men. Some observational data suggest that circumcision may be beneficial for MSM who practice primary insertive anal intercourse but there is insufficient evidence to date to determine whether or not this is generally true for MSM.<sup>26</sup>

5. A key biological component of HIV-prevention is effectively *reducing "viral load"* (HIV-RNA levels) in those infected with the virus. It has been known since 1993 that treating HIV-infected pregnant women with ART down to a viral load of  $< 1,000$  copies, dramatically reduced the incidence of mother-to-child transmission (MTCT) of HIV.<sup>27</sup> There have been fewer than 100 cases per year in the United States and when this does occur it is considered a sentinel event.\*

\*During the 19 years of our program at LGH we have had no newborn infections while providing care for more than 200 pregnant women.

6. In a similar fashion, a large international HIV prevention study (HPTN 052) found that *treating the HIV-infected partner with ART* and attaining viral suppression reduced HIV transmission in sero-discordant couples by 96%.<sup>28</sup> This pivotal study has been one of the key drivers of early ART for all people who are HIV-infected in both the United States and the developing world.

7. The most recent medical intervention to prevent new HIV infections is *pre-exposure prophylaxis* (PrEP), the use of antiretroviral drugs (specifically the combination of tenofovir/emtricitabine) in those who are HIV-negative. This practice has now been shown in multiple studies to markedly decrease the acquisition of HIV both sexually and via use of injected drugs.<sup>29,30</sup> This combination of two drugs was approved for HIV prevention by the FDA in 2012 but only in the last 1-2 years has there been significant uptake of this practice – especially in the United States and Western Europe. The CDC and U.S. Public Health Service issued a specific practice guideline for the use of PrEP in the spring of 2014.<sup>31</sup> Ongoing clinical trials and “real world” studies, especially done in MSMs, have found a consistent 80% to 90% relative risk reduction in HIV acquisition among men who take a fixed dose (Truvada™) tablet once-a-day.<sup>32,33,34</sup>

#### AN HIV CURE?

There has been a great deal of research and discussion about “curing AIDS” since the case of Timothy Brown was reported several years ago in the *New England Journal of Medicine*.<sup>35</sup> Brown, also known as the “Berlin Patient” underwent two stem cell transplants for acute myelogenous leukemia while living in Germany. His donor in both cases had a specific CD4+ mutation (delta CCR5) that does not allow viral binding to the cell surface. This mutation was described in the literature in 1996 and remains a focus of HIV research.<sup>36</sup> Brown was ultimately determined to be cured (“sterilizing cure”) of his HIV infection as numerous attempts failed to isolate virus from blood and tissue samples. Several attempts to repeat this intervention with other HIV patients have failed. There are case reports and small cohorts of individuals who can maintain viral control while not taking ART (“functional cure”) but these remain very uncommon. There remains significant scientific effort directed at developing ways to create a sterilizing cure, or functional cure for HIV infection. These approaches are being evaluated under the broad headings of gene

therapy, immune-based interventions, and antiviral treatments that depend upon HIV reactivation from latency, to cause the death of cells which harbor the virus. The degree of optimism regarding an HIV cure amongst HIV clinicians and the research community remains in flux.<sup>37</sup>

#### HIV/AIDS CARE AT LANCASTER GENERAL

Since 1997, we have had an HIV clinical program at LGH. With the support of Dr. Nikitas Zervanos and Dr. Christine Stabler, I was able to initiate a one-half day per week clinical session within the Family Medicine Residency Program (now DFM). At the time, many HIV patients were receiving fragmented care within our community or were traveling to Hershey Medical Center. Our goal was to provide consistent and comprehensive outpatient HIV medical care to the residents of Lancaster City and County. With the assistance of the late Jay Bucher, then vice president for development at LGH, we were awarded a \$900,000 federal “Ryan White Grant” from the HIV/AIDS Bureau of the Department of Health and Human Services in 1999, which began funding our program in January of 2000. Our program within LGH has been awarded more than \$7 million dollars in grant funding through 2016 and continues to be the federally funded site for HIV care for the residents of Lancaster County.

Through the years, our program has grown into an established separate practice now known as *Lancaster General Health Physicians Comprehensive Care*, located in the downtown campus at 554 North Duke Street. Comprehensive Care is one of the four “academic practices” – along with Family Medicine Downtown, Family and Maternity Care, and the Walter L. Aument Family Health Center that also provides training to residents and medical students.

Comprehensive Care currently delivers HIV specialty care as well as primary medical care to more than 600 adults with HIV/AIDS. We also care for many of the partners, spouses, and children of our HIV-infected patients. The practice is staffed by five physicians who are board-certified in Family Medicine and who also have HIV-Specialty certification through the American Academy of HIV Medicine. The practice provides free rapid HIV testing to the Lancaster community. In September 2015 Comprehensive Care was awarded a \$100,000 DHHS/CDC capacity building grant to expand and promote HIV testing in Lancaster County. Comprehensive Care also serves as a referral, clinical and educational resource for all of LG Health.



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