Perspectives

Changing Trends in Bacterial Infections: *Staphylococcus aureus*, Bacterial Pneumonia, *Clostridium difficile*  
John G. Bartlett, MD

Community-acquired Methicillin-resistant *Staphylococcus aureus* • Bacterial Pneumonias • *Clostridium difficile*

Recent Efforts in Biomedical Prevention of HIV  
Raphael J. Landovitz, MD

Male Circumcision • Pre-exposure Prophylaxis • Anti-HIV Microbicides • Vaccines

Review

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Charles C. Maponga, PharmD, MHPE, Qing Ma, PhD, Judianne C. Slish, PharmD, Gene D. Morse, PharmD

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Telling Stories

The Sky Is Falling  
Jacqui Scipio-Bannerman, RNC
About This Issue

This issue features 2 Perspectives articles from presentations given at recent International AIDS Society–USA Continuing Medical Education courses, a Review article, and a Telling Stories contribution.

New trends in bacterial infections that HIV practitioners should be aware of, including Staphylococcus aureus, bacterial pneumonias, and Clostridium difficile, are summarized as presented by John G. Bartlett, MD, in New York, New York, in March 2007. A second Perspectives article reviews recent developments in biomedical prevention of HIV, including microbicides and pre-exposure prophylaxis, as presented by Raphael J. Landovitz, MD, in Los Angeles, California. In their Review article Drs Charles C. Maponga, Qing Ma, Judianne C. Slish, and Gene D. Morse discuss issues in HIV pharmacotherapy in sub-Saharan African countries, including challenges in resource provision and opportunities for international collaboration. Finally, Jacqui Scipio-Bannerman, RNC, shares her experiences as a long-time HIV care provider in our Telling Stories column.

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Perspective

Changing Trends in Bacterial Infections: *Staphylococcus aureus, Bacterial Pneumonia, Clostridium difficile*

Changing bacterial diseases in the general population of which HIV practitioners should be aware include: new staphylococcal syndromes caused by community-acquired methicillin-resistant *Staphylococcus aureus* USA300 strains (eg, necrotizing skin infections, pneumonia, fasciitis); continued high rates of community-acquired pneumonia in the potent antiretroviral therapy era; increased rates and severity of *Clostridium difficile*-associated disease due to the fluoroquinolone-resistant NAP1 strain, and the new scare from extensively drug-resistant tuberculosis, primarily as a potential threat to health care in Africa. This article summarizes a presentation on important bacterial infections made by John G. Bartlett, MD, at the International AIDS Society–USA course in New York in March 2007. The original presentation is available as a Webcast at www.iasusa.org.

There are a number of recent changes in bacterial infections in the general population of which HIV practitioners should be aware. Those that are most important in HIV care include the new staphylococcal syndromes caused by community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), the continued high rates of invasive pneumococcal disease, increased rates and severity of *Clostridium difficile*-associated disease due to the fluoroquinolone-resistant NAP1 variant, and the recent outbreak of extensively multi-drug resistant (XDR) tuberculosis (TB) in Kwa Zulu Natal, South Africa (Ghandhi, Lancet, 2006).

The outbreak of XDR-TB consisted of 53 cases in which the pathogen was resistant to isoniazid/rifampin, fluoroquinolones, and at least 1 injectable agent (capreomycin, kanamycin, and amikacin). Of the 53 cases, 35 were nosocomial, 27 were previously untreated (indicating transmission of XDR-TB), each of the 44 patients tested for HIV was infected, and 52 of 53 patients died, with a median time-to-death of 16 days. It has been noted that spread of this disease threatens to undo improvements in health care for HIV that have been made in resource-limited settings. It is important to note that XDR-TB is not a health care problem in the United States, although many may remember the highly lethal outbreak of multidrug-resistant tuberculosis (MDR-TB) in HIV-infected patients in New York City a decade ago. The other pathogens to be discussed are more relevant to practice in the United States and Europe (Lawn et al, BMJ, 2006; Masjedi et al, Clin Infect Dis, 2006).

Community-acquired Methicillin-resistant *Staphylococcus aureus*

MRSA of the designated USA300 family has been found to be responsible for a number of new staphylococcal-related syndromes including necrotizing skin infections (“spider bite” abscesses), necrotizing pneumonia, necrotizing fasciitis, septic thrombophlebitis, and pelvic syndromes in pediatric patients (eg, septic arthritis of the hips and pelvic abscess). The USA300 family is unique compared with nosocomial MRSA and now accounts for greater than 50% of community-acquired infections due to *S aureus*. Features that distinguish the community-acquired MRSA (USA300 strains) are: 1) it involves a limited number of clones 2) it has the staphylococcal cassette chromosome mec (SCCmec) IV element as the mechanism of methicillin resistance 3) it is sensitive to a number of antibiotics and 4) it has the gene for production of the Panton-Valentine leukocidin (PVL) toxin.

Syndromes caused by these strains are now being found throughout the general population, but there is an increased risk of acquisition from close contact as seen in some HIV risk groups such as men who have sex with men (MSM), prison inmates, and injection drug users. MRSA-USA300 has been implicated in more than 10,000 cases of skin and soft-tissue abscesses, and there have been numerous case reports and small series of necrotizing pneumonia, necrotizing fasciitis, and pyomyositis.

A study of abscesses due to MRSA-USA300 involving a professional football team (Kazakova et al, N Engl J Med, 2005) used pulsed-field gel electrophoresis patterns to show that the implicated strain of MRSA was also found in outbreaks among other football teams, prison inmates in 5 states, fencers in Colorado, and pediatric patients in Texas, Minnesota, and North Dakota. This now appears to be an explosive epidemic throughout the United States, Europe, and other parts of the world.

As noted, the MRSA-USA300 family carries the gene for PVL toxin that ly- ses polymorphonucleocytes (PMNs) by creating pores in the cell membrane, resulting in cytokine release and cell death. A recent study provides evidence that PVL is indeed a major virulence factor in community-acquired MRSA (Labandeira-Rey et al, Science, 2007). In this study, mice given inoculation in the nares had lethal necrotizing pneumonia when challenged with PVL-positive organisms, but only mild pneumonia with PVL-negative strains. Most convincing was the demonstration of typi- cal necrotizing lung lesions and death when challenged by PVL alone.

The extent to which MRSA has spread in the community was indicat-
ed by a study of purulent drainage in skin and soft-tissue infections in a consortium of 11 emergency departments across the United States in August 2004 (Moran et al, N Engl J Med, 2006). The study included patients aged 18 years or older who had acute skin and soft-tissue infections with purulent collections. These were cultured and isolates were sent to the Centers for Disease Control and Prevention (CDC) for analysis. Of a total of 422 cases, MRSA was isolated in 60% and was the most common pathogen in 10 of 11 centers. Analysis of 218 MRSA isolates showed that 99% were USA300 strains, 98% had PVL genes, and 98% had SCCmeCIV elements for methicillin resistance. Of these 218, 74% were the USA300-0114 strain, the strain isolated from the football team and other community sources noted above. Antibiotic susceptibility testing showed 100% susceptibility to trimethoprim-sulfamethoxazole (TMP-SMX) and rifampin, 95% to clindamycin, 92% to tetracycline, 60% to fluoroquinolones, and 6% to macrolides. Treatment consisted of incision and drainage plus an antibiotic in 60% of cases, and incision and drainage alone in 19%. A beta-lactam antibiotic was used in 100 of 175 (57%) cases caused by MRSA, indicating that more than half of patients received antibiotics that would have no effect. Follow up at 15 to 21 days indicated that lesions had resolved in 96% of cases, regardless of whether the patients received an antibiotic active against MRSA, an antibiotic not active against MRSA, or no antibiotic. The implication is that incision and drainage was the essential component of treatment, and the role of antibiotics remains relatively unclear. If antibiotics are to be used, the standard recommendations of cephalexin and dicloxacillin should be avoided, in preference for agents more likely to be active against MRSA USA300 strains such as TMP-SMX, doxycycline, or clindamycin.

The other syndromes caused by MRSA-USA300 are less common but more devastating. Necrotizing pneumonia is usually found in young, previously healthy adults and children with influenza. A recent report from the CDC reviewed 10 cases with an average age of 18 years all of whom presented with critical illness. Six patients (60%) died with an average time-to-death of 5.5 days after the onset of symptoms (CDC. MMWR Morb Mortal Wkly Rep, 2007). According to the 2007 guidelines for treatment of community-acquired pneumonia from the Infectious Diseases Society of America (IDSA) and The American Thoracic Society (ATS, Mandell et al; Clin Infect Dis, 2007), the recommended treatment is vancomycin or linezolid. Clindamycin can be used if the simple disk approximation (D) test for resistance is negative.

**Bacterial Pneumonias**

A prospective study of pneumonia in 1130 HIV-infected and 167 noninfected individuals from 1988 to 1990 showed bacterial pneumonia attack rates of 5.5 per 100 person-years of observation and 0.9 per 100 person-years of observation, respectively. Rates among HIV-infected patients were 10.8 per 100 person-years at CD4+ counts below 200 cells/µL, 6.8 per 100 person-years at 200 to 500 cells/µL, and 2.3 per 100 person-years at above 500 cells/µL (Hirschtick et al, N Engl J Med, 1995). Recent data indicate that HIV-infected patients still have an approximately 10-fold increased risk for bacterial pneumonia. The HIV Epidemiology Research Study (HERS), a prospective study of 885 HIV-infected and 425 noninfected women from 1993 to 2000, showed attack rates of 8.5 per 100 person-years in patients with HIV infection compared with 0.7 per 100 person-years in noninfected patients. Rates by CD4+ count in HIV-infected patients were 17.9 per 100 person-years at below 200 cells/µL, 8.7 per 100 person-years at 200 to 500 cells/µL, and 4.9 per 100 person-years at above 500 cells/µL (Kohli et al, Clin Infect Dis, 2006). The vast majority of patients in this recent study had no bacterial etiologic diagnosis; an etiologic agent was reported in 21% of patients compared with 38% of patients in the study reported by Hirschtick and colleagues. This reflects the continuing deterioration of clinical microbiology in the evaluation of hospitalized patients with pneumonia.

Bacterial pathogens that were defined in the more recent study are shown in Table 1. Pneumococci accounted for 10% of all cases of pneumonia in HIV-infected individuals, compared with 15% in the older study. Risk for pneumonia in the HIV-infected women decreased with higher CD4+ counts (risk ratio [RR], 0.88 per 50 cell/µL increment) and use of TMP-SMX (in absence of potent antiretroviral therapy, RR, 0.86), and increased with higher plasma HIV RNA level (RR, 1.42) and smoking (RR, 2.12).

Several studies have shown that HIV infection predisposes patients to bacterial pneumonia, especially bacteremic pneumococcal pneumonia (Grau et al, Arch Intern Med, 2005; Trampuz et al, Mayo Clin Proc, 2004). This raises the issue of the use of pneumococcal vaccine in this population, especially in light of data showing the greatest

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benefit of this vaccine is to prevent bacteremia (Whitney et al, *N Eng J Med*, 2003). However, the most exciting pneumococcal vaccine development in recent years is the pediatric vaccine not only for children younger than 2 years who received the vaccine, but for adults who did not receive it. This vaccine was introduced in 2000 and subsequent analysis showed that risk of invasive pneumococcal pneumonia due to drug-resistant *Streptococcus pneumoniae* is dramatically reduced in young children and adults. Results showed a 98% reduction in rate of invasive disease due to serotypes covered in the vaccine among children (from 65.1 cases to 1.2 cases per 100,000 population). This might be expected, but there was also a 79% reduction in rate among individuals older than 65 years (from 12.3 to 2.6 per 100,000 population) in 2004, compared with 1999, before vaccine use. At the same time, the rate of cases due to nonvaccine serotypes increased slightly in children and older individuals, indicating the large reduction in rates of invasive pneumococcal infection was due to the vaccine. The implication of this observation is that young children are the vectors of most pneumococcal infections.

**Clostridium difficile**

*C difficile* is by far the most common identifiable cause of diarrhea in HIV-infected patients. In a study of bacterial infections in HIV-infected patients with diarrhea from 1992 to 2002, shown in Table 2, 44,778 patients were followed up for a mean of 2.6 years (Sanchez et al, *Clin Infect Dis*, 2005). During cumulative follow up of 115,979 person-years, diarrhea occurred in 11,320 patients, with a bacterial pathogen being found in 1091 cases (10%). The incidence of bacterial diarrhea was 7.2 per 1000 person-years and directly correlated with immunosuppression. The presence of AIDS was associated with an odds ratio (OR) for diarrhea of 10. *C difficile* accounted for 54% of causative organisms, followed by *Shigella* species (14%), *Campylobacter jejuni* (14%), *Salmonella* species (7%), *S aureus* (4%), and *Mycobacterium avium complex* (2%).

With regard to *C difficile* there are several important observations to highlight, reflecting extensive studies from 1974 to 2002 (Bartlett JG, *Ann Intern Med*, 2006):

- The major risks are advanced age, antibiotic exposure, and hospitalization
- The disease is nearly always restricted to the colon
- This is a protein-losing enteropathy that often results in large protein losses so that many or most patients present with hypoalbuminemia
- Like most enteric pathogens, *C difficile* causes a spectrum of enteric disease ranging from asymptomatic carriage of the *C difficile* toxin to its most fulminating and characteristic form: pseudo-membranous colitis (PMC)

- *C difficile* is the only anaerobic pathogen that is transmitted from person to person
- Complications include toxic megacolon, ileus, leukeroid reactions, anasarca, and sepsis syndromes.

In terms of management, the preferred diagnostic test is the tissue culture assay because it is the most sensitive and specific, but it has the disadvantage of requiring 24 to 48 hours to complete and is technically difficult. For this reason, 95% of laboratories in the United States use the enzyme immuno-assay (EIA) test, which is fast (2-4 hours) and inexpensive, and commercial reagents are readily available. The problem is that EIA has a sensitivity of only 70% to 80% (Ticehurst et al, *J Clin Microbiol*, 2006; Borek et al, *J Clin Microbiol*, 2005) so false negative tests are common. This means clinicians need to repeat the test or treat empirically if the clinical suspicion is strong despite a negative test.

Treatment consists of: 1) discontinuing the inducing agents, 2) supportive care, and usually 3) metronidazole or oral vancomycin. Metronidazole and vancomycin are each active against essentially all strains of *C difficile*, but vancomycin has the best pharmacokinetics since it is not absorbed, so colonic levels are usually higher than 100-times the highest minimum inhibitory concentration for any strain (Bolton et al, *Gut*, 1986). By contrast, metronidazole is well absorbed and reaches the colon lumen by diffusion across the colon mucosa or by “enteric leakage” in the presence of severe diarrhea. Nevertheless, metronidazole is preferred in recommendations from the CDC, IDSA, and the Society for Healthcare Epidemiology (SHEA; Bartlett, *N Eng J Med*, 2002) because metronidazole is less expensive, avoids possible vancomycin abuse, and most importantly the drugs appear comparable in clinical trials (Teasley et al, *Lancet*, 1985). Treatment is associated with 2 distinctive complications. First, some patients do not respond *owing to*advanced disease, usually ileus or toxic megacolon, reflecting the inability to gel oral antibiotics to the colon.
lumen. Recommendations are to deliver vancomycin (500 mg qid) using a long tube from above or by retention enema. Other tactics are intravenous immunoglobulin (IVIG), intravenous metronida-zole, and colectomy, but indications and efficacy with these interventions are not well established.

The second complication with treatment is relapse. Approximately 20% of patients have recurrence of symptoms within 60 days of stopping oral vancomycin or metronidazole (Bartlett, Gastroenterology. 1985; Fekety et al, Clin Infect Dis, 1997). The reflects failure to eradicate Clostridium difficile spores that then revert to vegetative forms with toxin production when treatment is stopped, or it represents infections by a new C difficile strain (Johnson et al, J Infect Dis, 1989). Relapse is treated by another course of metronidazole or vancomycin, and sometimes augmented by strategies that have minimal established efficacy such as probiotics (Saccharomyces boulardii or Lactobacillus rhamnosus), IVIG, tapering courses of oral vancomycin or pulse doses of vancomycin (125 mg orally every other day for 6 weeks). All of these tactics work some of the time and none work all of the time (Bartlett, Ann Intern Med, 2006).

The above summarizes cumulative data for C difficile and its management from 1974 to 2002. But in 2002, there was a new chapter. Jacques Pepin in Quebec, Canada, found a dramatic 10-fold increase in the incidence of this complication for persons older than 65 years for 1992 to 2000 compared with 2002 to 2003 (Pepin, CMAJ, 2004). He later showed that the attributable mortality for C difficile infection was an astonishing 17% (Pepin, CMAJ, 2005). Common findings in these patients were that fluoroquinolones were frequently implicated as inducing agents, relapse rates were high, and many failed to respond to standard therapy. Common complications included ileus, toxic megacolon, leukemoid reactions, renal failure, sepsis syndrome, the requirement for a colectomy, and death. This more serious form of the disease and its association with fluoroquinolones use was then found in several areas of the United State. The mechanism of severe disease in this strain is high quantities of toxin production, possibly due to deletion of the gene that down-regulates production of both toxin A and toxin B, the increased rate of disease and its association with fluoroquinolones use may reflect high levels of fluoroquinolones resistance in vitro, another property of NAP1 strains not seen in historic strains (McDonald et al, N Engl J Med, 2005; Warny et al, Lancet, 2005).


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Suggested Reading
Mathews WC, Caperna JC, Barber RE, et al. Incidence of and risk factors for clinically significant methicillin resistant Staphylococcus


**Perspective**

**Recent Efforts in Biomedical Prevention of HIV**

Despite major advances in HIV treatment and progress in distribution of antiretroviral therapy in the developing world, staggering rates of new HIV infections persist. Innovative approaches to prevention of transmission are needed. Recent data have confirmed previous observational studies that demonstrated a substantial reduction in acquisition risk with male circumcision and microbicide technology experienced a setback with the early termination of a large-scale vaginal microbicide trial of cellulose sulfate. Limited data from one trial of pre-exposure prophylaxis was not able to validate nor refute efficacy. This article summarizes a presentation on biomedical prevention of HIV infection made by Raphael J. Landovitz, MD, at an International AIDS Society-USA Continuing Medical Education course in Los Angeles in March 2007. The original presentation is available as a Webcast at www.iasusa.org.

Although substantial progress in distribution of antiretroviral therapy has been made in the resource-limited world, and drug development has yielded new antiretroviral agents and novel classes of compounds, new HIV infections continue to occur globally at the rate of 15,000 per day. New and innovative prevention strategies are needed. It is likely that behavioral interventions will be necessary, but not sufficiently sufficient, component of a successful prevention program both domestically and internationally.

Current data support the efficacy of a small number of therapeutics-based strategies for HIV prevention. These include antiretroviral therapy to prevent mother-to-child transmission (MTCT), male circumcision to prevent heterosexual HIV-acquisition, male condoms, sex partner reduction and selection, and use of female conception barriers to prevent MTCT (cervical caps, diaphragms).

Controversial or unproven strategies include herpesvirus type 2 (HSV-2) suppression (Nagot et al, N Engl J Med, 2007; Ouedraogo et al, AIDS, 2006; Dunne et al, 14th CROI, 2007), malaria prophylaxis and treatment (Filler et al, J Infect Dis, 2006), and treatment of curable sexually transmitted infections (STIs). Observational data suggest that suppression of HSV-2 replication reduces genital compartment shedding of HIV, although conclusions regarding definitive clinical benefit awaited controlled study results and will likely be available in 2008 and 2009. Thus far, there are conflicting data on the impact of treating curable STIs on prevention of HIV infection, including 1 positive and 4 negative trials (Grosskurth et al, Lancet, 1995; Wawer et al, Lancet, 1999; Garcia et al, Sex Transm Infect, 1998; Harrison et al, AIDS, 2000; Kamali et al, Lancet, 2003). Experts with an anthropologic overview of the epidemic point out that the differential effects seen on treatment of curable STIs and HSV-2 suppression likely stem from the evolutionary age of the epidemic in locations where studies were performed, with curable STIs maintaining a greater impact on early stages of the epidemic, and HSV-2 having a greater influence in a more well-established epidemic.

Dr Ward Cates, Jr, director of Family Health International (FHI), appropriately emphasizes that availability of oral contraceptive pills, if used to reduce unwanted pregnancy, would dramatically reduce MTCT and have a marked impact on the global HIV epidemic.

Strategies that have been shown not to be useful in HIV prevention include use of nonoxynol-9 or cellulose sulfate as vaginal microbicides and all vaccine strategies to date for which data are available. Despite the federal government requirement that abstinence-only education be part of United States government-funded prevention programs, review of scientifically rigorous data fails to support the efficacy of this strategy, and notes increased rates of condom non-use during sexual activity (Kirby, 2001; Manlove et al, 2004).

The following article focuses on recent findings or current status of the strategies of male circumcision, pre-exposure prophylaxis (PrEP), and use of anti-HIV microbicides.

**Male Circumcision**

On a worldwide basis, approximately 70% of HIV-seropositive men were infected via heterosexual insertive vaginal intercourse. A much smaller proportion acquired infection through insertive anal intercourse. The risk of acquiring HIV from an act of insertive vaginal intercourse is approximately 0.5%, whereas the risk of acquiring HIV from an act of receptive vaginal intercourse is approximately twice that, at 1%. Risk of acquisition from insertive anal intercourse has been estimated at approximately 0.65% per sex act (CDC, MMWR, 2005). Circumcision is associated with reduced risk of HIV acquisition likely because the large surface area of inner foreskin mucosal epithelium is a favorable environment for viral acquisition. The inner mucosal surface of the penile foreskin is not keratinized and is rich in Langerhans’ cells, making it particularly hospitable to viral translocation. The keratinized, stratified squamous epithelium covering the penile shaft and outer surface of the foreskin provides a protective barrier against virus acquisition; in circumcised persons, only the distal penile urethra is lined with mucosal epithelium, leaving only a small surface area particularly vulnerable.

Three trials in Africa have shown the effectiveness of circumcision in preventing HIV acquisition (Table 1). Acquisition risk reductions (from intent-to-treat analyses) were 60% in the Orange Farm trial in semiurban South Africa, 51% in a rural popula-

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such a strategy to increase sexual risk-taking behaviors. Since PrEP regimens currently consist of 1 or 2 antiretroviral drugs, there is also concern that the use of such regimens for prevention will result in increased emergence of resistance to the drug(s) when infections do occur.

With regard to the potential consequences of PrEP on behavioral disinhibition, it is worth noting that current research on postexposure prophylaxis, and preventive vaccines, both strategies in which disinhibition was considered to be a major danger, does not indicate that high-risk behavior markedly increases in such settings. Circumcision trials had more conflicting results, with 2 studies showing no increase in high-risk sex, but 1 showing a modest increase in risk behavior.

Despite the lack of evidence and ongoing concerns, there have been anecdotal reports in the United States of PrEP use in clubs, bath houses, and circuit parties, including in the form of “party packs” consisting of a methamphetamine stimulant, a phosphodiesterase inhibitor (eg, sildenafil), and antiretroviral medication (eg, efavirenz, tenofovir, or fixed dose combination [fdc] emtricitabine/tenofovir). Articles on this practice have appeared in the Los Angeles Times (December 2005), the New York Times (January 2005), and Out magazine (April 2006 and January 2007). The attention to this phenomenon has not been borne out in epidemiologic surveys in New York and San Francisco, where rates of knowledge about and reported use of PrEP were extremely low (Liu et al, IAC, 2006; Kellerman et al, JAIDS 2006).

PrEP trials to date have examined use of tenofovir alone or fdc emtricitabine/tenofovir. Ongoing trials of PrEP include a Centers for Disease Control and Prevention (CDC)-sponsored study in 400 men who have sex with men (MSM) in Atlanta, Boston, and San Francisco; a study of 1200 heterosexual men and women in Botswana; a study of 2000 injection drug users in Thailand, and a National Institutes of Health (NIH)-sponsored study of at least 1400 MSM in Peru and other South American countries.

Table 1. Results of Male Circumcision Trials in Africa

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<th>Orange Farm</th>
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<td>Population</td>
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<tr>
<td>Circumcision rate</td>
<td>20%</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Baseline HIV incidence</td>
<td>1.6%</td>
<td>1.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Age range</td>
<td>18-24 years</td>
<td>15-49 years</td>
<td>18-24 years</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>3128</td>
<td>4996</td>
<td>2784</td>
</tr>
<tr>
<td>Stopped</td>
<td>November 2006</td>
<td>December 2006</td>
<td>December 2006</td>
</tr>
<tr>
<td>Relative risk (IT)</td>
<td>0.40</td>
<td>0.49</td>
<td>0.47</td>
</tr>
<tr>
<td>Relative risk (PP)</td>
<td>0.24</td>
<td>0.45</td>
<td>0.40</td>
</tr>
</tbody>
</table>

IT indicates by intent-to-treat analysis; PP, per protocol. Table courtesy of Ward Cates, Jr, Family Health International.

Pre-exposure Prophylaxis

PrEP is a potentially promising but as yet unproven prevention strategy consisting of continuous (daily) antiretroviral medication taken by HIV-seronegative individuals beginning before potential exposure and continuing throughout periods of risk. The strategy is not intended as an alternative for condom use or other known effective preventive approaches. It has yet to be determined whether such a strategy reduces risk of HIV infection or whether antiretroviral drug use can be considered safe in uninfected individuals.

Modeling of the potential impact of PrEP on HIV transmission in resource-limited settings suggests that under the most optimistic of assumptions, a PrEP strategy could result in a 74% decline in cumulative new HIV infections after 10 years (Abbas et al, 14th CROI, 2007). However, there is considerable concern regarding the potential of care in trials of other preventive strategies. This may obscure the ability to detect additive preventive benefit attributable to new strategies layered on the background of circumcision — and achieving sufficient statistical power to determine efficacy may become prohibitively expensive.

Attention in Rakai, Uganda, and 53% in an urban population in Kisumu, Kenya (Auvert et al, PLoS Med. 2005; Bailey et al, Lancet. 2007; Gray et al, Lancet, 2007). As yet, prospective randomized data are not available on how circumcision might affect transmission of virus from infected men. Although an exciting result, an important caveat to these findings is that both cost and infrastructure limitations can be substantial impediments to implementing circumcision programs routinely in the developing world, despite their clear efficacy. Circumcision in these studies was performed by trained personnel using sterile technique in appropriately equipped facilities. The potential for complications, including surgical morbidity and mortality, infection, and need for reoperation, would likely increase under less-controlled conditions. There are many operational, religious, political, and logistic factors that may contribute to reluctance of local or national authorities to institute circumcision programs.

An often overlooked impact of such a highly effective prevention strategy is its impact on the ability to evaluate other prevention strategies. It is likely that circumcision, given the large protective effect in acquisition, will be considered part of a new standard of...
A number of PrEP trials have been stopped for a variety of reasons, including local government intervention, lack of community-perceived commitment to ongoing care of those who acquire HIV infection during study participation, and apparent lack of optimal communication between trial sponsors and community groups regarding the goals of the studies. Trials of PrEP in heterosexual men in Malawi and a trial of PrEP for commercial sex workers in Cambodia were halted owing to similar concerns. The only published efficacy data to date are from an FHI-sponsored PrEP trial of tenofovir versus a placebo in HIV-seronegative heterosexual women in Ghana, Cameroon, and Nigeria. This trial, although designed with adequate power to address both safety and efficacy endpoints, was ultimately unable to show sufficient statistical power to evaluate the efficacy of the strategy. This occurred primarily because of drastically reduced sample size after sites in Cameroon and Nigeria were closed. Additionally, there was a lower than expected HIV incidence rate in the placebo arm (Peterson et al, *PLoS Clinical Trials*, 2007).

In this study, 8 seroconversions occurred. Six were in the placebo arm and 2 were in the active tenofovir arm, a difference that did not attain statistical significance.

Although there were no marked safety concerns, including with regard to hepatitis B virus flares with treatment discontinuation, condom use increased. Concern about potential viral resistance in those who seroconvert through PrEP treatment should not be assuaged by the observation that 1 of the 2 seroconversions in the active tenofovir arm did not demonstrate any genotypic evidence of resistance.

### Anti-HIV Microbicides

Properties of an ideal anti-HIV microbicide include: virucidal activity against diverse HIV strains, cell-free and cell-associated virus, activity against other STIs, contraceptive activity, absence of effect on vaginal, cervical, or rectal epithelium and normal flora, and resistance to or enhancement of the low pH in the vaginal environment (itself an antiviral property). In addition, the ideal microbicide would be stable at tropical temperatures, nonteratogenic, and compatible with latex. And, of course, it would be inexpensive, easy to use, and accessible and acceptable to all.

Microbicides have the advantage of being receptive-partner controlled, an important feature for use in areas of the world in which individuals are not empowered to, or it is not culturally appropriate to, demand use of condoms or other means of HIV prevention. Microbical formulations that have been developed include vaginally (or rectally) applied gels, foams, and creams consisting of both HIV-specific and nonspecific compounds.

A randomized, double-blind trial of the anti-HIV microbical effect of cellulose sulfate was recently stopped owing to a trend toward harm in the active treatment group. Cellulose sulfate is a detergent with antifertility activity and in vitro activity against sexually transmitted pathogens, including HIV. The trial, conducted by the Contraceptive Research and Development Program (CONRAD), FHI, and the Institute of Tropical Medicine (ITM), had sites in Durban, South Africa (HIV seroprevalence of approximately 50%), Kampala, Uganda (approximately 32%), Cotonou, Benin (approximately 27%),

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Countries</th>
<th>Design</th>
<th>Target Population</th>
<th>Sample Size</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbomer 974 and PRO-2000 0.5% gel</td>
<td>HIV Prevention Trials Network</td>
<td>Malawi, South Africa, Tanzania, United States, Zambia, Zimbabwe</td>
<td>4-group Phase IIb/III</td>
<td>3220</td>
<td>Acid buffer, detergent</td>
</tr>
<tr>
<td>Carrageenan</td>
<td>Population Council</td>
<td>South Africa</td>
<td>2-group Phase III</td>
<td>6270</td>
<td>Detergent</td>
</tr>
<tr>
<td>PRO-2000 0.5% and 2%</td>
<td>UK Microbicides Development Program</td>
<td>Cameroon, South Africa, Tanzania, Uganda, Zambia, Swaziland</td>
<td>3-group Phase III</td>
<td>11,920</td>
<td>Detergent</td>
</tr>
<tr>
<td>C31G</td>
<td>Family Health International</td>
<td>Nigeria</td>
<td>2-group Phase III</td>
<td>2142</td>
<td>Detergent</td>
</tr>
</tbody>
</table>

*Adapted from Balzarini, *Lancet*, 2007.*
Table 3. Ongoing HIV Vaccine Trials

<table>
<thead>
<tr>
<th>Vaccine Candidate</th>
<th>Antigen (HIV clade)</th>
<th>Manufacturer</th>
<th>Start Date</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prime with cowpox vector expressing HIV-1 genes</td>
<td>Env (B, E), Gag, Pol (B)</td>
<td>Sanofi-Pasteur</td>
<td>October 2003</td>
<td>Will gp120 protein vaccine be useful in combination with a live recombinant pox vector prime?</td>
</tr>
<tr>
<td>Boost with gp120 protein</td>
<td>gp120 (B,E)</td>
<td>VaxGen</td>
<td>December 2004</td>
<td>Clinical benefit of adenovirus-based vector in patients infected after vaccination?</td>
</tr>
<tr>
<td>Replication-defective adenovirus-5 expressing HIV-1 genes</td>
<td>Gag, Pol, Nef (B)</td>
<td>Merck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prime with plasmid DNA encoding HIV-1 genes</td>
<td>Gag, Pol, Nef(B), Env (A,B,C)</td>
<td>Vical, NIH Vaccine Research Center</td>
<td>September 2005</td>
<td>Utility of prime-boost strategy with DNA and adenovirus-based vaccines containing 3-clade envelope proteins as well as structural proteins?</td>
</tr>
<tr>
<td>Boost with replication-defective adenovirus-5 expressing HIV-1 genes</td>
<td>Gag, Pol (B), Env (A,B,C)</td>
<td>GenVec, NIH Vaccine Research Center</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Letvin, National Rev Immunol, 2006.

and Bangalore (approximately 45%) and Chennai (approximately 16%), India. A total of 2733 HIV-seronegative women were screened for entry into the study; 1400 were excluded, including 1020 who were found to be HIV-seropositive and 94 who were found to be pregnant. A total of 1333 were randomized to use a 6% cellulose sulfate gel or a lubricant placebo. Condom use counseling and free condoms were provided at study visits.

An independent data monitoring committee evaluating the study in a planned interim analysis recommended stopping the study in January 2007. Thirty-five HIV seroconversions were observed, all occurring at sites in Africa. It has not been reported how many of the seroconversion events were in the active treatment group. Final results of the study are expected in late 2007 (Doncel and van Damme, 14th CROI, 2007).

Although an interim analysis of another large-scale FHI-sponsored trial of cellulose sulfate in Nigeria did not yield similar data, this study was also stopped owing to concern regarding the findings of the CONRAD, FHI, and ITM trial. Increased HIV acquisition associated with use of the spermicide nonoxynol-9 appears to have been due to vaginal inflammation caused by the product. In the case of cellulose sulfate, colposcopy, evaluation of microflora, and assessment of inflammatory cytokines in preclinical work showed no increased genital irritation after 6 to 14 days of administration, or at 6 months in a subpopulation of participants evaluated at the latter time point.

Ongoing advanced-phase trials of other microbicides are summarized in Table 2 (Balzarini, Lancet, 2007). Other HIV-specific agents such as TMC-120 (dapivirine) and tenofovir are in earlier stages of development.

**Vaccines**

Progress in HIV vaccine development has been slow, but efforts are ongoing to identify protective and therapeutic vaccine candidates. Ongoing HIV vaccine trials are shown in Table 3 (Letvin, Nat Rev Immunol, 2006). Current goals of research are to increase the magnitude and durability of vaccine-elicited immune responses by, for example, using DNA vectors or new viral vectors, and to achieve greater diversity of immune recognition through use of consensus gene sequences. Despite absence of marked progress, the strategies of achieving broadly neutralizing antibody responses and mucosal immunity are still being investigated.


Financial Disclosure: Dr Landovitz had served as a Scientific Advisor to Abbott, GlaxoSmithKline, and Pfizer. He was on the Speakers’ Bureaus of Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, and Merck. He is a former employee of Schering-Plough. He received fees for written materials from Massachusetts Medical Society-AIDS Clinical Care.

**Suggested Reading**


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HIV Pharmacotherapy Issues, Challenges, and Priorities in sub-Saharan African Countries

Charles C. Maponga, PharmD, MHPE, Qing Ma, PhD, Judianne C. Slish, PharmD, Gene D. Morse, PharmD

The use of potent antiretroviral drugs has led to successful treatment of HIV infection in most high-income countries. However, therapy remains largely unaffordable to the resource-limited world, particularly to countries in sub-Saharan Africa. The disparity and subsequent disease burden are devastating to the poorly resourced countries, hence creating a greater demand for international collaboration. This review outlines key examples of emerging HIV pharmacotherapy issues, challenges, and priorities within resource-limited settings in order to lay groundwork for potential enhancement of international research collaboration efforts. The prevalence and distribution patterns of HIV infection and sociocultural factors found in sub-Saharan African settings are discussed. Challenges include drug financing, drug distribution infrastructure, and government commitment to responding to the HIV pandemic. Priorities include prevention of HIV transmission, management of pediatric patients, availability of affordable medicines, and addressing concerns over the quality of medicines. The potential for effective international collaboration is enhanced when expertise and resources from the developed world are combined with an understanding of the unique priorities of resource-limited settings.

Introduction

Since the recognition of AIDS in the early 1980s, standards of treatment and care have evolved considerably. However, a great disparity exists between the extent of pharmacotherapy advancement in wealthy versus poor countries. In most developed countries, research has led to the discovery of therapeutic agents that reduce morbidity and mortality associated with HIV by more than 80%. In resource-limited countries AIDS continues to be the major cause of mortality. Of the estimated 40 million people living with HIV in December 2006, more than 95% were in resource-limited countries. More than 98% of deaths among adults and children from HIV or AIDS in 2006 were also from this setting.

The major challenge is translating and disseminating therapeutic advances in the developed world to the developing countries where the demand is greatest. Increased international collaboration has been called for as a method of addressing this question. However, collaboration does not simply consist of the implementation of experiences from the well-resourced settings. There are many epidemiologic, social, cultural, economic, political, and technologic differences that affect HIV and AIDS pharmacotherapy implementation in resource-limited settings. These need to be considered and addressed when designing relevant approaches to HIV and AIDS management in these countries.

The goal of this review is to provide some key examples of emerging HIV and AIDS pharmacotherapy issues, challenges, and priorities within resource-limited sub-Saharan African countries, and highlight how they contrast with those of the developed world. This review is intended to contribute to better understanding of the approaches needed in the developing countries and potentially lay the groundwork for improved international collaboration.

Issues that Impact HIV Pharmacotherapy Delivery

Prevalence and Distribution of HIV Infection

HIV infection rates are disproportionately higher in sub-Saharan African countries than in developed countries. Table 1 shows regional HIV statistics for the end of 2006 indicating an adult prevalence rate of 5.9% in sub-Saharan Africa. It has been estimated that there are 24.7 million HIV-seropositive adults and children in this region. Although the area consists of approximately 10% of the world’s population, it accounts for 60% of all people living with HIV. In the same region in 2006 an estimated 2.8 million people acquired HIV infection and 2.1 million adults and children died of AIDS.

Despite a high prevalence of HIV and AIDS in sub-Saharan Africa, national health programs in these resource-poor...
countries cannot afford the essential medicines, especially antiretroviral therapy. The net effect is that while high-income countries now focus on improving the effectiveness of already established antiretroviral regimens, resource-limited countries are still struggling to make medicines widely accessible. According to the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), at the end of June 2006, antiretroviral therapy coverage for sub-Saharan Africa was 23% of those deemed eligible for treatment by WHO/UNAIDS guidelines; the overall coverage for low- to middle-income countries was 24%.  

Faced with the overwhelming HIV and AIDS epidemic, sub-Saharan African countries with limited resources are managing the emergency using epidemiologic approaches as opposed to individualized patient therapy. Programs are more interested in regimens that can be used effectively and safely in the majority of patients than in regimens that focus on catering to individual patient differences. There is also greater focus on prevention than treatment programs.  

As a result, the WHO has responded to this need by promoting the Essential Drugs Program in these countries.  

In 2006, of the more than 4 million people who were newly infected with HIV, 8% were children, approximately 90% of whom live in sub-Saharan African countries and were infected through mother-to-child transmission.  

Despite tremendous progress in preventing mother-to-child transmission of HIV, the high incidence of disease among children raises a number of other important issues, such as the availability of suitable pediatric drug formulations, adherence issues among pediatric populations, and the effect of nutritional status on therapeutic response. Such issues can have a profound impact on therapeutic priorities in these countries, as later discussed.

### Sociocultural Factors

**Stigma.** Due to cultural factors and the culturally well-accepted stigma associated with HIV and AIDS, patients in sub-Saharan African countries tend to seek medical help only at advanced stages of disease. As a result, health care systems are forced to manage heavily ill patients. This poses an additional challenge in choosing therapeutic agents since research has suggested that heavily ill patients are more likely to suffer from adverse effects, in addition to finding it more difficult to take complicated regimens.

**Socioeconomic Status.** A good example of the role of socioeconomic status in HIV pharmacotherapy delivery is the debate over the use of protease inhibitors (PIs) in potent antiretroviral therapy for sub-Saharan African countries. In high-income countries, PIs are considered to be essential for the complete success of antiretroviral therapy, particularly in heavily ill patients with high viral loads. However, these drugs are more expensive than other antiretroviral medications, generally require more frequent dosing, and are associated with more drug interactions, making them less favorable in the sub-Saharan African countries even though they have become part of the standard of care in other countries.

### Traditional Beliefs

Sub-Saharan Africa is endowed with traditional and religious beliefs that may discourage the use of modern health facilities in these countries. Additionally, the medicines used for HIV and AIDS treatment according to certain traditional and religious beliefs may interact with antiretroviral therapy. Two commonly used South African herbal medicines from the plants *Hypoasix hemerocallidea* (African potato) and *Sunderlandia* have been shown to inhibit CYP3A4 activity by 34% to 87% and 64% to 96%, respectively, when their water and methanol extracts tested at concentrations of 100 mg/mL. This suggests a potential for clinically significant interactions with antiretroviral drugs, particularly PIs.

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**Table 1. Regional HIV and AIDS Statistics, December 2006**

<table>
<thead>
<tr>
<th>Region</th>
<th>HIV-seropositive Adults and Children</th>
<th>Adults and Children Newly Infected with HIV</th>
<th>Adult Prevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>24.7 million</td>
<td>2.8 million</td>
<td>5.9%</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>460,000</td>
<td>68,000</td>
<td>0.2%</td>
</tr>
<tr>
<td>South and Southeast Asia</td>
<td>7.8 million</td>
<td>860,000</td>
<td>0.6%</td>
</tr>
<tr>
<td>East Asia and Pacific</td>
<td>750,000</td>
<td>100,000</td>
<td>0.1%</td>
</tr>
<tr>
<td>Latin America</td>
<td>1.7 million</td>
<td>140,000</td>
<td>0.5%</td>
</tr>
<tr>
<td>Caribbean</td>
<td>250,000</td>
<td>27,000</td>
<td>1.2%</td>
</tr>
<tr>
<td>Eastern Europe and Central Asia</td>
<td>1.7 million</td>
<td>270,000</td>
<td>0.9%</td>
</tr>
<tr>
<td>Western and Central Europe</td>
<td>740,000</td>
<td>22,000</td>
<td>0.3%</td>
</tr>
<tr>
<td>North America</td>
<td>1.4 million</td>
<td>43,000</td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>39.5 million</td>
<td>4.3 million</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Adapted from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) AIDS Epidemic Update, December 2006.
This situation is further complicated when the active ingredients in these traditional medicines are unknown and when they are not used in consistent dosages. Therefore adjustment of HIV and AIDS therapeutic regimens becomes a rather complex problem.

**Ethical Issues.** Despite progress toward the provision of antiretroviral therapy, demand still outstrips availability, raising an ethical dilemma regarding for which populations the limited life-saving medications should be prioritized. A recent review of eligibility criteria used in Mexico, Senegal, Thailand, and Uganda outlines biomedical factors, adherence to treatment, prevention-driven factors, social and economic benefits, financial factors, and factors driven by ethical arguments as the criteria used. The review recommends that in order to ensure fair patient prioritization, widespread consultation with a variety of stakeholders, and not only policy-makers or physicians, is crucial.

In the case of clinical research studies that are conducted in resource-limited settings where antiretroviral therapy is not widely available, ethical issues may arise as to which patients to include in a study that may offer the only opportunity to access the life-saving therapy. This is in view of reported advantages of clinical trials in sub-Saharan African countries. At the same time, regulatory authorities may insist on guarantees for the availability of therapy, hence the literature reports of creation of funds for postclinical trial access to antiretroviral drugs.

**Lower Literacy Rates.** An important social issue of concern for HIV pharmacotherapy delivery is the low rate of literacy in many sub-Saharan African countries. For example, Malawi has a literacy rate of only 59%, Zimbabwe 88%, and Botswana, Zambia, and Swaziland have rates of 76%, 77%, and 79%, respectively. Studies have shown a correlation between literacy rates and adherence to therapy in high-income countries. It is not clear whether these findings would hold true in resource-limited countries. A recent Canadian study evaluated estimates of antiretroviral therapy adherence in sub-Saharan Africa and North America. A meta-analysis of 31 studies from North America (28 full-text articles and 3 abstracts) and 27 studies from sub-Saharan Africa (9 full-text articles and 18 abstracts) was performed. The African studies represented 12 sub-Saharan African countries. The analysis found that favorable levels of adherence, much of which was assessed via patient self-report, could be achieved in sub-Saharan African settings and that adherence remains a concern in North America. Perhaps strong potential motivating factors such as the privilege of being offered life-saving medications improve adherence in these countries, regardless of low literacy rates.

**Table 2. Pharmacy Infrastructure in 5 African Countries in 1999**

<table>
<thead>
<tr>
<th></th>
<th>Botswana</th>
<th>Malawi</th>
<th>Swaziland</th>
<th>Zambia</th>
<th>Zimbabwe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (million)</td>
<td>1.5</td>
<td>11.0</td>
<td>0.9</td>
<td>10.2</td>
<td>12.4</td>
</tr>
<tr>
<td>GNP per capita ($US)</td>
<td>6872</td>
<td>586</td>
<td>3987</td>
<td>756</td>
<td>2876</td>
</tr>
<tr>
<td>Number of pharmaceutical manufacturers/wholesalers</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Number of registered drug products</td>
<td>340</td>
<td>1500</td>
<td>No DRA</td>
<td>1200</td>
<td>1700</td>
</tr>
<tr>
<td>Number of registered pharmacists</td>
<td>160</td>
<td>60</td>
<td>33</td>
<td>100</td>
<td>530</td>
</tr>
<tr>
<td>Number of registered pharmacy outlets</td>
<td>63</td>
<td>16</td>
<td>13</td>
<td>78</td>
<td>240</td>
</tr>
</tbody>
</table>

Adapted from World Health Organization study of drug regulatory authorities, 1999. GNP indicates gross national product; DRA, drug regulatory authority.

**Challenges to Resource Provision for Supporting HIV and AIDS Pharmacotherapy**

**Drug Financing**

The Gross National Products (GNPs) per capita in most sub-Saharan African countries is low (see Table 2). Therefore, until recently, antiretroviral drugs have been beyond the economic reach of most. Owing to economic hindrances, most of these countries have used a variety of strategies to address the issue of equitable access to antiretrovirals. Such strategies include adopting the World Trade Organization’s Trade Related Intellectual Properties (TRIPS) safeguards into national legislation, actively encouraging generic competition, seeking differential pricing of drugs from international suppliers, creating high volume and demand through regional procurement, and encouraging local production through licensing and technology transfer. These countries also addressed the issue of drug financing by seeking to balance the contributions from user fees, donors, and their own governments, as well as local health insurance agencies, bearing in mind that the HIV and AIDS epidemic is a public health problem.

At the international level the situation has shifted positively. In 2003 commitments were made to set up the Global Fund to fight AIDS, Tuberculosis, and Malaria. The President of the United States, as well as many philanthropists,
promised large sums of money to combat the spread of the epidemic. In December 2003 WHO/UNAIDS published a policy document outlining a plan to bring antiretroviral treatment to 3 million people in developing countries by the end of 2005. This document was termed the “3 by 5” initiative. It outlined how the WHO/UNAIDS intended to work with governments and groups to get treatment to where it is most urgently needed. Technical assistance to upgrade health care infrastructure and training and assistance to coordinate efforts to scale up treatment were provided under this initiative.

The “3 by 5” initiative brought about a marked increase in the accessibility of antiretroviral therapy to developing countries, particularly those in sub-Saharan Africa. According to the latest WHO/UNAIDS “3 by 5” data, by the end of 2006 more than 1.6 million people were on antiretroviral therapy, representing a 4-fold increase since December 2003. Overall, antiretroviral coverage in resource-limited countries increased from 7% in 2003 to 24% in June 2006.

Drug Distribution Infrastructure

The HIV and AIDS epidemic has highlighted the weakness of health care systems in resource-limited sub-Saharan African countries in terms of referral systems, human resources, and laboratory capacity, as well as drug procurement and supply chains. Lack of capacity in the educational system has led to an overall shortage of qualified health personnel including pharmacists and pharmacy staff. In addition, loss of health professionals to the private sector, to metropolitan areas, to wealthier countries, and to the epidemic itself has starved the public sector in these countries of the people on whom delivery of antiretroviral therapy depends.

Most sub-Saharan African countries have a shortage of health care professionals, including pharmacy personnel. Table 2 summarizes data on pharmacy support infrastructure in the 5 heavily HIV-affected African countries of Botswana, Malawi, Swaziland, Zambia, and Zimbabwe. With the shortage of fully qualified pharmacy personnel, drugs are primarily dispensed by untrained persons. Unregistered and unregulated drug stores or chemist shops are the major sources of prescription products being sold illegally in many of these countries. There is also a shortage of dispensary facilities that can coordinate pharmacotherapy management. Provision of antiretroviral drugs becomes particularly difficult under these circumstances because of the need for strict monitoring.

Innovative methods of delivering therapy that have been developed include utilizing specifically trained technicians, nurses, and lay community workers. Furthermore, simplification of treatment regimens has allowed for a shift from a pharmacist-centered model to one that relies on team efforts that include nurses, medical assistants, and people living with HIV and AIDS who are employed and trained to perform community outreach and treatment support.

Government Commitment

The governments of sub-Saharan African countries initially struggled to accept the reality of the HIV and AIDS epidemic. South Africa ignored suggestions to adopt antiretroviral therapy as part of their national health policies, instead choosing to stir debate on whether HIV was the real cause of AIDS. Recent reports suggest a significant shift toward accepting the reality of the need for antiretroviral therapy even though obstacles remain.

According to the recent WHO/UNAIDS report progress in expanding treatment and care provision in sub-Saharan Africa in the past year has been positive but uneven. At least one-third of the people in need of antiretroviral therapy are receiving it in such countries as Botswana and Uganda, while in Cameroon, Cote d’Ivoire, Kenya, Malawi, and Zambia between 10% and 20% of the people requiring antiretroviral drugs were receiving them in mid-2005. There is an extensive unmet need in most of the region. The WHO/UNAIDS reports that at least 85% (almost 900,000) of South Africans who needed antiretroviral drugs were not yet receiving them in mid-2005. The same applied to 90% or more of those in need in countries such as Ethiopia, Ghana, Lesotho, Mozambique, Nigeria, Tanzania, and Zimbabwe. Establishing an effective and efficient pharmacotherapy delivery system represents a great upcoming challenge for the governments of these countries.

Priorities in HIV and AIDS Pharmacotherapy

Emphasis on Prevention Versus Curative Therapy

As described above, approximately 90% of newly infected children in 2006 lived in sub-Saharan African countries, where the major route of infection is through mother-to-child transmission. As a result of the limited accessibility to antiretroviral therapy, the emphasis in sub-Saharan African countries is still largely on the prevention of HIV transmission. Therefore antiretroviral use is commonly found in prevention programs such as the prevention of mother-to-child transmission (PMTCT) and postexposure prophylaxis (PEP). Most sub-Saharan African countries have started integrating PMTCT in antenatal care services, although so far approximately only 1 in 4 pregnant HIV-infected women have access to those services.

The long-term treatment regimens proven to work in wealthy countries are often not affordable in the sub-Saharan African countries. Therefore, shorter duration regimens are often implemented. For PMTCT, single-dose nevirapine given to the mother just before delivery is the most commonly used regimen. The WHO Technical Consultation has recently recommended regimens in the resource-limited world to include zidovudine alone, fixed-dose zidovudine/lamivudine, and nevirapine.

Management of Pediatric Versus Adult Population

The WHO/UNAIDS target of treating 5 million patients by the end of 2005 aimed to ensure that at least 10% to 15% of those patients would be infants.
and children. One major obstacle that prevented the attainment of that target was that the medicines were not easily available in the appropriate formulations and at affordable prices. Lack of tools for forecasting requirements accurately made supply and procurement difficult, and pharmaceutical manufacturers seemed hesitant to invest in the development of pediatric formulations of antiretroviral products.

Challenges of treatment for HIV-infected children include the physiologic changes that occur during child growth that impact the pharmacokinetics of drugs. Palatability, chemical stability at various conditions found in resource-limited settings, and convenience of dispensing and dosing are also important considerations in pediatric pharmacotherapy, and are of particular importance in resource-poor settings where alternative options are few. Pediatric dosage regimens are usually based on either age or body surface area and can therefore be complicated. For example, zidovudine, nevirapine, and didanosine for infants each give dose requirements for body surface area. This is complicated in resource-poor settings where equipment, facilities, and trained staff are limited. A simplified weight-based method for pediatric drug dosing for zidovudine and didanosine in resource-limited settings has recently been published.27

In the year 2000, one pharmaceutical company announced a 5-year program to provide nevirapine free of charge to resource-limited countries for the PMTCT of HIV. Since nevirapine was not used for this purpose in wealthier countries, the donated drug originally was provided without a suitable pediatric package. Nevirapine suspension was only available in 240 mL containers even though only approximately 0.6 mL was needed for dosing for an infant. This posed difficulties in handling nevirapine for PMTCT programs, resulting in significant delays in the implementation of such programs that were meant to benefit from the donation program.28

It should be noted that over the past few years along with the WHO/UN-AIDS “3 by 5” initiative, significant efforts have been underway to address the above problem. The United States President’s Emergency Plan (PEPFAR), The Clinton Foundation, the Mother-to-Child Transmission (MTCT) Plus Initiative, The Elizabeth Glaser Pediatric AIDS Foundation (EGPAP), and other international non-governmental organizations (NGOs) have each developed specific programs to address the issue. In November 2004 the United Nations Children’s Fund (UNICEF) and WHO convened a meeting of technical experts to urgently identify ways and mechanisms to overcome key obstacles to access of appropriate, acceptable, and affordable antiretroviral formulations for children.29

Médecins Sans Frontières addressed this issue in its campaign for access to essential medicines.30 In its pricing guide for antiretroviral drugs for resource-limited countries it is recognized that certain pediatric solutions such as syrups are not always the most appropriate in resource-limited settings. Alternative options, including low-dosage capsules that can be opened and mixed with food and dosage-dispersible tablets should be considered for sub-Saharan African countries.

**Emphasis on Affordable Versus the Most Effective Available Regimens**

When antiretroviral medications become widely available in the sub-Saharan African countries the use of affordable drugs should be of high priority.30 As discussed earlier, there is a great emphasis on exploring strategies to enable equitable access to drugs. This includes encouraging generic competition, adopting WTO-TRIP safeguards into national legislation, bulk regional procurement, and encouraging local production through licensing and technology transfer. The use of formularies or essential drug lists (EDLs) also promotes availability of the drugs. However, cost is a major criterion for a drug product to be listed in EDLs in sub-Saharan African countries. Therefore, antiretrovirals are easily omitted from these EDLs and are not included as part of their health policies.

Focusing on essential generic medicines in sub-Saharan African countries is in sharp contrast with the situation found in wealthy countries such as the United States, where the most effective regimens available on the market are sought in spite of their high cost. Antiretroviral therapy is often individualized for the specific needs of the patient in the United States and in most European countries because most drugs available on the market are accessible. Patients with HIV infection are prescribed the newest antiretrovirals available, not always due to necessity, but as a result of treatment individualization or even pharmaceutical marketing.

**Concerns with Counterfeit and Substandard Products**

The shortage of essential drugs in combination with high prices raises concerns regarding counterfeit drugs. Many resource-limited sub-Saharan African countries have underdeveloped drug regulatory systems that are vulnerable to counterfeiting of drug products.31 Although this problem can affect developed countries as well, they often have the means to deal with it promptly. The challenge remains for sub-Saharan African countries to ensure that genuine products are distributed on their markets.

With the use of generic antiretroviral products also comes the concern of quality. Patent laws are often overridden well before the normally stipulated 20 years to allow for distribution of generic antiretrovirals due to the HIV and AIDS public health emergency. Information on the pharmacologic properties of the innovator (branded) drugs is therefore often not widely available by the time the generic forms of antiretrovirals enter the market. In addition, generic drugs may be produced using methods that differ from those of the innovator brands, leading to the potential for impurities and instabilities. There is a need to ensure that generic products are bio-equivalent to the innovator products.32 Prequalification of generic manufacturers and postmarketing quality and bio-equivalence surveillance systems in sub-Saharan African countries have been recommended.
Prospects and Opportunities for International Collaboration

Reports have appeared on ways of fostering international collaboration for the transfer of technical and logistic support in various health-science related areas including an oral health research collaboration in Guatemala, a collaborative biomedical research network in Brazil, global collaboration in epidemiology, and a pilot telemedicine project in Western Africa. Training of local personnel for sub-Saharan African countries is also being advocated as a way to ensure sustainable scaling up of the response to HIV and AIDS.

In the areas of HIV pharmacotherapy, a growing number of international organizations are being developed to assist in sub-Saharan African countries. Generally, these groups focus on strengthening human resource capacity, developing common education strategies for prevention of HIV transmission, treating and preventing opportunistic infections, and recently, providing antiretroviral therapy.

The National Institute for Allergy and Infectious Diseases (NIAID) and other international advisory groups such as UNAIDS have identified the need to increase the capacity of resource-limited countries to undertake HIV and AIDS research. This has resulted in such initiatives as the Comprehensive International Program of Research on AIDS (CIPRA) and the AIDS International Training and Research Program (AITRP). These initiatives are aimed at supporting fundamental research on interventions relevant to resource-limited countries, enabling them to enhance their research capabilities. The same initiatives also generate knowledge and resource bases that benefit all nations.

The International Center for HIV/AIDS Pharmacotherapy Research and Training (ICHAPRT) is an initiative from the School of Pharmacy and Pharmaceutical Sciences at the University at Buffalo in collaboration with the School of Pharmacy at the University of Zimbabwe. The HIV ePharmacotherapy Network (www.hiv.buffalo.edu) at the University at Buffalo enhances expertise among caregivers, educators, and researchers in HIV and AIDS and establishes an interactive forum for knowledge advancement and patient care.

ICHAPRT identifies methods that have been successful in developed countries and, through formalized training and educational initiatives, seeks to transfer these approaches to Zimbabwe. Examples of such areas include the promotion of sustainable access to essential drugs (antiretrovirals and medications for opportunistic infections) as well as pharmacotherapy research topics such as adherence to therapy, clinical pharmacokinetics, adverse drug reactions, drug interactions, pharmacogenomics, and therapeutic drug monitoring. Several joint research and clinical service programs have been implemented with the involvement of visiting scholars. Notable achievements so far include the implementation of a community-based adherence support program, capacity building for quality and bioequivalence surveillance of generic antiretrovirals, and the development of a Website covering international perspectives. These endeavors have laid the groundwork for further international collaborations.

Summary

In the area of HIV pharmacotherapy in resource-limited settings, particularly in sub-Saharan Africa, countries possess specific issues and challenges that need to be well understood and taken into consideration when setting priorities for collaborative efforts. Many resource-limited countries are too preoccupied with other issues to address the accessibility of good quality products that are appropriate for their specific patient populations. Understanding these disparities could lead to more effective collaboration linkages. Academic institutions are best placed to lead in the development of such partnerships since they seek the same goals of information generation and dissemination.

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Telling Stories
The Sky Is Falling

Jacqui Scipio-Bannerman, RNC

When Chicken Little ran through the streets warning the town of impending danger, no one listened. Last Monday, I informed the 36th young woman of my career of her infection with the HIV virus. For 17 years, I and the countless others who work in women’s health have been screaming “the sky is falling”—and it appears that no one is listening.

As I mentally prepared myself for the HIV disclosure, my mind started going back to 3 of my most memorable experiences. The first was Stephanie; my discussion with Stephanie was traumatic and I wrote about it in an article that was published in Nursing Spectrum in October of 1994. Stephanie was in college making unwise sexual decisions. I’ve been there and done that—truthfully, we all have. The only difference is that we dodged the bullet, and Stephanie was not so lucky. The discussion was difficult because it felt like I was looking into a mirror. I was hearing myself share information that could have easily been applied to my life. As I spoke with Stephanie, I was looking in her eyes, but I was seeing my face.

By 1994 HIV and AIDS was changing. No longer were gay, white men the face of the disease. By that time, we, African American, heterosexual women, had the bullseye on our backs. Thirteen years later, Stephanie is doing okay. I say “okay”, and not “well”, because Stephanie is still making unwise sexual decisions. And though luck is currently on her side, we all know, luck usually runs out.

In 2007, at a weekly HIV conference at Pennsylvania Hospital, I heard Michael Braffman, MD, say that “history concerning HIV is being written as we speak.” Times and treatments have and are changing drastically. I have changed also. Since the article in 1994, I have become a parent, which is why my last 2 HIV disclosure encounters have been so heart wrenching.

Allow me to explain. When a positive HIV laboratory result comes across my desk, I always look at the patient’s age and the number of dependents first. When I saw that Danielle was 15 years old, my mind flooded with memories of my own life when I was 15. Life was easy and fun. That would not be Danielle’s story.

I told her that her blood contained the HIV virus, and even though she understood conceptually, her response was minimal. She made no sound, and had a blank stare with no emotion. I knew that she had no frame of reference; she had no life experiences to draw from. She was a baby! And she was clueless. I made a direct linkage with a pediatric provider and wished her well. From a personal standpoint, it was an easy encounter. From a public health standpoint, it was a tragedy.

My experience with Shante was not so easy. Shante was 17 years old and though I felt prepared to conduct an HIV disclosure with an adolescent, I was not prepared for what happened next. I told Shante about her infection with the HIV virus, and she called her mother from the waiting room into my office. Shante told her mother, who sat down in a chair and cradled her daughter on her lap, where the two of them sat, quietly sobbing.

As a parent, I quickly identified with Shante’s mother and began to cry also. I was crying not because HIV is the same life-threatening illness as 15 years ago, but because I am a mother. And without formal induction, I have accepted the role and responsibilities that come with parenthood. I have taken the unspoken oath to make all the boo-boos better.

Shante’s mother could not make this boo-boo better, and everyone in the room knew it. I gathered my composure and as with Danielle, I made a linkage to a pediatric HIV specialist.

On that day, I realized that the motive behind my message had changed. For years I had been counseling young men and women from a nursing point of view. Watching Shante’s mother made me realize that my “Chicken Little” message had now taken on a life of its own. The message had become personalized, had gone from medical advice to a personal plea.

Nurses and counselors can become burned out and find themselves tired of talking. Parents do not. A parent’s job is never done. So I have inhaled, found my second wind, and have begun to shout with the chorus again, “the sky is falling… the sky is falling… the sky is falling!”

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