

Chapter 3

HIV/AIDS Comorbidities: Impact on Cancer, Noncommunicable Diseases, and Reproductive Health

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INTRODUCTION

The total number of people living with human immunodeficiency virus (HIV) worldwide continues to grow annually, attributable to both new infections and the increased longevity of infected persons treated with potent antiretroviral therapy (ART). This growing population bears the burden of associated health conditions that complicate long-term HIV infection. Specifically, secondary epidemics of cancer; reproductive ill health; and noncommunicable diseases, such as cardiovascular disease, diabetes, renal dysfunction, and liver damage, have been observed across the globe. This wide spectrum of illnesses complicating ongoing HIV infection is a challenging global health threat and underscores the need for a greater understanding of these comorbidities, broader access to treatment, and increasingly sophisticated treatment to avoid widespread preventable morbidity and death.

This chapter provides an overview of some of the most common, most rapidly increasing, or most morbid complications of persistent HIV infection; it is not meant to be exhaustive. Additionally, many comorbidities of long-term HIV infection are addressed in detail in other chapters of this volume.

The first portrayals of the epidemic in the early 1980s in the United States described a surge of cancer cases among men who have sex with men (MSM). Since the initial reports from the early epidemic, it has become clear that HIV threatens the reproductive health of women across income settings and populations. Paradoxically, in an age of new hope for prolonged lifespan stemming from the success of ART, increased longevity is also bringing a host of noncommunicable chronic comorbidities (NCCs).

Among cancers—the focus of the first section of this chapter—the pandemic initially saw an annual rise through 1996 in what came to be known as acquired immune deficiency syndrome (AIDS)-defining cancers (ADCs), including Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer (CDC 1992). These cancers decreased in incidence with the widespread availability of ART in high-resource settings but never fell to the levels seen before HIV; they continue with little change in incidence in low- and middle-income countries (LMICs). Additionally, a troubling rise in other, non-AIDS defining cancers (NADCs)—such as anal cancer, hepatocellular carcinoma (HCC), and lung cancer—continues to be observed globally despite access to ART.

The next section of the chapter considers the multifaceted impact of HIV on women's reproductive health.

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Girls and women who are at risk of HIV or who are already infected are vulnerable to problems of access to adequate reproductive choice and contraceptive options. Yet, the evidence suggests that preventing mother-to-infant transmission of HIV can effectively be achieved through the prevention of unplanned or unwanted pregnancies. Barrier contraceptive methods, although suboptimal at preventing pregnancy, do protect against HIV. The section also examines the complicated influence of HIV on infertility in women and the transmission of human papillomavirus (HPV), herpes simplex virus (HSV), pelvic inflammatory disease, bacterial vaginosis, and others.

The final section of the chapter highlights the wide range of NCCs associated with long-standing HIV infection, including cardiovascular and metabolic illnesses.

Taken together, the data from many parts of the world clearly show that despite the dramatic decrease in deaths due to HIV with the continued expansion of access to successful treatment, access to ART alone will not prevent, and in some cases may precipitate, a wide spectrum of complications of long-term HIV infection. These challenges require the attention of health care providers, policy makers, and researchers, empowered by access to accurate information on the burden of these diseases and the growing number of potential solutions.

HIV AND CANCER

At the beginning of the global HIV pandemic, an outbreak of cancer among MSM in the United States was described in 1981 (Hymes and others 1981). Since then, the evidence suggests that the risk of cancer is 2–3,000 times higher among people with HIV than those who are not infected (Grulich and others 2007); up to 9 percent of people living with long-term HIV infection will develop cancer over the course of their HIV care (Shiels and others 2011). Cancer is the leading non-AIDS cause of death worldwide among people with HIV (Smith and others 2014).

Epidemiology of Cancer among People with HIV

In high-income countries (HICs), the incidence of cancer in people with HIV rose annually until 1996, when access to potent ART became widely available and observers noted a sharp decline in new cancer cases (Shiels and others 2011).

Since 1998, however, the incidence of cancer among people with HIV has been gradually rising annually in the United States. Initially, the overwhelming number were ADCs (CDC 1992), including KS; NHL; Burkitt, immunoblastic, and primary central nervous system lymphomas;

and cervical cancer. These malignancies, all associated with a viral oncogenic infection, were frequently found in individuals with low CD4 T-cell counts, and therefore common before ART became widely available.

Over time, additional cancers were observed to be more common in people with HIV, but these were not considered to be AIDS defining (Patel and others 2008; Shiels and others 2011; Silverberg and others 2015). These NADCs—which are significantly more common in people with HIV than in peers without it in the same population—include anal cancer, HCC, and lung cancer.

Today, incident cancer cases are roughly equally divided between ADCs and NADCs. In the United States, approximately one person will develop cancer for every 100 people with HIV each year (Riedel and others 2013). One study estimates a similar incidence of cancer among HIV-infected South Africans receiving ART (0.87 cases of cancer developing for every 100 people with HIV followed over a year) (Sengayi and others 2016).

The time that has passed since initial infection with HIV also influences which cancer arises; ADCs are more common soon after diagnosis, and NADCs are more common after five or more years (Robbins and others 2015). Survival after a diagnosis of cancer accompanying HIV appears to be considerably shorter, on average, especially for NADCs, compared with similar cancers in people without HIV (Achenbach and others 2011; Coghill and others 2015).

Less is known about the epidemiology of cancer among people with HIV in LMICs. Cancer registries that cover the entire population are few in these areas and do not routinely capture HIV status of cancer cases. A retrospective analysis from 13 clinical sites in the East Asia and Pacific region, as part of the TREAT Asia HIV Observational Database study, revealed data comparable to that seen among the non-Asian HIV populations. In that analysis, CD4 T-cell counts greater than 200 cells per cubic millimeter (mm^3) were found protective against ADCs; older patients and those not on potent ART were more likely to be diagnosed with an NADC (Petoumenos and others 2010).

Attempts to match cancer registries with data on individual HIV status have been conducted in Uganda (Mbulaiteye and others 2006), Nigeria (Akarolo-Anthony and others 2014), and South Africa (Sengayi 2016), and found the cancers to be more common among people with HIV, similar to the United States. Hospital-based cancer registries in India also show a similar spectrum of cancer in people with HIV, except for a notably lower frequency of KS (Venkatesh and others 2012).

Few studies have assessed survival after diagnosis of HIV-associated malignancies (HIVAMs) in resource-limited

settings, but the odds of death appear to be significantly higher among people with HIV (Coghill and others 2013). Cohort studies conducted in high-income regions have found cancer to be among the leading causes of death of people with HIV (Bonnet and others 2004; Kowalska and others 2012; Smith and others 2014).

Pathogenesis of HIV-Associated Malignancies

People with HIV are predisposed to a higher risk of cancer through a variety of mechanisms. First, the immunosuppression that accompanies CD4 T-cell depletion may lead to the development of cancer when the immune system fails to seek out early cancer occurrences and destroy them. This helps explain why the risk for many HIVAMs is inversely related to CD4 T-cell count (Biggar and others 2007).

The observation that some cancers (cervical cancer and Hodgkin lymphoma) in people with HIV were not associated with lower CD4 T-cell counts—coupled with epidemiologic studies suggesting that the risk for cancer was greater among people with HIV than among highly immunosuppressed recipients of organ transplantation (Grulich and others 2007)—led to the exploration of mechanisms beyond CD4 T-cell depletion that could lead to cancer in people with HIV.

HIV replication itself may foster the development of cancer, potentially through the induction of angiogenic, anti-apoptotic, or proliferative signaling. That failure to suppress HIV replication (or time spent with HIV detectable in the plasma) is independently associated with risk of cancer (Bruyand and others 2009) supports this hypothesis. Other mechanisms being explored that cause cancer in persons with HIV include immune activation, immune exhaustion, and HIV integration. The individual components of ART may also reduce cancer risk beyond their effect on immune reconstitution. Gantt, Casper, and Ambinder (2013) found that protease inhibitors have antineoplastic properties, and nucleoside reverse transcriptase inhibitors (NRTIs) suppress viruses that cause cancer in people with HIV.

Specific HIV-Associated Malignancies

Cervical Cancer

Globally, cervical cancer, caused by HPV (Forman and others 2012), is the fourth most common cancer and third leading cause of cancer-related death among women; the incidence in LMICs is second only to breast cancer (De Vuyst and others 2013; Ferlay and others 2013). In Sub-Saharan Africa, cervical cancer is the leading cause of cancer-related death among women (Bosch and others 2013; Lozano and others 2012).

In a meta-analysis involving nearly 200 studies and more than 1 million women who had a normal cervical cytologic examination, HPV DNA was detected in nearly 12 percent of women globally, although with marked geographic variation. Regions of frequent HPV detection include the Caribbean (35 percent) and Eastern Africa (34 percent), yet frequency is only 10 percent or less in Northern Europe (10 percent), Northern Africa (9 percent), Western Europe (9 percent), Southern Europe (9 percent), Southern Asia (7 percent), North America (5 percent), and Western Asia (2 percent) (Bruni and others 2010).

More than 100 types of HPV exist, but HPV 16 and 18 cause 70 percent of cancers. HIV may increase cervical cancer risk by increasing the rates of persistent HPV infection, in contrast to HPV in women without HIV whose immune systems often clear the infection (Ahdieh and others 2000).

The risk of cervical cancer in women with HIV increases with age and has no direct association with CD4 T-cell count (Yanik and others 2013); the risk, however, is reduced in women receiving ART (Blitz and others 2013). For all women, comprehensive screening and treatment programs dramatically reduce deaths from this disease.

Kaposi Sarcoma

KS, the most common HIV-associated malignancy worldwide, is caused by infection with human herpes virus 8 (HHV-8). In the United States and Europe, KS is 10 times more common among men than women; in Sub-Saharan Africa, the rates are nearly equal. In part, KS incidence mirrors HHV-8 prevalence, which is high among MSM in HICs and endemic in many parts of Sub-Saharan Africa (Nguyen and Casper 2010).

KS incidence declined nearly tenfold by 1996, the year after potent ART became available in the United States (Eltom and others 2002); it has declined more slowly in Sub-Saharan Africa since ART was rolled out (Mutya and others 2015). Mortality from KS is unusual in HICs, although the disease persists in up to 50 percent of patients treated with ART and chemotherapy (Achenbach and others 2011; Nguyen and others 2008). In LMICs, KS mortality is high and response to treatment is poor (Gondos and others 2005; Mosam and others 2012). Taken together, these factors mean that prevention of KS is paramount, calling for new therapies.

Lymphoma

The pathogenesis of AIDS-related lymphomas is often attributable to tumor-causing viruses, including Epstein-Barr virus, HHV-8, and hepatitis C virus. Although the incidence of such NHLs has significantly decreased since the widespread implementation of ART, incidence among

people with HIV remains approximately 10 times greater than in the general population (Robbins and others 2014; van Leeuwen and others 2009). Patients with more severe immunodeficiency, as measured by CD4 T-cell count, are at an even greater risk (Guiguet and others 2009).

The incidence of Hodgkin lymphoma is significantly increased among people with HIV, and its incidence has not declined in parallel with the falling incidence of NHL. Data suggest, however, that prolonged ART use does reduce the risk of Hodgkin's lymphoma (Kowalkowski and others 2014).

People with HIV who also have lymphoma are more likely to present with symptomatic extranodal and central nervous system involvement (Carbone and Ghoghini 2005). Independent of these factors, cancer-specific mortality among these patients is higher compared with patients without HIV (Coghill and others 2015).

Hepatocellular Carcinoma

HCC is the seventh most common cause of all cancers globally and the third leading cause of cancer-related death; nearly 85 percent of cases of HCC and of death secondary to HCC occur in LMICs (Ferlay and others 2013). Although the pathogenesis is not entirely clear, most cases of HCC worldwide are secondary to hepatitis B, a double-stranded DNA virus that can be transmitted sexually and can lead to chronic infection. A significant proportion of the remaining burden is secondary to hepatitis C (Arzumanyan, Reis, and Feitelson 2013; McGlynn, Petrick, and London 2015).

HIV routes of transmission are similar to those of hepatitis B virus and hepatitis C virus, so co-infection is high. In a cohort study of more than 3,000 patients, approximately one-third of people with HIV were co-infected with hepatitis C virus (Fultz and others 2003). The prevalence of hepatitis C virus infection tends to be higher, and the aggressiveness of hepatitis C virus disease is greater, among people with HIV (Puoti and others 2004). A separate analysis documented that nearly 10 percent of HIV patients were chronic carriers of hepatitis B virus. Accordingly, cancer prevention efforts need to target the treatment of hepatitis B and hepatitis C before the development of HCC.

Persons with HIV and chronic viral hepatitis do not progress more rapidly to HCC than do HIV negative persons, in marked contrast to other viral-associated malignancies. However, the use of antiviral medications in the treatment of HIV or associated diseases, including interferon and nucleoside or nucleotide analogs, markedly reduces the risk of developing HCC in both HIV positive and HIV negative persons (Sung and others 2008). Although current treatment options for hepatitis C virus are effective, the high cost of treatment is

limiting widespread global implementation (Jacobson and others 2011; Poordad and others 2011). Chapter 16 of this volume (Wiktor 2017) provides additional information on viral hepatitis.

Anal Cancer

Anal cancer, like other urogenital cancers, is caused primarily by HPV infection. Anal cancer is nearly 30 times more common among people with HIV (Grulich and others 2007). Despite long-term use of ART, however, the incidence of anal cancer among people with HIV has not declined (Piketty and others 2012). One large cohort study in the United States revealed that rates of anal cancer had increased fivefold over those before 1996, that is, before ART became potent (Crum-Cianflone and others 2010).

Although anal-cancer-specific mortality among patients with HIV does not appear elevated (Coghill and others 2015), prevention strategies to reduce morbidity, including anal cytology and high resolution anoscopy, merit further consideration (Chiao and others 2006) and are being evaluated.

Lung Cancer

HIV infection is associated with approximately a three-fold increased risk of lung cancer, which is the most common NADC and third most common cancer overall (Engels and others 2006; Kirk and others 2007; Robbins and others 2015). Although the higher incidence of lung cancer among HIV patients appears to be in part independent of tobacco use, the prevalence of tobacco use is several-fold higher among patients with HIV in the United States compared with the general population (Mdodo and others 2015). Smoking is associated with lung-cancer-specific mortality, which has increased in the era of ART (Kirk and others 2007). Mortality from lung cancer has not been associated with either immunosuppression or HIV viral load (Clifford and others 2012).

Strategies for Prevention of HIV-Associated Malignancies

Vaccines

Vaccines against HPV and hepatitis B virus offer outstanding opportunities to reduce the burden of cancer in people with HIV. The most current HPV vaccine targets nine HPV types and is capable of eliminating more than 90 percent of cervical cancer cases. The effect of the vaccine on other HPV-related cancers and the efficacy among people with HIV are yet to be determined.

The World Health Organization (WHO) recommends universal vaccination of girls ages 9–13 years.

Uptake has been limited globally by gaps in funding and, in the United States, by sensitivities around vaccines for sexually transmitted diseases. Furthermore, this age group is not covered by the routine Expanded Program on Immunization, and alternative delivery strategies such as school-based vaccination need to be further explored (Watson-Jones and others 2015). Although HPV vaccines are approved for three doses administered over a six-month period, a two-dose HPV vaccine schedule in HIV-negative populations has been shown to be non-inferior (Dobson and others 2013; Kreimer and others 2015).

The use of the HPV vaccine among people with existing HIV infection has been the subject of several studies; preliminary data show good rates of seroconversion and lower peak antibody levels, but efficacy data are pending (Money and others 2016). A highly effective vaccine against hepatitis B has been seen to reduce the incidence of HCC in hepatitis B–endemic regions (Chang and others 1997; Chang and others 2009; Hsu and others 1988).

The WHO recommends universal vaccination against hepatitis B with the primary infant vaccination series; this vaccine is now included in national infant immunization programs in more than 90 percent of countries (Kane 1995, 2012).

Although vaccination against hepatitis B virus in susceptible people with HIV is part of national and international guidelines (CDC 2006; WHO 2013a), the hepatitis B virus vaccine has reduced immunogenicity in people with HIV (Landrum and others 2009). Programs for catch-up vaccinations among groups at high risk of HIV infection are also absent in low-resource settings.

Screening

Women in the general population in the United States, ages 21–65 years, are recommended to have cervical cancer screening with cytology every three years (Moyer 2012); the recommendation for women with HIV, in contrast, is screening twice in the first year after initial diagnosis and then annually for the rest of their lives (Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents 2016). The WHO, however, recommends that if a woman with HIV has an initial negative screening test (that is, normal cytology, negative visual inspection with acetic acid, or negative cervical HPV screening test), then she should undergo subsequent screening within three years (WHO 2013b).

Such screening recommendations, independent of the screening modality, may not be feasible in low-income countries (LICs) with stressed health care systems. Additionally, the economic costs and the human resources required for standard cervical screening through either cytology or HPV testing are limited in LICs. Low-cost screening techniques (for example, visual inspection with

acetic acid) are being widely adopted, although the accuracy of these tests in high-risk populations needs to be more completely defined (Campos and others 2015; Chung and others 2013; Moses and others 2015). Novel approaches, including self-swabbing testing for oncogenic HPV, are being evaluated for use in LMICs. High-risk lesions detected during screening can be locally ablated to prevent the development of invasive cervical cancer (WHO 2013b).

Few other HIV-associated cancers have been shown to be preventable with screening efforts. Because of the biological similarities between cervical and anal cancer, screening for preinvasive anal cancer has been evaluated. When performed by highly trained and experienced clinicians and laboratories, screening techniques such as high-resolution anoscopy can detect high-grade dysplasia (Dalla Pria and others 2014). However, evidence is still lacking from prospective randomized trials that ablation of these high-grade lesions reduces the risk of invasive anal cancer.

Screening for lung cancer with computed tomography has been evaluated among patients with HIV and may be effective. However, the incidence of the disease is low, and strategies for targeting screening efforts are needed (Hulbert and others 2014).

Chemoprevention of Cancer

Increasing evidence suggests that the risk of cancer in people with HIV can be reduced through the use of ART. In a randomized trial of early or delayed initiation of ART in people recently diagnosed with HIV, the risk of cancer overall was reduced by nearly two-thirds among people who initiated therapy at a CD4 T-cell count of more than 500 cells/mm³, compared with those who initiated at CD4 T-cell of less than 350 cells/mm³ (Klingman and others 2015). The findings included a 50 percent reduction in NADCs, a 91 percent reduction in KS, and a 70 percent reduction in lymphoma. The use of ART is also active in preventing the acquisition of some viral oncogens, such as hepatitis B, which in turn reduces the risk of cancer (Heuft and others 2014).

Finally, treatment with antiviral therapy of chronic infections that cause cancer, such as hepatitis B or hepatitis C, has been shown to reduce the risk of HCC (Shen and others 2012), although the efficacy of this strategy in people with HIV has not been further evaluated.

Other Approaches to Prevention of HIV-Associated Malignancies

Behavioral interventions to reduce smoking among people with HIV have been moderately effective and may reduce a broad spectrum of HIV comorbidities (Keith and others 2016).

HIV and Cancer Conclusions

Cancer is an increasingly common complication and is a leading cause of death in people with HIV. Strategies for cancer prevention—including vaccination, screening, and early ART initiation—can reduce the cancer burden, but additional strategies for reducing the burden of HIVAMs are needed.

IMPACT OF HIV AND OTHER SEXUALLY TRANSMITTED INFECTIONS ON FEMALE REPRODUCTIVE HEALTH

The ongoing burden of HIV in women is substantial, with 1,000 new infections per day (UNAIDS 2014). This concentration of the HIV epidemic has therefore had substantial impact on women's reproductive health, and intersects with the ongoing and long-standing burden of other sexually transmitted infections (STIs) in women.

Impact of HIV Infection on Family Planning Methods and Conception

Family Planning

Girls and women at risk of HIV or who are already infected are particularly vulnerable to the global problems of access to adequate reproductive choice and contraceptive options (WHO 2006). HIV often magnifies the lack of personal control over reproductive decisions. Beyond the importance of reproductive health for women themselves, transmission of HIV from mother to infant at a population level can most effectively be prevented by providing improved protection from HIV to women of reproductive age and preventing unplanned and unwanted pregnancies (WHO 2006).

Among contraceptive methods, barrier methods such as male condoms, female condoms, and cervical caps are suboptimal in preventing pregnancy, but they do protect against HIV acquisition and transmission (Weller and Davis 2002). Dual methods of protection and contraception, such as condoms and oral contraceptives, are not acceptable to many couples, resulting in inferior methods of contraception being used in partnerships in which one partner is HIV positive and the other partner is HIV negative (serodiscordant couples) (Heffron and others 2010; Nieves and others 2015).

Concerns about the potential interactions between antiretroviral drugs and the estrogen component in combination oral contraceptives notwithstanding (Robinson, Jamshidi, and Burke 2012; Thurman, Anderson, and Doncel 2014), recent data suggest that contraception efficacy for women with HIV is not inferior to that for other women (Pyra and others 2015).

Long-acting, injectable progestin or progestin-based implants offer effective contraception. However, concerns have arisen about declining bone mineral density with long-term progesterone use in women with HIV, who are already more susceptible to bone loss (Lopez and others 2014).

Furthermore, a prospective trial of preexposure prophylaxis (PrEP) with ART for serodiscordant couples found that women using injectable hormonal contraception were more likely than other women to acquire or transmit HIV infection (Heffron and others 2012). Formal studies of this association are underway.

Other relevant factors include the regional differences in cost, acceptability, and access to contraception. More recently, data suggest that intrauterine devices are safe in women with HIV and are highly effective, yet affordability limits their uptake (Wanyenze and others 2013).

Infertility

HIV affects fertility in women in a variety of ways. Women with HIV may wish to prevent transmission by avoiding sexual contact with partners; additionally, the biology of HIV itself may have an impact on fertility. Some studies have found higher infertility in women with HIV (Yaro and others 2001), although most such studies involved cohorts with inadequately managed HIV disease; no data support the notion that infertility is higher among women with HIV and who are in good health on ART.

For women with HIV whose partners do not have HIV, timed self-insemination with partner sperm is a simple and effective way to prevent risk of transmission to the male partner. However, many serodiscordant couples will choose to have unprotected sex if the female partner is on adequate suppressive ART (Loutfy and others 2012). Suppressive ART has been shown to eliminate the risk of HIV transmission between serodiscordant couples, at least in one study (Rodger and others 2016).

For women without HIV whose male partners have HIV, prevention of acquisition from the male partner ideally includes ensuring that the male partner is on fully suppressive ART. However, with individuals not engaged in care or in regions where access to ART is limited, alternative approaches are important (Loutfy and others 2012). One option is for the woman to use PrEP. Among women given oral tenofovir and emtricitabine PrEP who became pregnant, the PrEP was discontinued when the pregnancy became known. Of note, in this study, pregnancy outcomes and infant growth did not differ in women taking PrEP compared with those taking a placebo (Mugo and others 2014).

Overall, most HIV serodiscordant couples cannot afford the expensive assisted reproductive treatments for

reduction of HIV transmission. In vitro fertilization and intracytoplasmic sperm injection have been used to decrease male-to-female HIV transmission; more recently, sperm washing and intrauterine insemination provides a less complex, less costly alternative and appears to be safe, with no reported cases of HIV transmission (Barnes and others 2014; Ohl and others 2005).

Although no data suggest that couples in which both partners have HIV have higher rates of infertility than other couples, they may face infertility treatment issues if they coincidentally have other fertility issues. In addition to issues of access and affordability, women with HIV may also face discrimination in infertility treatment. A cross-sectional study in the United States found that public attitudes toward people with HIV who seek infertility treatment are typically negative; only 38 percent of respondents favor offering it (Mok-Lin and others 2011). However, health care providers have generally been supportive of women with HIV who want children; in a facility in Ghana, 94.3 percent of health care workers providing care to women with HIV were supportive of their rights to reproduction (Laar 2013).

Regarding pregnancy outcomes after infertility treatment, a case-control study of women who received in vitro fertilization treatment showed that well-controlled HIV had no impact on fertility outcomes for women with HIV compared with those without HIV (Nurudeen and others 2013). Beyond fertility, greater risks of stillbirth, premature birth, and low birth weight have been observed in pregnancies of women with HIV (Turner and others 2013).

HIV prevention strategies aimed at men have included voluntary male circumcision, most widely offered in high-endemic areas in Sub-Saharan Africa. A review of published literature in this area suggests that opportunities for more extensive engagement of adolescents in sexual and reproductive health care have been missed (Kaufman and others 2016).

Other Sexually Transmitted Infections

Human Papillomavirus

HPV infection is associated with the great majority of squamous cell cancers of the cervix, vulva, vagina, penis, anus, and oropharynx. Women with HIV are at greater risk of contracting a persistent HPV infection and are often infected by a broader range of HPV genotypes (Salters and others 2016).

Infection with HPV may also serve as a marker of increased risk for HIV infection because both infections may be sexually transmitted. Massad and others (2004) found that women with HIV were four times as likely to have vulvar intraepithelial neoplasia and almost five

times more likely to have genital warts. This risk can be reduced in individuals with suppressed HIV (Blitz and others 2013).

Among women undergoing in vitro fertilization, detection of HPV in the cervix was associated with substantial reduction in pregnancy (Depuydt and others 2016). Detection of HPV in semen was associated with substantially lower rates of pregnancy after intrauterine insemination, and also associated with more miscarriages (Garolla and others 2016).

Herpes Simplex Virus

Global distribution, incidence, and prevalence of infection with HSV—HSV-1 and HSV-2—vary widely by country, region, and population subgroup. Women are more susceptible than men to HSV-2 infection. Primary HSV infection contracted in the third trimester of pregnancy may result in neurocognitive problems in the fetus, developmental delays, or death if the infant becomes infected (Watts and others 2003). For women with recurrent HSV or primary HSV infection occurring before 34 weeks gestation, prevention of transmission to the infant can be achieved with acyclovir or valacyclovir suppression therapy during pregnancy (Workowski and Bolan 2015).

In the United States, the prevalence of HSV-2 among adult men and women with HIV is three times higher than in the general population (Patel and others 2012). HSV-2 may also accelerate HIV disease progression in co-infected individuals. However, in a randomized clinical trial involving couples in which the HIV-1–infected partner was co-infected with HSV-2, acyclovir did not reduce the risk of HIV-1 transmission, despite a reduction in plasma HIV-1 RNA and a 73 percent reduction in the occurrence of genital ulcers due to the HSV-2 virus (Celum and others 2010).

Pelvic Inflammatory Disease

Pelvic inflammatory disease is classically associated with the ascension of microorganisms, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, from the lower genital tract to the upper genital tract and of bacterial vaginosis-associated organisms from the vagina or cervix into the endometrium and fallopian tubes (Cohen and others 1998). Long-term consequences of pelvic inflammatory disease can include ectopic pregnancy, chronic pelvic pain, tubal infertility, adnexal tenderness, tubo-ovarian abscesses, fallopian tube dysfunction, difficult or painful sexual intercourse (dyspareunia), pelvic adhesions, and recurrent pelvic inflammatory disease.

Among women with pelvic inflammatory disease, those with HIV present with tubo-ovarian abscess

more often than women without HIV. Among Kenyan women with lower abdominal pain and suspected pelvic inflammatory disease, histologically confirmed endometritis was three times more common in those with HIV than among those without (Cohen and others 1998). Nevertheless, treatment of pelvic inflammatory disease has been found to be equally successful in all women, regardless of HIV status (Bukusi and others 1999).

Bacterial Vaginosis

A meta-analysis of 23 studies found a significantly increased risk of HIV incidence among women with bacterial vaginosis (relative risk 1.6, 95 percent confidence interval 1.2, 2.1) (Atashili and others 2008). In a case-control analysis of 5,110 women in South Africa, bacterial vaginosis at baseline enrollment was associated with double the risk of acquiring HIV infection during 36 months' follow-up, after adjusting for demographic characteristics, other STIs, and sexual behavior (Myer and others 2005). Bacterial vaginosis is also associated with higher risk of transmission of HIV to a male partner (Cohen and others 2012).

In addition, bacterial vaginosis has been associated with increased risk of acquiring other STIs, with developing pelvic inflammatory disease, with several adverse outcomes of pregnancy (for example, fetal loss, spontaneous abortion, stillbirth, preterm delivery, low birth weight, and disease in the offspring), and with infertility. A large and growing number of possible mechanisms by which any vaginal dysbiosis may contribute to these complications have been identified (Brotman 2011; Hillier and others 1995).

Sexually Transmitted Intestinal and Enteric Infections

A study early in the HIV epidemic identified diverse pathogens, often of a polymicrobial nature, associated with proctitis, proctocolitis, and enteritis (Quinn and others 1983). Sexually associated proctitis, proctocolitis, or enteritis, which occur more commonly in MSM, but also in heterosexual women and men through unprotected anal intercourse, may increase susceptibility to HIV (Fleming and Wasserheit 1999). Such infections are occurring with greater frequency (Cone and Whitlow 2013).

HIV and Women's Reproductive Health Conclusions

HIV and other STIs have been associated with major direct and indirect harm to the reproductive health of women in many settings and populations.

IMPACT OF NONCOMMUNICABLE CHRONIC COMORBIDITIES IN PEOPLE WITH HIV

Expanded access to ART and accompanying increases in longevity of people with HIV have led to an increase in NCCs, including cardiovascular disease (CVD), diabetes and other metabolic conditions, renal disease, liver disease, cancers, and mental illness. Data demonstrating the importance of these conditions among people with HIV are often predominantly from HICs. Unfortunately, much less of the data and research advances for these conditions are from LMICs, where most people with HIV live (Narayan and others 2014). In many regions, such as Sub-Saharan Africa, HIV care, including with ART, is more widely available, but is not accompanied by care for NCCs, resulting in preventable morbidity and death (Narayan and others 2014).

Cardiovascular Disease

Burden and Epidemiology of CVD in People with HIV

CVD is one of the most important causes of NCC among people with HIV for several reasons. First, CVD, specifically ischemic heart disease, was the number one cause of death, years of life lost, and disability-adjusted life years in 2010 in the United States, and the number one cause of disability-adjusted life years globally (Murray and Lopez 2013). CVD and its risk factors are increasing in many LMICs as an emerging epidemic, even among those without HIV (Mensah 2008).

Second, rates of CVD, particularly myocardial infarction, are much higher among people with HIV than among those without, most likely due in part to chronic inflammation and immune activation (Freiberg and others 2013; Silverberg and others 2014; Triant 2014). The clinical classification of myocardial infarction was divided into five types in 2007 as part of the universal myocardial infarction definition (Thygesen and others 2007); type 1 and type 2 constitute almost the entirety. Type 1 or primary myocardial infarction events result spontaneously from atherosclerotic plaque instability. Type 2 myocardial infarction events are secondary events due to other illnesses or causes resulting in myocardial ischemia from increased oxygen demand or decreased supply, as can occur in the setting of hypotension or hypoxia. Little is known about myocardial infarction types in people with HIV in either HICs or LMICs. However, in the United States, type 2 myocardial infarction events make up close to half of all myocardial infarction events among people with HIV, a much higher proportion than in the general population. Understanding myocardial infarction types among people with HIV may help clarify unanswered questions regarding risk

factors and higher prevalence among people with HIV (Crane and others 2014).

Third, the effect of CVD among people with HIV may be even more profound in LMICs than in HICs, given that most people with HIV live in LMICs and may have additional CVD risk factors unique to these areas (Bloomfield and others 2014). In a comparison of NCCs among two cohort studies of people with HIV on ART, one from Botswana and one from Tennessee, event rates were higher in Botswana in comparisons standardized to the U.S. population; the largest discrepancies were for CVD disease (Wester and others 2011). As a result, the major public health impact of CVD among people with HIV has been increasingly recognized in HICs and LMICs (Bloomfield and others 2014; Currier and others 2003).

Factors Associated with CVD among People with HIV

Causes of CVD among people with HIV are multifactorial and include long-term HIV exposure, consequences of ongoing inflammation, progressive immune dysfunction, and possible adverse effects associated with ART (Aberg 2009). These factors are compounded by the aging of the population of people with HIV in many regions and by higher rates of traditional CVD risk factors such as smoking, diabetes, and dyslipidemia (Silverberg and others 2014; Triant 2014).

While modifying traditional CVD risk factors may be important in preventing CVD, these factors have not been shown to explain the entire CVD risk increase among people with HIV, highlighting the importance of novel and HIV-specific factors influencing CVD risk (Triant 2014). HIV may also accelerate CVD through chronic inflammation. The increase in myocardial infarction risk in people with HIV is similar to that in inflammatory diseases like rheumatoid arthritis (Solomon and others 2003). Inflammatory and coagulation markers have been shown to predict CVD (Ford and others 2010; Triant, Meigs, and Grinspoon 2009), but the most appropriate intervention targets remain unclear.

Impact of ART on CVD Risk

ART has greatly reduced morbidity and mortality (Palella and others 1998); paradoxically, however, ART may theoretically increase CVD risk (Friis-Moller and others 2007) because of altered metabolism or atherogenic effects (Behrens and others 1999; Holmberg, Moorman, and Greenberg 2004; Holmberg and others 2002). CVD risk may be higher with longer ART or protease inhibitor duration (Currier and others 2003; DAD Study Investigators 2004; Friis-Moller and others 2007; Holmberg and others 2002), or with recent abacavir or

didanosine use (Sabin and others 2008), although both are controversial (Cutrell and others 2008).

The Strategies for Management of Antiretroviral Therapy (SMART) study found a trend toward increased CVD with delayed ART or ART interruptions (El-Sadr and others 2006), suggesting that despite potential metabolic impacts of ART, the overall effect is protective. This finding is several years old; in most regions, current regimens now have even lower negative metabolic impacts.

Several studies have found that low recent and nadir CD4 T-cell counts are associated with CVD (Drozd and others 2014; Lang and others 2012; Silverberg and others 2014). Elevated or detectable HIV RNA levels (viremia) have also been associated with CVD (Drozd and others 2014; Freiberg and others 2013; Lang and others 2012; Silverberg and others 2014). These studies, as well as findings from the SMART trial, support the hypothesis that CVD risk is reduced by control of HIV itself, and they provide additional support for recommendations for earlier ART initiation (Silverberg and others 2014; Triant 2014). However, overall risk and relative contributions of specific risk factors require more study in HICs and LMICs, including assessment of the effects of interventions that address these risk factors.

Other CVD Outcomes

Although much of the CVD and HIV literature has focused on myocardial infarction, this is not the only CVD outcome of relevance to people with HIV. In the United States, people with HIV have 1.8 times the risk of heart failure (Butt and others 2011); a meta-analysis suggested a prevalence of 8 percent for systolic dysfunction and 43 percent for diastolic dysfunction (Cerrato and others 2013).

Data on cardiac dysfunction are more limited in other parts of the world; several studies present such data, but they precede the widespread availability of ART. In Zimbabwe, 50 percent of people with HIV had cardiac dysfunction, including 22 percent with left-ventricular dysfunction, 6 percent with isolated right-ventricular dilation, and 9 percent with dilated cardiomyopathy (Hakim, Matenga, and Siziya 1996). A Rwanda study showed dilated cardiomyopathy in 18 percent of people with HIV who were not receiving ART (Twagirimukiza and others 2007).

More recently, in South Africa, cardiomyopathy was the most common cardiac disease manifestation (38 percent) among people with HIV with newly diagnosed heart disease (Sliwa and others 2012). These findings suggest that heart failure and cardiomyopathy are important complications among people with HIV. However, the data are insufficient to address whether these outcomes are more common among people with HIV in LMICs than in

HICs (Bloomfield and others 2014), how accurate these estimates might be in the current treatment era, and how these outcomes may have improved in LMICs with more widely available ART or in HICs with earlier initiation of ART.

Factors associated with CVD outcomes, such as heart failure, among people with HIV also include traditional risk factors such as smoking, prior myocardial infarction, hypertension, and higher age (Cerrato and others 2013). Other factors possibly associated with cardiomyopathy among patients in Sub-Saharan Africa not receiving ART include nutritional factors, low CD4 T-cell counts, higher viral load, and advanced HIV stage (Nzuobontane, Blackett, and Kuaban 2002; Twagirumukiza and others 2007).

Type 2 Diabetes Mellitus

Burden and Epidemiology of Diabetes Mellitus in People with HIV

In North America and Europe, people with HIV more often have glucose abnormalities and type 2 diabetes mellitus than do people without HIV (Brown and others 2005; Guaraldi and others 2011). In analyses adjusted for age and body mass index, men with HIV who were not receiving ART had 2.2 times the prevalence of diabetes mellitus than men without HIV (Brown and others 2005). The prevalence was more than four times higher among men with HIV who were receiving ART than among uninfected men (Brown and others 2005). Estimated prevalence rates among people with HIV have varied based on the patient population, from 3 percent to 21 percent (Hadigan and others 2001; Salehian and others 2005; Visnegarwala and others 2005). Diabetes mellitus prevalence and impaired glucose tolerance rates are higher among those older than age 60 years (Guaraldi and others 2011), ranging from 21 percent to 66 percent (Arama and others 2013; Araujo and others 2014; Hadigan and others 2001).

More is known about rates of diabetes mellitus and impaired glucose tolerance in HICs than in LICs. The estimated prevalence of diabetes mellitus among people with HIV is higher in HICs than in LMICs; however, the estimated absolute number of people with HIV with diabetes mellitus is greater in LMICs (Ali and others 2014). A study of countries in South America estimated diabetes mellitus prevalence rates to be from 0.8 percent in Columbia to 6.5 percent in Brazil (Cahn and others 2010).

Although the data on people with HIV in Asia are particularly limited, a study in Thailand found that among 580 people with HIV, 4.7 percent had hyperglycemia; this rate was higher among ART-experienced

than among ART-naive individuals (Jantarapakde and others 2014).

In Uganda, people with HIV had slightly higher mean glucose levels over time, as evidenced by elevations in HbA1c measurements, compared with those without HIV (Dillon and others 2013).

The incidence of diabetes mellitus in people with HIV was higher in the earlier years of the ART era than in recent years (Capeau and others 2012). The decline in diabetes mellitus incidence during the ART era is likely because ART medications, such as didanosine, were more often used earlier and had greater negative metabolic impacts. These more toxic agents are used less often today, suggesting the global incidence of diabetes mellitus among people with HIV may continue to decline. However, other factors may serve to increase the risk of diabetes mellitus in the contemporary ART era, especially the increasing burden of diabetes in countries moving from low- to middle-income status.

Factors Associated with Diabetes Mellitus among People with HIV

Factors that may predispose people with HIV to diabetes mellitus are often similar to those of the general population, including older age (Butt and others 2004; Capeau and others 2012; Hughes and others 2005), obesity (Hughes and others 2005), and racial or ethnic minority group (Butt and others 2004; Hughes and others 2005). In many parts of the world, including the United States, increasing obesity and sedentary lifestyles will contribute to increasing diabetes mellitus incidence among people with and without HIV (Samaras 2009).

Hepatitis C virus is another established risk factor for diabetes mellitus in the general population (Fallahi and others 2013). Hepatitis C virus has a higher prevalence in many populations of people with HIV; as such, it may be a more important risk factor in individuals co-infected with HIV and hepatitis C virus (Butt and others 2004; Visnegarwala and others 2005).

HIV-specific risk factors for diabetes mellitus include the use of protease inhibitors, particularly indinavir (Capeau and others 2012) or ritonavir (Brown and others 2005), and longer duration of exposure to NRTIs (Tien and others 2007), particularly didanosine and stavudine (Capeau and others 2012). However, a meta-analysis of Sub-Saharan African studies found that among people with HIV, ART use was associated with a lower HbA1c value (Dillon and others 2013). People with HIV with a lower CD4 T-cell nadir (< 300 cells/mm³) have a higher incidence of abnormal glucose metabolism than those with a higher CD4 T-cell nadir (Brown and others 2005). This finding suggests that current treatment recommendations that include starting people with

HIV on ART at higher CD4 T-cell counts may contribute to a decrease in diabetes mellitus incidence among people with HIV.

Dyslipidemia

Burden and Epidemiology of Dyslipidemia in HIV

Dyslipidemia is an important NCC, given both the high prevalence among people with HIV and impact of dyslipidemia on CVD risk (Giannarelli, Klein, and Badimon 2011). The condition is common among people with HIV who are untreated and is the most common metabolic abnormality associated with ART (Friis-Moller and others 2003).

HIV infection itself, before initiating effective ART, has been associated with changes in lipids, including reductions in total cholesterol, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL), as well as increases in triglyceride values, particularly among those with more advanced HIV disease (Riddler and others 2003).

Among people with HIV on ART, HIV-associated dyslipidemia may include decreased HDL, increased LDL, increased non-HDL cholesterol, and hypertriglyceridemia. Some of the lipid changes after ART initiation are due to a return to health with HIV treatment (Liu and others 2013). One large cross-sectional study found elevated total cholesterol levels in 27 percent of people with HIV receiving protease inhibitors and 23 percent receiving non-nucleoside reverse transcriptase inhibitors (NNRTI), compared with 8 percent of ART-naïve people with HIV (Friis-Moller and others 2003). Cohort studies have suggested that the effect of ART on lipids may be greatest in the first six months after ART initiation (Papadopoulos and others 2012).

A large cross-sectional study of people with HIV in New York City, most of whom were receiving ART, found that the prevalence of elevated LDL was 37 percent in men and 31 percent in women (Myerson and others 2014). Furthermore, 30 percent of black people with HIV, 40 percent of Hispanic people with HIV, and 37 percent of white people with HIV had elevated LDL levels (Myerson and others 2014). Women with HIV have lower HDL and higher triglyceride values compared with women without HIV (Schwartz and others 2014).

Although less is known about dyslipidemia in people with HIV in LMICs than in HICs, it remains one of the better investigated NCCs in LMICs. Cross-sectional studies from Cameroon and Tanzania of people with HIV not receiving ART found low HDL levels and elevated triglyceride levels; high triglyceride levels were particularly associated with advanced stages of immunodeficiency (Armstrong and others 2011; Nguemaim and others 2010).

South Africa has one of the highest prevalence rates of HIV, but the prevalence and effect of dyslipidemia is less clear. Black Africans often exhibit lower fasting triglyceride, total cholesterol, and LDL levels, and higher HDL levels, than white Africans (Seedat 1999); however, in 300 black individuals in South Africa newly diagnosed with HIV, HDL levels were found to be lower than levels normally associated with increased CVD risk (Fourie and others 2010). A cross-sectional study of 580 people with HIV in Thailand found that 41 percent had triglyceride levels greater than 150 milligrams per deciliter (mg/dL), 40 percent had total cholesterol values greater than 200 mg/dL, and 12 percent had LDL values greater than 160 mg/dL (Jantarapakde and others 2014). A study of 129 people with HIV from Thailand who had survived with HIV more than 10 years found that more than 50 percent had lipid abnormalities (Kiartiburanakul, Luengroongroj, and Sungkanuparph 2012).

Factors Associated with Dyslipidemia among People with HIV

Dyslipidemia among people with HIV is associated with a number of factors, such as gender, older age, race, and CD4 T-cell count (Crane and others 2011). However, ART is likely to be one of the most important factors in dyslipidemia risk among people with HIV. Dyslipidemia is associated with most protease inhibitors; among the protease inhibitors, darunavir and atazanavir have been found to have better lipid profiles than older protease inhibitors (Carey and others 2010; Mills and others 2009) (table 3.1).

The NNRTIs tend to have a smaller impact on lipid levels than the protease inhibitors, except for atazanavir and darunavir (Daar and others 2011). Etravirine and rilpivirine, in particular, are NNRTIs with less impact

Table 3.1 Antiretroviral Medications Associated with Little or Less Negative Impact on Lipid Levels

Class	Agents
Protease inhibitors	Atazanavir
	Darunavir
NNRTI	Etravirine
	Rilpivirine
Integrase inhibitors	Raltegravir
	Dolutegravir
	Elvitegravir
NRTI	Tenofovir

Note: NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors.

on lipid levels than other NNRTIs (Cohen and others 2013; Fatkenheuer and others 2012) (see table 3.1). Integrase inhibitors are increasingly important components of both follow-up or salvage regimens (Capetti and others 2014) and naive regimens (Gunthard and others 2014). Their use will likely continue to increase, particularly in regions with access to the once-daily integrase inhibitor dolutegravir and the single daily pill coformulation of dolutegravir with the NRTIs abacavir and lamivudine.

An important advantage of the integrase inhibitors is their minimal impact on lipid levels. In ART-naive people with HIV initiating a regimen with raltegravir or efavirenz, those on raltegravir had smaller increases in total cholesterol, HDL, LDL, and triglycerides with up to five years of follow-up (Gotuzzo and others 2012; Rockstroh and others 2013). The impact of dolutegravir is likely similar to raltegravir (Raffi and others 2013).

The impact of the NRTI class of agents on lipids is variable. Among the NRTIs, tenofovir has the least negative impact on lipid levels (see table 3.1). A study of treatment-naive people with HIV who initiated atazanavir/ritonavir or efavirenz with abacavir/lamivudine or tenofovir/emtricitabine found that those on abacavir/lamivudine generally had greater increases in lipid levels, including total cholesterol, LDL, and HDL levels, than those on tenofovir/emtricitabine at 48 and 96 weeks (Sax and others 2011). A United States–based cohort study found that people whose ART regimen contained tenofovir (in combination with lamivudine or emtricitabine) had lower concentrations of total cholesterol, LDL, non-HDL cholesterol, HDL, and triglyceride levels, compared with other pairs of NRTIs (Crane and others 2011). Those who received didanosine and stavudine—a combination that is no longer recommended—had the highest levels of LDL (Crane and others 2011). While stavudine leads to elevated total cholesterol and triglyceride values, it is rarely used in the United States any longer; however, it has been more widely used in LMICs (Ali and others 2014). Unfortunately, many of the newer agents with little or no impact on lipid levels are not as widely available in LMICs (Ali and others 2014).

Several studies in LMICs have examined the influence of ART in general on lipid levels; fewer studies in LMICs have focused on individual ART regimens or agents. Dyslipidemia, such as low HDL levels, was more common among patients with longer exposure to ART in several studies from South America (Albuquerque and others 2005; Cahn and others 2010). However, a Brazilian study found that low HDL was common before ART initiation; with initiation of ART, increased triglyceride levels were

much more notable, with half of the patients having elevated triglyceride levels after ART (Pinto Neto and others 2013).

In Cameroon and Ethiopia, lipid levels were higher among people with HIV on NNRTI-based ART compared with those not on therapy (Abebe and others 2014; Pefura Yone and others 2011). Similarly, Nigerian people with HIV on ART had higher total cholesterol levels and lower HDL levels than those who were ART naive (Muhammad, Sani, and Okeahialam 2013).

Among Sub-Saharan African women randomized to regimens containing nelfinavir versus lopinavir/ritonavir, larger increases in lipid levels except HDL were found over time among those on lopinavir/ritonavir (Shaffer and others 2014). Variable increases in triglyceride, LDL, and HDL values have been reported after ART initiation (Ceccato and others 2011). Among Ugandan people with HIV with CD4 T-cell < 200/mm³ or symptomatic HIV who initiated predominantly stavudine/lamivudine/nevirapine, substantial increases in HDL occurred during the initial 24 months of ART, with less frequent elevations in total cholesterol, LDL, and triglyceride values (Buchacz and others 2008). Among patients in Tanzania, one of the largest longitudinal studies found low HDL and high triglyceride levels were common before ART initiation; after ART was initiated, unfavorable changes were more common among those on stavudine and efavirenz compared with zidovudine- and nevirapine-based regimens (Liu and others 2013).

Summary of HIV and Dyslipidemia

To summarize, HIV itself is associated with changes in lipid levels, particularly elevated triglyceride levels, most notably among those with more pronounced immune deficiency. Initiating ART is also associated with dyslipidemia, but the effect is variable, depending on the regimen. Protease inhibitors as a class are associated with increased lipid levels, particularly triglycerides, but darunavir and atazanavir have less effect.

Other classes of ART are more variable. NNRTIs raise lipid levels, but etravirine and rilpivirine have less impact, as do integrase inhibitors such as raltegravir and dolutegravir. Among the NRTIs, tenofovir has little effect, while agents such as stavudine have a substantial negative impact on lipids. Data from LMICs on class- and agent-specific impacts, particularly of newer regimens, are sparse.

Recommendations for initial ART regimens have varied over time but more recently have included regimens less likely to cause dyslipidemia than those used a few years ago (Gunthard and others 2014), suggesting

that in HICs the rate of newly developed dyslipidemia may drop. However, these benefits may not apply to other regions of the world where these regimen choices are less widely available.

HIV and NCCs Conclusions

NCCs among people with HIV present an increasing global health challenge in the era of increasing access to ART, which is leading to older populations of people with HIV.

Even though this chapter briefly summarizes several NCCs, many serious NCCs are not addressed here because of space considerations. These include strokes, bone disease, cognitive impairment, renal disease, and frailty. A very important NCC is liver disease, which is an area in flux, with increasing treatment options for hepatitis C virus (chapter 16 in this volume, Wiktor 2017).

Those covered here can be considered the tip of the iceberg. As access to ART continues to expand, particularly in LMICs, access to care for NCCs will also be needed to avoid widespread preventable morbidity and death. Notably, a theme common to many NCCs is the benefit of early ART. Many NCCs are worsened by the lack of treatment or late treatment initiation, leading to increased burden of illness. Focused efforts on engagement in care, expanded access to ART, and earlier initiation of ART are likely to reduce the rates of these NCCs, particularly in areas with access to newer ART agents with less metabolic and other associated toxicities.

However, as the population of people with HIV ages, the burden of many NCCs will continue to increase. The importance of NCCs among people with HIV as a global health challenge cannot be underestimated.

Data demonstrating the importance of these conditions among people with HIV are predominantly from HICs; unfortunately, much less of the data and research advances for these conditions are from LMICs, where most people with HIV live (Narayan and others 2014).

In many areas, such as Sub-Saharan Africa, HIV care, including ART, is more widely available than it has previously been, but this care is not accompanied by care for NCCs, resulting in preventable morbidity and death (Narayan and others 2014).

CONCLUSIONS

This chapter reviews the complex association of HIV with a host of other diseases and conditions; not least is the rise in those that have occurred because people with HIV have been living longer thanks to the widespread

availability of ART. In the era of effective therapy for HIV, health professionals will need to deploy more complex strategies and treatments that recognize the rising impact of comorbidities complicating long-term HIV infection.

Cancer Prevention

Strategies for cancer prevention, including vaccination, screening, and early ART initiation, can reduce the cancer burden, but additional strategies for reducing the burden of HIVAMs are needed.

Reproductive Health

In the areas of reproductive health beyond fertility issues, evidence has also suggested a greater risk of still-birth, premature birth, or low birth weight in pregnancies of women with HIV. Providing women with access to appropriate fertility and contraception to ensure safe and planned pregnancies will be paramount in strategies to reduce these risks associated with HIV and reproduction.

Noncommunicable Chronic Comorbidities

Among NCCs, ART has changed the nature of the global health challenge. This chapter only brushes the surface of a major issue, leaving out other diseases associated with HIV. Notably, and as with cancers, a theme common to many NCCs is the benefit of early ART. Many of the diseases are worsened by lack of treatment or late treatment. Better care, expanded access, and earlier initiation of ART are likely to help lower disease rates. Because populations of people with HIV will continue to rise, however, these comorbidities cannot be underestimated as a looming public health challenge.

The burden of NCCs will be concentrated in areas of the world, such as Sub-Saharan Africa, where the number of HIV infections continue to rise and access to life-prolonging ART is expanding.

Taken together, the great success in treating HIV has been met by a set of considerable challenges for persons with the infection and for the public health community in the form of chronic noncommunicable diseases. However, improvements in the treatment of HIV infection, attention to preventive measures for chronic disease in persons at high risk for their complications, and increased research and awareness offer hope that the same successes enjoyed in the fight against HIV infection can be brought to bear to reduce the complications of long-term infection.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - (a) lower-middle-income = US\$1,046 to US\$4,125
 - (b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

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