Review of Human Immunodeficiency Virus Type 1–Related Opportunistic Infections in Sub-Saharan Africa

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Understanding the natural history of human immunodeficiency virus type 1 (HIV-1) and opportunistic infections in sub-Saharan Africa is necessary to optimize strategies for the prophylaxis and treatment of opportunistic infections and to understand the likely impact of antiretroviral therapy. We undertook a systematic review of the literature on HIV-1 infection in sub-Saharan Africa to assess data from recent cohorts and selected cross-sectional studies to delineate rates of opportunistic infections, associated CD4 cell counts, and associated mortality. We searched the MEDLINE database and the Cochrane Database of Systematic Reviews and Cochrane Clinical Trials Register for English-language literature published from 1990 through April 2002.

Tuberculosis, bacterial infections, and malaria were identified as the leading causes of HIV-related morbidity across sub-Saharan Africa. Of the few studies that reported CD4 cell counts, the range of cell counts at the time of diagnosis of opportunistic infections was wide. Policies regarding the type and timing of opportunistic infection prophylaxis may be region specific and urgently require further study.

Once infected with HIV-1, the progression to AIDS and premature death is the reality for people in most poor countries [1, 2]. Infection has spread to >20% of the population in 7 sub-Saharan countries, and several others are close behind [3]. This disease burden resulted in >2 million HIV-related deaths in 2001 and has reduced the average life expectancy in sub-Saharan Africa from an anticipated 62 years to ~47 years today [2]. On the basis of current trends, a 15-year-old Zimbabwean, born in 1997, will have a 40%–50% risk of acquiring HIV infection and early death [4]. The impact on individuals, families, and the economies of Africa is profound [5, 6].

Although behavioral prevention efforts continue, increasing attention is being given to the treatment of those already infected with HIV-1 [7]. Trimethoprim-sulfamethoxazole (TMP-SMZ) therapy, the mainstay of Pneumocystis carinii pneumonia (PCP) prophylaxis in North America, Europe, and Australia, has shown promising results, especially in the prevention of serious bacterial infections [8–10]. There is also a growing body of knowledge regarding the role of tuberculosis prophylaxis, prophylaxis against Cryptococcus species, and the use of vaccines [11]. In addition, the use of HAART in Côte d’Ivoire, Senegal, Uganda, and other low-income countries demonstrates the promise of further significant reductions in HIV-1–related morbidity and mortality [12–14].

The existing framework of clinical care and policy in the United States and Europe was developed by use of cohort studies delineating rates of opportunistic infections and the role of laboratory testing in determin-
ing susceptibility to opportunistic pathogens and in survival [10, 15–18]. In sub-Saharan Africa and most low-income settings, the relationships of these parameters are far less clear, in part because of the scarcity of cohorts with complete laboratory testing and diagnostic capabilities [19, 20].

Here, we review the existing literature on individual HIV-1–associated opportunistic infections sub-Saharan Africa, with an emphasis on recent cross-sectional studies and cohorts providing incidence rates, CD4 cell counts at the time at which opportunistic infections occurred, and survival associated with specific infections. We discuss the implications of these data for the prophylaxis of opportunistic infections and the introduction of HAART, and we discuss directions for future areas of research.

METHODS

Literature search. We searched the MEDLINE database and the Cochrane Database of Systematic Reviews and Cochrane Clinical Trials Register for English-language literature published from 1990 through April 2002. Database search terms included “Africa,” “HIV,” “AIDS,” “bacteremia,” “Candida,” “candidiasis,” “Cryptococcus neoformans,” “cryptococcosis,” “Cryptosporidium,” “cytomegalovirus,” “diabetes,” “enteritis,” “herpes zoster,” “Isospora belli,” “isosporiasis,” “malaria,” “meningitis,” “Microsporidium,” “Mycobacterium avium complex,” “Mycobacterium tuberculosis,” “Pneumocystis carinii pneumonia” (PCP), “pneumonia,” “Salmonella,” “Streptococcus pneumoniae,” “Toxoplasma gondii,” “toxoplasmosis,” and “varicella zoster virus.” We also conducted a manual search of references from publications and consulted experts in the field. Two reviewers (C.B.H. and E.L.) reviewed the lists of titles and abstracts and used the inclusion criteria to select potentially relevant articles for full review.

Inclusion criteria. To assess the incidence of opportunistic infections in HIV-1–infected adults, we included observational cohort studies of HIV-1–infected patients and placebo arms of randomized, controlled trials of preventive therapy or vaccine trials performed in sub-Saharan Africa. Studies selected were assessed for reported CD4 cell counts at or near the time of infection and for mortality. Cross-sectional studies were assessed for 1 of the following 3 study designs: consecutive or systematic selection of HIV-1–infected patients admitted to the hospital or clinic, yielding prevalence of an opportunistic infection; consecutive HIV-1–infected patients presenting to health care facilities with a symptom complex (e.g., cough and fever), yielding the prevalence of an opportunistic infection in patients presenting with that symptom complex (e.g., pneumococcal pneumonia); or autopsy studies of consecutive deaths of HIV-1–infected individuals, yielding the prevalence of an opportunistic infection.

RESULTS

For each of the opportunistic infections described in this section, prevalence rates are presented first, followed by incidence rates, CD4 cell data, and data on mortality. The countries in which studies of specific infections have been performed are also shown (figure 1).

Mycobacterial Infections

M. tuberculosis. Tuberculosis was diagnosed in 27%–34% of consecutive HIV-1–infected patients admitted to hospitals in Kenya [21] and South Africa [22], 39% of rural Tanzanians presenting with respiratory symptoms [23], and 61% of Burundian patients with AIDS [24]. Tuberculosis was diagnosed by smear or culture of a sputum sample and/or bronchoalveolar lavage or transbronchial biopsy in 23% of smear-negative Rwandan patients [25], 27% of inpatients in Burundi [26], 51% of patients in a respiratory ward in Abidjan [27], and 69% of highly selected patients in Tanzania [28]. The incidence of tuberculosis varied widely among cohorts of HIV-infected patients (table 1) [29–40].

Median CD4 cell counts from cross-sectional studies of inpatients among whom all forms of tuberculosis were diagnosed had a range of 27–191 cells/μL in 2 studies from Côte d’Ivoire [27, 41] and were similar in cohort studies (table 1) [29, 31, 34, 36, 37]. Ambulatory patients who had pulmonary tuberculosis diagnosed had median CD4 cell counts of 317 cells/μL in the Democratic Republic of Congo [42] and from 198 cells/μL (patients with extrapulmonary tuberculosis) to 257 cells/μL (patients with pulmonary tuberculosis) in Côte d’Ivoire [43]. Autopsy studies of HIV-1–infected patients from medical wards in Côte d’Ivoire [44] and Kenya [45] found tuberculosis to be the primary cause of death in 32% and 47% of deaths, respectively.

M. avium complex. In cross-sectional studies involving acutely ill HIV-1–infected patients, the prevalence of M. avium complex bacteremia was 0%–6% of inpatients in Zambia [46], Kenya [47, 48], Malawi [49], Tanzania [50], and Uganda [51, 52], and it was as high as 10% in a study of patients who met criteria for suspected tuberculosis in South Africa [53]. The mean CD4 cell count at the time of diagnosis of disseminated M. avium complex was 10–23 cells/μL in Kenyan [47] and South African studies [53].

The rate of in-hospital mortality associated with M. avium complex bacteremia was 67% (2 patients) in Kenya [47], 14% (1 patient) in South Africa [53], and was not reported in most studies. Autopsy studies from Côte d’Ivoire and Kenya did not show M. avium complex as a cause of death [44, 45].

Bacterial Infections

S. pneumoniae. The prevalence of S. pneumoniae infection found by blood and sputum cultures ranged from 25% of cases
of pneumonia in Cameroon [54] to 31% in Uganda [55]. By use of examination of transthoracic lung aspirates, thoracentesis, and bronchoscopy in selected patients, the prevalence was found to be 30% in Côte d’Ivoire [27] and 44% in Kenya [56]. Incidence rates of pneumonia and pneumococcal disease are presented in table 2 [29, 57, 58].

Of consecutive, febrile, HIV-1–infected patients with bloodstream infections, 5% had pneumococcal infection in Tanzania (during the rainy season) [50], 17% had infection in Uganda [52], and 34% had infection in Malawi (during the dry season) [49]. The prevalence of *S. pneumoniae* bacteremia among patients with bloodstream infections in Côte d’Ivoire ranged from 10% in an infectious disease ward [41] to 36% in a respiratory ward [27]; it was 26%–28% among HIV-1–infected bacteremic patients admitted to the general medicine service at a central hospital in Kenya [21, 65].

Pyogenic pneumonia was the primary cause of 8% of inpatient deaths in Côte d’Ivoire [44] and of 27% inpatient deaths in Kenya [45]. The case-fatality rate for invasive pneumococcal disease was 0% among community-based patients in a Kenyan research cohort [58], 7% in Cameroon [54], 21%–29% in Kenya [21, 65], and 43% (3 deaths) among inpatients in Côte d’Ivoire [27].

**Salmonella species.** Episodes of bacterial enteritis in HIV-1–infected patients accounted for 7% of admissions to an infectious disease ward in Côte d’Ivoire [41]. In HIV-1–infected inpatients with acute diarrhea, nontyphoidal *Salmonella* (*Salmonella enteritidis* and *S. enteritidis* serotype Typhimurium) were the most frequently recovered bacterial stool isolates in Bangui, Central African Republic [66], and Kenya [67]. Nontyphoidal *Salmonella enteritidis* was an infrequent cause of hospital admissions (<1 case per 100 person-years of observation) in 2 cohorts [29, 60].

Of febrile, HIV-1–infected patients with bloodstream infection, nontyphoidal *Salmonella* bacteremia was detected in 18%–20% in Tanzania [50], Malawi [49], and Uganda [52]. It was detected via blood culture in 7%–12% of patients admitted to hospitals in Kenya [21] and Côte d’Ivoire [27, 41]. In the studies that provided in-hospital mortality data, 7% of patients with bacterial enteritis died in Abidjan [41], whereas 17% of inpatients with nontyphoidal *Salmonella* bacteremia died in Kenya [21].
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study design</th>
<th>Location</th>
<th>Population</th>
<th>Median CD4 count, cells/μL[^c]</th>
<th>Incidence rate/100 PYO[^b]</th>
<th>HIV/TB-associated case-fatality rate, %[^d]</th>
<th>Comments/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>[29]</td>
<td>2002</td>
<td>Prospective cohort</td>
<td>Welkom, South Africa</td>
<td>Gold miners</td>
<td>1792</td>
<td>164[^c]</td>
<td>8.5</td>
<td>8.6[^d]</td>
</tr>
<tr>
<td>[30]</td>
<td>2002</td>
<td>Prospective cohort</td>
<td>Uganda</td>
<td>Rural patients</td>
<td>275</td>
<td>NA</td>
<td>2.1[^e]</td>
<td>NA</td>
</tr>
<tr>
<td>[31]</td>
<td>2001</td>
<td>RCT</td>
<td>Abidjan, Côte d'Ivoire</td>
<td>Placebo group in a TMP-SMZ prophylaxis study</td>
<td>103</td>
<td>&lt;200</td>
<td>10.9</td>
<td>NA</td>
</tr>
<tr>
<td>[32]</td>
<td>2001</td>
<td>RCT</td>
<td>Lusaka, Zambia</td>
<td>Placebo group in an INH prophylaxis study</td>
<td>350</td>
<td>≥200</td>
<td>10.1</td>
<td>NA</td>
</tr>
<tr>
<td>[33]</td>
<td>2000</td>
<td>Retrospective cohort</td>
<td>Welkom, South Africa</td>
<td>Gold miners</td>
<td>1374</td>
<td>NA</td>
<td>4.9</td>
<td>NA</td>
</tr>
<tr>
<td>[34]</td>
<td>2000</td>
<td>Prospective cohort</td>
<td>Cape Town, South Africa</td>
<td>Urban patients</td>
<td>1206</td>
<td>113/159[^g]/90[^g]</td>
<td>10.4</td>
<td>NA</td>
</tr>
<tr>
<td>[38]</td>
<td>1995</td>
<td>Prospective cohort</td>
<td>Kigali, Rwanda</td>
<td>Postpartum women</td>
<td>215</td>
<td>NA</td>
<td>2.9</td>
<td>NA</td>
</tr>
<tr>
<td>[39]</td>
<td>1995</td>
<td>Retrospective cohort</td>
<td>Kinshasa, Congo</td>
<td>Postpartum women</td>
<td>249</td>
<td>NA</td>
<td>3.1</td>
<td>26.3[^l]</td>
</tr>
<tr>
<td>[40]</td>
<td>1992</td>
<td>Prospective cohort</td>
<td>Kigali, Rwanda</td>
<td>Women of childbearing age</td>
<td>401</td>
<td>NA</td>
<td>2.4</td>
<td>NA</td>
</tr>
</tbody>
</table>

**NOTE.** NA, not available; PYO, person-years of observation; RCT, randomized, clinical trial; TB, tuberculosis; TMP-SMZ, trimethoprim-sulfamethoxazole; TST, tuberculin skin test.

[^a]: Measured at the time of study entry, unless otherwise specified.
[^b]: All forms of TB, unless otherwise noted.
[^c]: CD4 cell count stratum at the time of hospitalization for acute event.
[^d]: One year of follow-up.
[^e]: Pulmonary tuberculosis.
[^f]: Up to 7 years of follow-up.
[^g]: Extrapulmonary tuberculosis.
[^h]: Tuberculin skin test-positive patients.
[^i]: Tuberculin skin test-negative patients.
[^j]: Overall or total.
[^k]: Mean CD4 cell count in asymptomatic women.
[^l]: Two years of follow-up.
Table 2. Incidence of other opportunistic infections among HIV-infected patients.

<table>
<thead>
<tr>
<th>Type of infection, reference</th>
<th>Year</th>
<th>Study design</th>
<th>Location</th>
<th>Population</th>
<th>Specific infection</th>
<th>( n )</th>
<th>CD4 count, cells/( \mu L )^a</th>
<th>Incidence in HIV-infected/100 PYO</th>
<th>Comments/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[29] 2002 Prospective cohort</td>
<td>Welkom, South Africa</td>
<td>Gold miners</td>
<td>All cause pneumonia(^b)</td>
<td>1792</td>
<td>NA</td>
<td>6.9</td>
<td>Men only; passive follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[57] 2000 RCT Entebbe, Uganda</td>
<td>Placebo group in a pneumococcal vaccination study</td>
<td>Invasive pneumococcal disease</td>
<td>576</td>
<td>All counts &lt;200</td>
<td>1.4</td>
<td>Mostly WHO stage 2 and 3 HIV disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[58] 1996 Prospective cohort</td>
<td>Nairobi, Kenya</td>
<td>Female sex workers</td>
<td>Invasive pneumococcal disease</td>
<td>587</td>
<td>302(^c)</td>
<td>4.3</td>
<td>32% Of subjects lost to follow-up at study conclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[59] 2002 RCT Entebbe, Uganda</td>
<td>Placebo and treatment groups in a pneumococcal vaccination study</td>
<td>Cryptococcal disease</td>
<td>1372</td>
<td>All counts &lt;200</td>
<td>4.0</td>
<td>Mostly WHO stage 2 and 3 HIV disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[29] 2002 Prospective cohort</td>
<td>Welkom, South Africa</td>
<td>Gold miners</td>
<td>Cryptococcal disease</td>
<td>1792</td>
<td>28.5(^d)</td>
<td>2.2</td>
<td>Men only; passive follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[60] 1999 RCT Abidjan, Côte d’Ivoire</td>
<td>Placebo group in a TMP-SMZ prophylaxis study</td>
<td>Cryptococcal disease</td>
<td>385</td>
<td>NA</td>
<td>0.3</td>
<td>All patients had tuberculosis; 12% in placebo arm were lost to follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[29] 2002 Prospective cohort</td>
<td>Welkom, South Africa</td>
<td>Gold miners</td>
<td>PCP</td>
<td>1792</td>
<td>NA</td>
<td>0.5</td>
<td>Men only; passive follow-up; sputum stain examination used for PCP diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[61] 2001 RCT Dakar, Senegal</td>
<td>Placebo group in a TMP-SMZ prophylaxis study</td>
<td>PCP</td>
<td>49</td>
<td>NA</td>
<td>0</td>
<td>Small placebo group; mean follow-up of 8 months because of study suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[31] 2001 RCT Abidjan, Côte d’Ivoire</td>
<td>Placebo group in a TMP-SMZ prophylaxis study</td>
<td>Oral candidiasis</td>
<td>103</td>
<td>&lt;200</td>
<td>43.8</td>
<td>Mostly WHO stage 2 and 3 HIV disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[30] 2002 Prospective cohort</td>
<td>Uganda</td>
<td>Rural</td>
<td>Oral candidiasis</td>
<td>275</td>
<td>NA</td>
<td>3.8</td>
<td>Mix of prevalent and incident cases of HIV; most cases were WHO stage 1 at enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[38] 1995 Prospective cohort</td>
<td>Kigali, Rwanda</td>
<td>Postpartum women</td>
<td>Oral candidiasis</td>
<td>215</td>
<td>NA</td>
<td>5.2</td>
<td>Women were recruited at delivery and were likely at an earlier stage of HIV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Year</td>
<td>Study Design</td>
<td>Placebo and treatment groups</td>
<td>Condition</td>
<td>Vaccine</td>
<td>PYO</td>
<td>Median CD4 cell count</td>
<td>CD4 cell count strata</td>
<td>WHO stage of HIV disease</td>
</tr>
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</tr>
<tr>
<td>Entebbe, Uganda</td>
<td>2001</td>
<td>RCT</td>
<td>Placebo and treatment groups in a pneumococcal vaccination study</td>
<td>Malaria</td>
<td></td>
<td>1371</td>
<td>&lt;200</td>
<td>200–500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Rural Uganda</td>
<td>2000</td>
<td>Prospective cohort</td>
<td></td>
<td>Malaria</td>
<td></td>
<td>222</td>
<td>&lt;200¹</td>
<td>200–499</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Dakar, Senegal</td>
<td>2001</td>
<td>RCT</td>
<td>Placebo group in a TMP-SMZ prophylaxis study</td>
<td>Toxoplasmosis</td>
<td></td>
<td>49</td>
<td>NA</td>
<td>0</td>
<td>Small placebo group; mean follow-up of 8 months because of study suspension</td>
</tr>
<tr>
<td>Abidjan, Côte d’Ivoire</td>
<td>1999</td>
<td>RCT</td>
<td>Placebo group in a TMP-SMZ prophylaxis study</td>
<td>Toxoplasmosis</td>
<td></td>
<td>385</td>
<td>NA</td>
<td>1.2</td>
<td>All patients had tuberculosis; 12% in placebo arm were lost to follow-up</td>
</tr>
<tr>
<td>Abidjan, Côte d’Ivoire</td>
<td>2001</td>
<td>RCT</td>
<td>Placebo group in a TMP-SMZ prophylaxis study</td>
<td>Isosporiasis</td>
<td></td>
<td>103</td>
<td>&lt;200</td>
<td>167</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Rural Uganda</td>
<td>2001</td>
<td>Prospective cohort</td>
<td></td>
<td>Herpes zoster</td>
<td></td>
<td>250</td>
<td>NA</td>
<td>5.4</td>
<td>Mix of prevalent and incident cases of HIV; most cases were WHO stage 1 at enrollment</td>
</tr>
<tr>
<td>Kigali, Rwanda</td>
<td>1995</td>
<td>Prospective cohort</td>
<td></td>
<td>Herpes zoster</td>
<td></td>
<td>215</td>
<td>NA</td>
<td>3.7</td>
<td>Women were recruited at delivery and were likely at an earlier stage of HIV disease</td>
</tr>
</tbody>
</table>

**NOTE.** NA, not available; PCP, Pneumocystis carinii pneumonia; PYO, person-years of observation; RCT, randomized, controlled trial; TMP-SMZ, trimethoprim-sulfamethoxazole.

a Measured at the time of study entry, unless otherwise specified.
b A total of 31% of these cases were caused by Streptococcus pneumoniae.
c Mean CD4 count measured in healthy women, before or after they had acute pneumonia.
d CD4 cell stratum <6 months after diagnosis of cryptococcal disease.
e Median CD4 cell count at the time of hospitalization for an acute event.
f CD4 count stratum measured <7 months after clinical diagnosis of malaria.
**Fungal Infections**

*C. neoformans.* In studies of suspected cases of meningitis in HIV-1–infected patients, the prevalence of cryptococcal meningitis was 0% in Ghana (using only India ink staining for diagnosis) [68], 25% in Ethiopia [69], and 12%–50% in South Africa (determined by means of staining, latex agglutination testing, and culture) [70, 71]. Six percent of patients admitted to a general medicine ward in the Democratic Republic of Congo were diagnosed [72]. Incidence rates are shown in table 2 [29, 59, 60].

The median CD4 cell count in patients with *C. neoformans* and HIV coinfection was 16 cells/µL in South African [70] and Ugandan meningitis studies [59], and it was 70 cells/µL among consecutive patients in a Zimbabwean cohort [73]. Cryptococcal meningitis was the cause of 2% of deaths in a Côte d’Ivoire autopsy study [44] and 11% of deaths in an HIV-1–infected cohort in Uganda [74]. In a cohort from South Africa with a lower background mortality rate, cryptococcal meningitis accounted for 44% of deaths [29].

**PCP.** Among HIV-1–infected patients with respiratory disease, the prevalence of PCP was 1%–4% in Tanzanian studies (determined by examination of induced sputum and bronchoalveolar lavage specimens, in some cases) [23, 28], 5% in Burundi [26], and 22% in a study from Zimbabwe (in this study, nearly all patients underwent bronchoscopy) [75]. By use of bronchoalveolar lavage and/or transbronchial biopsy in patients with pulmonary disease that failed to respond to standard antibiotic therapy and with normal findings of initial tuberculosis diagnostic evaluations, studies in Rwanda [25], Malawi [76], Zambia [77], and the Democratic Republic of Congo [78] found a prevalence of 5%–11%. The prevalence was 27% in South Africa [79] and 33% in Zimbabwe; in the latter study, patients were required to have classic radiographic findings of PCP [80]. The incidence of PCP was low in cohort trials (table 2), although variable diagnostic modalities were used [29, 61].

The median CD4 cell count at the time of diagnosis of PCP was 134 cells/µL in Zimbabwe [80] and was not reported in other studies. PCP was the primary cause of death in 0%–2% of HIV-1–infected patients in autopsy series from Kenya [45] and Côte d’Ivoire [44].

**Candida species.** The prevalence of oral and esophageal candidiasis ranged from 14% in pregnant women with HIV [81] to 67% of Senegalese inpatients with AIDS [22, 24, 82, 83]. Incidence rates are presented in table 2 [30, 31, 38]. *Candida* infection was not a cause of death in these studies or in autopsy studies [44, 45].

**Parasitic Infections**

**Malaria.** Multiple cross-sectional studies performed across sub-Saharan Africa showed no association between malaria and HIV-1 infection [19, 84–86]. Two subsequent cross-sectional studies of pregnant women from Malawi found that the prevalence of malaria parasitemia on the first prenatal visit was higher among HIV-1–infected women (32% and 54%, respectively) than among HIV-1–seronegative women (19% and 42%, respectively), a trend more pronounced with multigravidity [87, 88].

The risk of clinically diagnosed malaria (parasitemia and fever) was also significantly higher in HIV-1–infected patients in a cohort of Ugandan adults [63]. In this cohort, and in the placebo arm of a Ugandan vaccine trial, rates of clinical malaria were inversely related to CD4 cell counts (table 2) [62].

**Toxoplasma gondii.** Four percent of HIV-1–infected inpatients in Côte d’Ivoire received a confirmed diagnosis of cerebral toxoplasmosis, as assessed via CT scan and/or a therapeutic response to treatment [41]. The incidence of toxoplasmosis was low in cohorts with available data (table 2) [60, 61]. The median CD4 cell count in inpatients in Côte d’Ivoire was 44 cells/µL, and 60% of these patients died during that hospital admission [41]. An autopsy study from Côte d’Ivoire found toxoplasmosis to be a likely cause of death in 10% of HIV-infected patients [44], and toxoplasmosis was noted incidentally in 3% of autopsies in Kenya [45].

**Cryptosporidium parvum, Microsporidium species, and I. belli.** The prevalence of Cryptosporidium infection among patients with chronic diarrhea varied from lows of 6%–9% in studies from the Central African Republic [66], Tanzania [89], and Zimbabwe [90] to 17% in Kenya [67], 25%–32% in Zambian studies (which examined multiple specimens, including small bowel biopsy specimens) [91, 92], and 35%–42% in rural Tanzanian studies [93, 94] and among Ugandan and Ethiopian patients with AIDS [95, 96]. Cryptosporidiosis was the primary cause of 1% of inpatient deaths in Côte d’Ivoire [44] and was not identified as a cause of death in Kenya [45].

Among patients with chronic diarrhea, *Microsporidium* infection (most commonly due to *Enterocytozoon bieneusi*) had a prevalence of 3%–5% (determined by trichrome staining or fluorescent examination of stool specimens) in Tanzania [89], Kenya [67], and the Central African Republic [66], and the prevalence was 11% (determined by water-ether sedimentation technique) in Zimbabwe [97]. In Zimbabwe, the prevalence was found to be 18% by trichrome staining, and it was found to be 51% by PCR [90]; in a Zambian study in which small bowel samples were obtained by biopsy, the prevalence was 35% [91].

The prevalence of *I. belli* infection ranged from 1% (urban patients) to 21% (rural patients) in Tanzania [89, 94]. The prevalence was 3% in the Central African Republic [66], and the prevalence was 16%–28% in a study from Zambia in which small bowel biopsy specimens were examined [91, 92]. Table 2 provides incidence data for Côte d’Ivoire [31]. The median CD4 cell count
among inpatients was 105 cells/μL in Côte d’Ivoire, and 11% of these inpatients died while hospitalized [41].

Viral Infections

**Varicella zoster virus.** Among consecutive HIV-1–infected persons, herpes zoster was clinically diagnosed in 13% of outpatients in Botswana [98] and 24% of inpatients in Zimbabwe [99]. The incidence in cohorts from Uganda and Rwanda is shown in table 2 [38, 64]. After controlling for CD4 cell count and age, herpes zoster was not a predictor of early mortality in Uganda [64].

**Cytomegalovirus.** Several cross-sectional studies performed eye exams on HIV-infected individuals to identify cytomegalovirus retinitis. No cases were found among 120 HIV-1–infected patients in The Gambia [100], 2 cases of cytomegalovirus retinitis were diagnosed among 154 patients in Burundi [24], and 1 case was diagnosed among 99 Malawian patients with AIDS [101]. Cytomegalovirus pneumonitis was a primary cause of death in 4% of Kenyan inpatients [45], and disseminated cytomegalovirus disease caused 2% of deaths among inpatients in Côte d’Ivoire [44].

**DISCUSSION**

**Burden of illness.** Data from studies performed across sub-Saharan Africa demonstrate the many infections to which HIV-1–infected individuals are susceptible in this region. Across studies, tuberculosis, bacterial infections, and malaria were the most common serious infections diagnosed in HIV-1–infected individuals. Tuberculosis not only caused a high proportion of cases of respiratory disease [23, 25–28], it contributed substantially to the overall burden of disease, as measured in autopsy studies [44, 45]. Bacterial diseases, including *S. pneumoniae* and *Salmonella* infections, also accounted for a great deal of morbidity in this population [27, 54–56]. The mortality rates for *S. pneumoniae* bacteremia in the research cohort setting [58] were much lower than the rates for hospital admissions elsewhere, which may demonstrate the advantages of early diagnosis and institution of appropriate therapy [21, 27, 54, 58, 65]. The evidence that malaria is a pathogen that differentially affects HIV-infected patients is strengthening, bolstered by several recent trials [62, 63, 87, 88]. Although autopsy studies show that malaria is not a frequent cause of death in HIV-infected patients [44, 45], any association between malaria and HIV infection could have important public health consequences as a result of their respective prevalences.

*C. neoformans* caused a high proportion of cases of meningitis among HIV-1–infected patients, and the high associated case-fatality rate reflects, in part, the absence of affordable treatment [69–71, 73]. Although PCP did not have a similar impact on mortality (as assessed by autopsy data), it was probably underdiagnosed as a result of the limited invasive testing in sub-Saharan Africa [25, 76–78] and may often be partially treated, given the frequency of use of TMP-SMZ and other antibiotics in the region. Parasites, such as *Cryptosporidium*, *Microsporidium*, and *Isospora* species, caused the majority of cases of chronic diarrhea in cross-sectional studies, and infections with these parasites have an increased incidence among HIV-infected patients.

*M. avium* complex was found infrequently in the sickest patients and was associated with high mortality rates, although studies were few and limited in size [47, 48, 53]. Toxoplasmosis was also rarely noted, but it was the cause of nearly 10% of deaths among HIV-1–infected patients in Côte d’Ivoire [44], indicating its lethality and likely underdiagnosis—the result of its insidious development and lack of diagnostic modalities. Limited studies assessed patients for cytomegalovirus infection and found very few cases [24, 100, 101]. *Candida* infection and herpes zoster were both frequently diagnosed, likely because of the high prevalence of infection and the relative ease of diagnosis.

**Limitations.** Although investigators have made a great deal of progress in understanding HIV disease in sub-Saharan Africa, data on prevalence and incidence in the literature are constrained by several major shortcomings: first, there are few studies from sub-Saharan Africa that observe HIV-infected patients from the time of seroconversion and that record data on CD4 cell counts and opportunistic infections over long periods of time. Even fewer studies perform active follow-up; most rely on passive follow-up to diagnose infections. Loss to follow-up was often substantial. Second, many opportunistic infections may be substantially underdiagnosed because of clinical and laboratory limitations. Third, many of the studies that do exist have widely varying methodologies and include small populations. Although we have attempted to highlight the features of studies that may account for the variable results, comparisons between studies and countries must be made with caution.

**Implications for prophylaxis and HAART.** Maximizing effective prophylaxis to reduce the incidence of opportunistic infections is the current medical strategy in many areas where HAART is not yet widely available [9, 11]. Given the burden of tuberculosis among HIV-1–infected Africans, the use of preventive therapy for tuberculosis has been the subject of multiple studies [102, 103]. A recent meta-analysis of tuberculosis prophylaxis trials in HIV-1–infected patients showed a reduction in tuberculosis by more than one-half only in skin test–positive patients, and there was no mortality-related benefit [103].

Trials of TMP-SMZ involving HIV-1–infected patients have found variable reductions in the incidence of severe events, such as bacterial pneumonia, *Isospora* enteritis, nontyphoidal *Salmonella* infection, and febrile parasitemia [8, 9]. Control of these high-impact infections with a simple, relatively well-tolerated regimen is attractive. However, this intervention may
be limited by the threat of resistance. Rates of TMP-SMZ resistance in nontyphoidal \textit{Salmonella} species are low in Côte d’Ivoire \cite{9, 104} but are $\geq 50\%$ among \textit{Salmonella} species in Kenya \cite{105}, Dakar \cite{106}, and Malawi \cite{107}. Rates of \textit{S. pneumoniae} resistance are similarly variable \cite{107–109}. The clinical effect of these resistance patterns remains unclear \cite{110}, and there is further concern about cross-resistance with other drugs \cite{107}. Although widely used in the United States, an initial trial of pneumococcal vaccine in sub-Saharan Africa showed an increase in the rate of morbidity that was associated with the vaccine \cite{57}.

Several preliminary studies show that HAART can improve immune function and decrease HIV RNA levels in sub-Saharan Africa \cite{12–14}. The incidence of opportunistic infections in that region will likely decrease as a result, as has been observed with the introduction of antiretroviral therapy in the United States \cite{16}. However, as efforts to implement these therapies are being developed, prophylaxis for opportunistic infections is an important concomitant step in preventing associated morbidity and mortality.

Many pressing questions remain about the risk of HIV-1–associated opportunistic infections in sub-Saharan Africa. How will widespread use of prophylactic regimens change the distribution of opportunistic infections, and what competing risks will emerge? What will be the effects of increasing antibiotic use on resistance patterns? How can initial efforts involving HAART be rapidly expanded to decrease the incidence of both opportunistic infections and mortality? Finally, what combination of vaccination, opportunistic infection prophylaxis, and HAART will be optimal? Combining observational data with ongoing intervention studies will help answer these questions.

Acknowledgment

We thank Jonathon Kaplan, M.D., for his assistance with this project and manuscript.

References