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PART 5 Infectious Diseases FIGURE 233-6 Mucosal leishmaniasis in a Brazilian patient. There is extensive inflammation around the nose and mouth, destruction of the nasal mucosa, ulceration of the upper lip and nose, and destruction of the nasal septum. (Courtesy of R. Dietz, Universidade Federal do Espírito Santo, Vitória, Brazil.) ■ ■PREVENTION OF LEISHMANIASIS No vaccine is available for humans for any form of leishmaniasis, although several candidates are in early phases of development. Inocu lation with live L. major (“leishmanization”) is practiced in Iran; 80% of recipients were protected, according to one report. Anthroponotic leishmaniasis is controlled by case finding, treatment, and vector control with insecticide-impregnated bed nets and curtains and residual insecti cide spraying. Control of zoonotic leishmaniasis is more difficult. Use of insecticide-impregnated collars for dogs, treatment of infected domestic dogs, and culling of street dogs are measures that have been used with uncertain efficacy to prevent transmission of L. infantum. In Brazil, canine vaccines have been found to promote a decrease in the human and canine incidence of zoonotic VL. Two vaccines, Leishmune and LeishTec, are licensed in Brazil; Leishmune provides significant protection to vaccinated dogs. CaniLeish and LetiFend are the two licensed canine vaccines approved for use in Europe. Personal prophylaxis with bed nets and repellants may reduce the risk of CL infections in the New World. ■ ■FURTHER READING Dorlo TP et al: Optimal dosing of miltefosine in children and adults with visceral leishmaniasis. Antimicrob Agents Chemother 56:3864, 2012. Mann S et al: A review of leishmaniasis: Current knowledge and future directions. Curr Trop Med Rep 8:121, 2021. Pan American Health Organization: Synthesis of evidence and recommendations: Guideline for the treatment of leishmaniasis in the region of the Americas 47:e43, 2023. Singh OP, Sundar S: Visceral leishmaniasis elimination in India: Progress and the road ahead. Expert Rev Anti Infect Ther 20:1381, 2022. World Health Organization: WHO guideline for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia. Geneva: World Health Organization, 2022. Available at https://iris.who.int/bitstream/handle/10665/354703/9789240048294-eng. pdf?sequence=1. Accessed September 15, 2023.

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Chagas Disease and

African Trypanosomiasis Myriads of protozoan parasites of the genus Trypanosoma infect plants and animals worldwide. Among these, three are of clinical significance for humans: T. cruzi causes Chagas disease, and T. brucei gambiense and T. brucei rhodesiense cause human African trypanosomiasis (HAT), which is also known as “sleeping sickness.” Despite obvious differences in their geographic distribution, parasitic life cycle, clinical presentation, treatment, and outcome, these vector-borne diseases are archetypal examples of neglected tropical diseases. More broadly, these infectious diseases affect neglected populations of the lowest socio economic class who have limited access to care and who live either in remote rural areas of low- or middle-income tropical/subtropical countries or in urban areas of both endemic and nonendemic coun tries. Most drugs to treat these conditions are several decades old, their availability is limited, and their efficacy and/or safety is suboptimal. Other trypanosome species (e.g., T. congolense and T. evansi) pre dominantly cause nonhuman zoonoses and only occasionally cause illness in humans. CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS) ■ ■DEFINITION First described in 1909 by Carlos Chagas, Chagas disease (American trypanosomiasis) is a zoonosis caused by the flagellated protozoan T. cruzi. After a frequently asymptomatic acute phase, 30–40% of patients develop potentially life-threatening chronic cardiomyopathy and/or digestive tract dysfunction over decades. Acute reactivation may occur in immunocompromised patients. Chagas disease imposes an important human and social burden in Latin America and has recently spread outside its natural boundaries to become a global public health problem. The vast majority of affected individuals are unaware of being infected and do not have access to appropriate clini cal management and counseling. ■ ■TRANSMISSION Vectorial Transmission T. cruzi infection is primarily a zoonosis transmitted to a range of wild and domestic mammals by blood-sucking triatomine bugs. Sylvatic, peridomiciliary, and intradomiciliary vec torial cycles sometimes overlap. Over a large geographic area in the Americas (from northern Argentina to the southern United States), most human infections are intradomiciliary, arising from a triatomine bite during nighttime sleep. Feces released by triatomines during a blood meal contain the infective metacyclic form of T. cruzi that enters the human body through cutaneous breaks, mucosae, or conjunctivae. Despite some laboratory research showing the potential for transmis sion by bedbugs, there is no evidence that bedbugs actually transmit T. cruzi to humans. Nonvectorial Transmission Other modes of transmission can cause infection in both endemic and nonendemic regions. T. cruzi can be transmitted congenitally from mother to newborn, by transfusion of blood products, by tissue or organ transplantation, or by ingestion of contaminated food or drink. Congenital infection occurs in 1–10% of newborns of infected mothers. The risk of infection from contami nated blood products is low (1.7% overall, 13% for platelet recipients, and close to 0 for recipients of red blood cells and plasma). Transmis sion by infected organ and tissue transplants mostly affects heart, liver, and kidney recipients. Oral transmission is increasingly reported after ingestion of contaminated food (berries) or drinks (fruit or sugar cane juice) and occasionally causes outbreaks.

■ ■EPIDEMIOLOGY An estimated 6–7 million people are infected by T. cruzi, including

> “1 million individuals with chronic cardiomyopathy. However, the true global burden of Chagas disease is in fact uncertain. The highest num bers of infected individuals reside in Argentina, Brazil, and Mexico; the prevalence is highest in Bolivia (6.1%), Argentina (3.6%), and Paraguay (2.1%). In highly endemic

regions of these countries, the prevalence may exceed 40%. Formerly restricted to poor rural populations, the distribution of cases—and, to some extent, T. cruzi transmission—has progressively extended to cities in the context of rapid urbanization and rural migration. A recent history of migration from a rural area is the main risk factor in urban settings. Overall, the prevalence and incidence of Chagas disease have sharply declined in recent decades because of improved housing and socio economic conditions as well as public health interventions, includ ing regional vector-control initiatives, implementation of systematic screening of blood products, and improved detection of congenital transmission. Several countries have been declared free of domicili ary transmission as a result of sustained residual insecticide-spraying campaigns. This progress is threatened by adaptation of the vector to the periurban environment, its resurgence in areas where spraying has been discontinued, the development of resistance to pyrethroid insec ticides, and the persistence of peridomiciliary transmission. A growing number of localized outbreaks are being reported in previously stable areas, with the Amazon basin particularly at risk. Chagas disease distribution has expanded to nonendemic countries in the context of increased global travel, with cases reported more fre quently in North America, Western Europe, Australia, and Japan. The United States harbors up to 300,000 cases, mostly among immigrants from Central America. In addition, sporadic vector-borne infec tions occur in the southern states. Western Europe has an estimated 68,000–123,000 cases, and Japan and Australia a few thousand cases. Despite the implementation of blood bank screening and of some dedicated medical programs, only a small proportion of cases have been identified and properly managed to date. A low level of awareness among health care professionals and difficulties experienced by some groups in accessing care appear to be major drivers. At-risk migrant communities are frequently subject to factors that render them socially, legally, or economically vulnerable. Moreover, the cultural perception of Chagas as a disease embedded in poverty can create a social stigma that complicates its management at the community level. In contrast to immigrants, international tourists visiting endemic countries are at very low risk of being infected, whether by reduviid bug bites or by other routes, and reports of Chagas disease in travelers are rare. ■ ■PATHOLOGY Several T. cruzi strains have been identified. These strains have par tially overlapping transmission cycles and geographic distributions, but no definitive evidence supports an association of certain strains with specific clinical manifestations or with variation in disease severity. The rarity of digestive tract involvement north of the Amazon basin suggests that specific parasitic and host genetic factors may influence the disease course. The pathogenesis of Chagas disease results from the complex interactions between the pathogen and the host immune response. Many questions about the relative importance of these inter actions, including the role of autoimmune mechanisms, remain unan swered. After local penetration of trypomastigotes, parasites rapidly enter the bloodstream and disseminate through the body, infecting a wide range of

> nucleated cells in which they differentiate into amasti gotes (Fig. 234-1). The innate immune response triggered by parasite mucins and DNA leads to a predominantly T helper 1 response. The production of various proinflammatory cytokines and the activation of CD8+ T lymphocytes reduce parasitemia to a subpatent level within 4–8 weeks, a point marking the end of the acute phase. Immune evasion mechanisms allow persistent low-intensity prolif eration of amastigotes and their release into the bloodstream, with sub sequent infection of potentially all types of nucleated cells—notably cardiac, skeletal, and smooth-muscle cells. Mechanisms that have been postu lated to determine the pathogenic evolution toward cardiomyopathy

FIGURE 234-1 A cluster of Trypanosoma cruzi amastigotes with an inflammatory infiltrate in the placenta of a congenitally infected newborn infant. include the parasites' persistence and the host's inability to downregu late the initial immune response, resulting in cell-mediated damage and an imbalance of T helper 1 and 2 responses with excessive produc tion of proinflammatory cytokines. Secondary mechanisms, such as microcirculation abnormalities and dysautonomia, also may influence the progression of tissue damage. Genome-wide association stud ies suggest that genetic variation may contribute to cardiomyopathy development. CHAPTER 234 In the myocardium, chronic inflammation results in cellular destruction and the development of fibrosis leading to a segmental loss of contractility and dilation of the chambers, with the associated risk of left ventricle apical aneurism. Focal hypoperfusion and tissue damage are sources of ventricular arrhythmias, while scarring lesions mostly affect the conduction system. Autonomic cell destruction leads to vagal and sympathetic denervation whose exact clinical significance remains to be clarified. Chagas Disease and African Trypanosomiasis T. cruzi appears to have a direct toxic effect on digestive tract intra mural autonomic ganglion cells. Over time, the loss of neural cells affects muscular tone, leading to motility disorders and ultimately to organ dilation (megaviscera syndrome). The esophagus and colon are primarily affected, but lesions may occur along the whole digestive tract. Inadequate relaxation of the lower esophageal sphincter causes symptoms of achalasia, whereas damage to the colon ultimately mimics Hirschsprung's disease, with severe constipation and the risk of volvu lus and toxic dilation. Factors reducing the cellular immune response, such as HIV infection, posttransplantation immunosuppressive therapies, or hematologic malignancies, may increase intracellular replication of amastigotes, with increased parasitemia (reactivation). Lesions develop predominantly in the central nervous system (CNS), the heart, and the skin. Among HIV-positive patients, the risk of reactivation is ~20% in the absence of antiretroviral therapies and occurs when the CD4+ T cell count falls to <100/μL. Clinically manifest T. cruzi reactivation is an AIDS-defining opportunistic infection. ■ ■CLINICAL MANIFESTATIONS The clinical manifestations of T. cruzi infection vary greatly among individuals. The infection course is divided into two phases that are associated with different clinical features, duration, and prognosis (Table 234-1). The acute phase remains undetected and undiagnosed in most individuals. While 5–10% of these early infections spontaneously resolve without treatment, T. cruzi persists for life in most individuals (the chronic phase); 60–70% of these individuals never develop appar ent tissue damage (the indeterminate form), but the remaining 30–40% progress toward detectable organ damages of variable severity over decades (the determinate form). These chronic complications include cardiac (20–30%), digestive (5–20%), or mixed (5–10%) disorders. There

TABLE 234-1 Characteristics of the Stages of Trypanosoma cruzi Infection PHASE OR SETTING CONTEXT ONSET OF FIRST SYMPTOMS CLINICAL MANIFESTATIONS DURATION PROGNOSIS Acute (congenital) ~5% risk of maternal transmission to newborn At birth or weeks after delivery

> 90% asymptomatic; rare lymphadenopathy, hepatosplenomegaly, jaundice, respiratory distress, growth retardation Acute Vector-borne transmission; oral transmission (ingestion of contaminated food/ drinks); blood product transfusion; tissue/organ transplantation 1–2 weeks after vectorial transmission; may be sooner (days) after oral transmission or later (months) after transfusion/ transplantation 90% asymptomatic or mild febrile illness; local swelling at inoculation site (eyelid [Romaña sign] or skin [chagoma]); polyadenopathy; splenomegaly; myocarditis, hepatitis, and encephalitis more frequent with oral transmission Chronic (indeterminate form) Balanced immune response after acute phase subsides No symptoms Normal clinical examination and ECG result Chronic (determinate form) Predominant inflammatory response (in cardiomyopathy only) Years to decades after initial infection Dyspnea, chest pain, palpitation, syncope, sudden death, stroke, dysphagia, regurgitation, constipation, fecaloma, volvulus, peripheral neuropathy Acute (reactivation) Severe immunosuppression Variable Myocarditis, erythema nodosum, panniculitis, Toxoplasma-like focal brain lesion, meningoencephalitis Abbreviation: ECG, electrocardiography. is no predictor of evolution toward clinical manifestations during the chronic phase. In patients with cardiomyopathy, bundle branch blocks are usually the first signs and may cause no symptoms for years until more severe conduction system disease, arrhythmias, and left ventricular dysfunction occur. Advanced cardiac damage entails a worse prognosis than other cardiomyopathies—notably, ischemic heart disease. PART 5 Infectious Diseases APPROACH TO THE PATIENT Chagas Disease (American Trypanosomiasis) More than 90% of infections go undiagnosed, and cases are fre quently identified at a late stage once chronic complications develop. The vast majority of T. cruzi–infected individuals are asymptomatic (i.e., in the indeterminate form of the chronic phase). An awareness of potential Chagas disease is important for general practitioners as well as for physicians from various specialties, including gastroen terologists, cardiologists, neurologists, obstetricians, pediatricians, and infectious disease specialists. Outside endemic areas, screening for Chagas disease should be proposed when any Latin American individual has evocative symptoms and signs, including abnormali ties on electrocardiography (ECG) or increased risk of (1) T. cruzi infection (Chagas disease in the mother or other family members; origins in a highly endemic country or area; history of unscreened blood transfusion in Latin America); (2) transmission to others (e.g., via pregnancy or blood or organ donation); or (3) reactivation (current or pending immunosuppression). Screening of the rela tives of an index case may identify additional cases. ■ ■DIAGNOSIS AND STAGING Diagnostic Confirmation Diagnostic strategies depend on the clinical phase (Table 234-2). Detection of circulating parasites by

> microscopy of the blood after concentration (e.g., by the Strout method, microhematocrit) or by nucleic acid–based assay (polymerase chain reaction [PCR]) is the best diagnostic approach when the parasit emia level is high—i.e., during the acute phases, including reactivation. Once parasitemia becomes undetectable by microscopy (a point mark ing the end of the acute phase), diagnosis relies on immunologic tests that detect anti–T. cruzi IgG. The most common techniques include a conventional or recombinant enzyme-linked immunosorbent assay (ELISA) and immunofluorescence assays. Two positive serologic tests using different techniques and targeting different antigens confirm the

2–8 weeks Favorable when infant is born alive; unknown rate of in utero or neonatal death 4–8 weeks Mortality: 0.1–5% with oral transmission or myocarditis/ encephalitis Lifelong or until determinate phase No attributable mortality Chronic 5-year mortality: 2–63%, depending on extent of cardiac damage; most important causes of death: cardiac failure and sudden death, followed by stroke Variable Mortality depends on rapidity of diagnosis and treatment and on underlying conditions diagnosis of Chagas disease during the chronic phase. In the presence of discordant serologic results, a third serologic test is warranted. Some of the immunochromatographic rapid diagnostic tests on the market have sufficient sensitivity and specificity to be used as first-line screen ing tests where laboratory facilities are not easily accessible. If the rapid diagnostic test result is positive, at least one conventional serologic assay is necessary to confirm infection. Diagnosis of congenital infection relies on examination of cord and/ or peripheral blood by microscopy or PCR during the first days or weeks of life. A test conducted after 4 weeks of age is most accurate: PCR earlier in life may be falsely positive, likely because of the passage of T. cruzi DNA fragments from the mother to the child. If results are negative, serologic tests should be performed at 9 months of age, once maternal antibodies have been cleared. During the chronic phase, the limited sensitivity (50–80%) of con ventional PCR restricts its usefulness for primary diagnosis; however, PCR can document therapeutic failure if it yields positive results after the completion of treatment. In the United States, the Centers for Disease Control and Prevention (CDC) provides reference laboratory testing (see contact information in the treatment section). TABLE 234-2 Diagnostic Procedures of Choice for Clinical Stages of T. cruzi Infection TECHNIQUE OF CHOICE SAMPLE DIAGNOSTIC CRITERIA STAGE Acute Microscopy after concentration, PCR Peripheral blood, cerebrospinal or other body fluids Positivity in one test Acute (early congenital during first

9 months of life) Microscopy after concentration, PCR Cord or peripheral blood Positivity in one test Chronic (indeterminate and determinate forms) Serology Peripheral blood Positivity in two tests with different techniques and antigens Reactivation Microscopy after concentration, PCR Peripheral blood, cerebrospinal or other body fluids Positivity with evidence of increasing parasitemia on serial samples or extremely high parasite load Abbreviation: PCR, polymerase chain reaction.

D1 V1 D2 D3 AVR AVL AVF FIGURE 234-2 Electrocardiogram of a 43-year-old patient shows bradycardia with high-grade atrioventricular blocks. Disease Staging Once T. cruzi infection is confirmed, clinicians should assess the presence of complications and concomitant factors that may influence the course of the disease. The initial evaluation includes a thorough cardiac,

neurologic, and digestive history and a clinical examination. Twelve-lead ECG with a 30-s strip is a good screening test for Chagas-associated cardiomyopathy. The most fre quently found abnormalities are right bundle branch block, left anterior fascicular block, ventricular premature beats, repolarization disorders, Q waves, and low QRS voltage (Fig. 234-2). An abnormal ECG result or the presence of suggestive cardiac symptoms warrants further investiga tion. Echocardiography and the 24-h Holter test are the preferred meth ods for assessment of chamber dilation, apical aneurysm, ventricular dysfunction, and arrhythmias. Depending on the findings, the workup can be supplemented by MRI or electrophysiologic studies. Gastro enterologic investigations are performed in patients with suggestive symptoms, such as dysphagia and severe constipation. Barium esopha gography and enema are first-line diagnostic procedures, which can be supplemented by esophageal manometry. Megacolon is diagnosed when the sigmoid or descending colon diameter is ≥6.5 cm. Comorbidities, including other cardiovascular risk factors, immu nosuppressive conditions, and other chronic infections (e.g., with Strongyloides stercoralis or HIV) should be investigated. TABLE 234-3 Chagas Treatment Regimens and Adverse Reactions to Benznidazole and Nifurtimox DRUG REGIMEN DURATION ADVERSE EVENTS IN ADULTS (FREQUENCY) Benznidazole Age <12 years: 5–7.5 mg/kg per day in 2 doses Age >12 years: 5 mg/kg per day in 2 doses 30–60 days Allergic dermatitis (29–50%), anorexia and weight loss (5–40%), Nifurtimox Age <10 years: 15–20 mg/kg per day in 3 or 4 doses Age 11–16 years: 12.5–15 mg/kg per day in 3 or 4 doses Age >16 years: 8–10 mg/kg per day in 3 or 4 doses 60–90 days Anorexia and weight loss (50–81%), nausea and vomiting Source: From C Bern: Chagas' Disease. N Engl J Med 373:456, 2015. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

V2 V3 V4 V5 V6 CHAPTER 234 TREATMENT Chagas Disease (American Trypanosomiasis) Chagas Disease and African Trypanosomiasis ETIOLOGIC TREATMENT Only two drugs, benznidazole and nifurtimox (Table 234-3), have shown persistent efficacy against T. cruzi infection when adminis tered for ≥30 days. While these drugs have been used since the early 1970s, many questions remain about their mode of action and effi cacy at the different stages of infection. The treatment goal depends on the clinical stage; the overall objectives are to cure patients who have recent infection or reactivation, to reduce morbidity, and to prevent transmission at later stages. Treatment is most effective during the acute (including congenital) phase and the early chronic phase (i.e., in patients <18 years of age), with a 60–100% cure rate. The efficacy of treatment during the indeterminate form of the chronic phase in patients >18 years old is not known; however, treatment may protect against the development of cardiac damage later in life and eliminate the risk of vertical transmission when given before conception. In adults with chronic cardiomyopathy, benznidazole has no impact on disease progression and mortal ity risk. Neither benznidazole nor nifurtimox is effective against PREMATURE DISCONTINUATION (RATE) 7–20% paresthesia (0–30%), peripheral neuropathy (0–30%), nausea and vomiting (0–5%), leukopenia and thrombocytopenia (<1%) 6–44% (15–50%), abdominal discomfort (12–40%), headaches (13–70%), dizziness and vertigo (12–33%), anxiety and depression (10–49%), insomnia (10–54%), myalgia (13–30%), peripheral neuropathy (2–5%), memory loss (6–14%), leukopenia (<1%)

digestive complications. Treatment is contraindicated during preg nancy and in advanced renal or hepatic failure. Preferred regimens and drug tolerance vary with age. Adverse events are more frequent among adults, who are therefore at increased risk of premature treatment discontinuation (Table 234-3). As benznidazole seems better tolerated than nifurtimox in adults, it is the

recommended first-line drug in this age range. Close (e.g., weekly) clinical and biologic monitoring is necessary during treatment. While treatment is usually prescribed for 60 days, the optimal duration remains a matter of debate, with a growing interest in shorter courses.

Treatment should be undertaken for all children, women of child-bearing age, patients in the acute phase, and patients with reactivation. Given the uncertainties about the impact of treatment, the decision to treat patients >18 years old who have the indeter minate form of the chronic phase should be made on an individual basis after discussing the pros and cons with the patient. A nega tive pregnancy test is mandatory before initiating treatment, as the recommended drugs have not been proven to be safe in pregnancy. The efficacy of second-line treatment (e.g., nifurtimox after failure with benznidazole) has not been evaluated to date. The limited efficacy of current regimens and the understanding that living parasites are a driver of immunopathologic processes have fueled interest in novel therapeutic approaches. These include the addition of immunomodulatory interventions to antiparasitic treatment and the use of combinations of antiparasitic drugs. Information on drugs can be obtained through the CDC (Parasitic Diseases Public Inquiries line [404-718-4745] or chagas@cdc.gov), or the CDC Emergency Operations Center (770-488-7100). The U.S. Food and Drug Administration has approved the use of benznidazole for treatment of children 2–12 years and nifurti mox for those 0–17 years of age, and in older patients based on clinical decision. PART 5 Infectious Diseases NONETIOLOGIC TREATMENT The management of Chagas cardiomyopathy generally follows the management guidelines for heart failure, conduction disturbances, or ventricular arrhythmia of other etiologies. Given the high risk of sudden death, early initiation of treatment with amiodarone or implantation of a cardioverter defibrillator should be considered in the presence of pathologic electrophysiologic abnormalities. Anti coagulation is recommended for primary and secondary prevention of cardioembolic events in the presence of an intramural thrombus or apical aneurysm. Strict control of other cardiovascular risk fac tors is warranted. Chagas cardiomyopathy is a prominent indication for heart transplantation in Latin America; some evidence indicates that the results are better than in cardiomyopathy of other etiolo gies. Posttransplantation immunosuppression requires close moni toring, given the high risk of reactivation. Treatment of digestive dysmotility includes dietary counseling and meals rich in fiber and hydration, with smaller portions eaten more frequently. Drugs releasing the lower esophageal sphincter (e.g., nifedipine or isosorbide dinitrate before meals), pneumatic balloon dilatation, or laparoscopic myotomy improve upper gas trointestinal symptoms in the early stage. Use of botulinum toxin is effective but requires repeated injections. Laxatives and enemas alleviate chronic constipation in most patients. Surgery is indicated in patients with distressing symptoms that are refractory to medical treatment. CLINICAL FOLLOW-UP Defining the optimal cure after treatment remains very challenging and is a crucial topic of research. While the search for biomarkers (including through proteomics) to identify early indicators of treat ment response holds some promise, serologic follow-up remains the cornerstone of posttreatment monitoring in the acute phase. In the chronic phase, there is no assay of proven value for documentation of response. The time needed for negative seroconversion after treatment indeed depends on the duration of infection. The interval is short (usually months, sometimes up to 2 years) when infection

is treated during the acute (including congenital) phase. In contrast, decades are required in adults infected during childhood. A posi tive result in a posttreatment PCR indicates treatment failure, but a negative result cannot be interpreted because of the low sensitivity of PCR during the chronic

phase. The status of patients with nega tive PCR results but persistent positive serology is therefore uncer tain, but these patients should be considered potentially infective as long as serologic tests continue to yield positive results. All patients, treated or not, should be regularly monitored. The basic yearly assessment includes history-taking for detection of new symptoms, clinical examination, and 12-lead ECG. ■ ■PREVENTION In the absence of a vaccine, preventive measures—primary (prevention of T. cruzi transmission), secondary (avoidance of complications), and tertiary (reduction of morbidity and mortality)—are necessary. Screen ing of blood donations is being progressively implemented in endemic areas and in countries to which high-risk groups are immigrating, and screening should be extended to organ donation. When sustained over prolonged periods, vector control is an effective and cost-effective strat egy to curb intradomiciliary transmission. Insecticide-impregnated bed nets (as used for malaria) provide individual protection against reduviid bug bites. Screening of child-bearing-age and pregnant Latin American migrant women has been highly cost-effective in Spain, although the cost per case detected varies with the prevalence of infec tion in the targeted population. Early identification of cases through passive and active screening of the population at risk, along with provi sion of treatment, may reduce the risk of complications and secondary transmission, particularly congenital transmission. Finally, identifica tion and treatment of cardiac complications and prevention of cardio embolic events at an early stage positively influence the disease course. ■ ■GLOBAL CONSIDERATIONS With its geographic expansion, Chagas disease has become a global health issue, predominantly affecting vulnerable people on four con tinents. Yet, as with other neglected tropical diseases, progress against Chagas is limited by a lack of research and development and a lack of financial and political commitment. For example, the production and registration of existing drugs, and access to them, are still prob lematic in many countries, including the United States. Difficulties in research on and development of new drugs are compounded by the lack of financial incentives. The future of Chagas disease is likely to be influenced by global phenomena. Climatic changes, population aging, increasing prevalence of noncommunicable comorbidities (e.g., diabetes, hypertension) in low- and middle-income countries, and increasing use of immunosuppressive drugs are likely to impact the epidemiology, clinical course, and burden of Chagas disease. To tackle these challenges, clinical, public health, and policy interventions need to be scaled up and improved in areas of high or hidden prevalence (e.g., in the Chaco Region of Argentina, Bolivia, and Paraguay and in Mexico, Western Europe, and the United States, respectively). HUMAN AFRICAN TRYPANOSOMIASIS (SLEEPING SICKNESS) ■ ■DEFINITION HAT is a life-threatening illness caused by infection with extracellular protozoan parasites that are transmitted by tsetse flies in sub-Saharan Africa. T. b. gambiense and T. b. rhodesiense are the two pathogenic subspecies affecting humans; their epidemiologic and clinical features largely differ. ■ ■EPIDEMIOLOGY The geographic range of HAT is restricted to sub-Saharan Africa in line with the distribution of its vector, the tsetse fly (Glossina species; Fig. 234-3). HAT due to T. b. gambiense is endemic in 24 countries of western and central Africa. Between 1999 and 2020, the number of reported cases fell by 98% (from 27,862 to 565) as a result of success ful control measures based on systematic screening of populations at

FIGURE 234-3 Areas at risk for human African trypanosomiasis, 2016–2020. (Reproduced from Franco JR et al: The elimination of human African trypanosomiasis: Achievements in relation to WHO road map targets for 2020. PLoS Negl Trop Dis 2022; 16(1): e0010047, Figure 4.) risk, diagnostic confirmation, and treatment of infected individuals. During the same period, the number of reported cases of HAT due to T. b. rhodesiense fell by 84% (from 619 to 98) in the 10 diseaseendemic countries of eastern and southeastern Africa. However, the ratio of reported to

unreported cases remains uncertain for disease caused by both species. In 2020, most cases of T. b. gambiense HAT were reported by the Democratic Republic of the Congo (DRC; 70%), whereas Malawi reported most of the cases caused by T. b. rhod esiense (91%). The geographic distributions of T. b. gambiense and T. b. rhodesiense do not overlap, but the two species are present in distinct regions of Uganda. A roadmap for HAT elimination as a public health problem by 2020 was mapped out by the World Health Organization (WHO) with two primary indicators: the number of cases reported annually (target: <2000; reached since 2018) and the area at risk reporting ≥1 case/10,000 people/year (target: reduction of 90% by 2016−2020 compared with the 2000−2004 baseline; 83% reduction reached in 2020). The next goal set by WHO is the global elimination of transmission by 2030. Humans are the predominant reservoir of T. b. gambiense. Rare cases of vertical (in utero) or transfusional transmission have been reported, but almost all patients are infected by the bite of tsetse flies during their daily activities along or near rivers, where the flies live and reproduce. In contrast, T. b. rhodesiense causes zoonosis in a variety of wild and domesticated animals (e.g., antelopes and cattle, respectively), which act as reservoirs. Humans are infected by T. b. rhodesiense via tsetse bites in woodland savannah. Honey gatherers, game park rangers, poachers, and firewood collectors are particularly at risk. Imported cases of HAT are occasionally diagnosed among African immigrants and other travelers. While long-term travelers (>30 days) are at increased risk of T. b. gambiense HAT, most imported cases of T. b. rhodesiense HAT are seen in short-term travelers, typically following visits to game parks.

CHAPTER 234 Chagas Disease and African Trypanosomiasis ■ ■PATHOLOGY AND PATHOGENESIS T. b. rhodesiense and T. b. gambiense, unlike other trypanosome spe cies, can infect humans because they resist lytic factors in human serum—namely, apolipoprotein L-1 (APOL1). Human APOL1 variants are prevalent in individuals of African ancestry, conferring protection against livestock trypanosome species, but at the cost of increasing the likelihood of chronic kidney disease. The serum resistance–associated protein is responsible for resistance in T. b. rhodesiense, whereas other mechanisms, notably involving the T. b. gambiense–specific glycopro tein (TgsGP) gene, are used by T. b. gambiense. Trypanosomes are transmitted to humans by the tsetse bite, pro liferate, and induce a local inflammatory reaction that is sometimes clinically apparent as a chancre. Trypanosomes then disseminate into the hematolymphatic system, with lymph nodes becoming enlarged after infiltration by mononuclear cells and lymphocytes. The degree of enlargement of the liver and spleen is usually mild to moderate, with infiltration by mononuclear cells as a prominent feature. Trypanosomes multiply in the blood, but their presence and density vary. This variation is mainly due to a cyclic immuneevasion process, whereby the parasite population can be decimated by the host’s immune response until the reemergence of offspring parasites that express a different variant surface glycoprotein to which the immune system is temporarily blind. Each trypanosome genome encodes a repertoire of ~1000 variant surface glycoproteins between which the parasites can switch genetically. Trypanosomes also multiply in extravascular tissues during the first stage of illness. The skin, skeletal muscles, serous membranes (peritoneum, pleurae, and pericardium), and heart can be involved, with interstitial infil tration of mononuclear cells and vasculitis evident on microscopic examination. Myocarditis and pericarditis with myocardial degeneration and interstitial hemorrhage are common features of T. b. rhodesiense infection.

The CNS is invaded weeks to months (T. b. rhodesiense) or months to years (T. b. gambiense) after initial infection. This invasion cor responds to the second stage of HAT, which is defined by the

presence of trypanosomes or mononuclear cells in the cerebrospinal fluid (CSF). The white matter is predominantly affected, with perivascular prolifera tion of astrocytes, microglial cells, and Mott's (morular) cells that contain IgM in intracellular vacuoles. The location of white-matter lesions in the brain correlates with the main neurologic clinical features. The cere bral cortex and neurons are spared until the terminal stages of illness. Because reversible inflammatory lesions predominate over the irrevers ible destruction of tissue, neuropsychiatric symptoms and signs resolve partially or completely during or after treatment of second-stage HAT.

APPROACH TO THE PATIENT Human African Trypanosomiasis HAT is usually lethal in the absence of treatment. Therefore, early diagnosis is crucial; physicians should include HAT in the dif ferential diagnosis of several clinical syndromes when a patient has traveled or lived in at-risk sub-Saharan African countries, and obtaining a thorough recent and remote travel history from the patient is a prerequisite for diagnosis. In particular, HAT due to

T. b. gambiense should be suspected in patients with persistent and intermittent fever or headaches, progressive neuropsychiatric dis orders, and biologic signs of systemic inflammation, even if the last exposure occurred several years previously. HAT due to T. b. rhod esiense should be suspected in patients with an acute febrile illness and a recent exposure to tsetse flies in an eastern African country, especially if diagnostic tests for malaria are negative. PART 5 Infectious Diseases ■ ■CLINICAL MANIFESTATIONS The clinical presentations of T. b. gambiense and T. b. rhodesiense HAT usually differ. T. b. gambiense HAT is a slowly evolving illness with a long incubation period (months to years) and a prolonged disease course. In contrast, T. b. rhodesiense HAT is an acute febrile illness with a short (<3-week) incubation period and a shorter (weeks to months) disease course. There are exceptions to this classic pattern. Acute forms of T. b. gambiense HAT have been reported, especially among travelers, and chronic forms of T. b. rhodesiense HAT occur in the southern range of its geographic distribution (e.g., Zambia and Malawi). Trypano-resistance (i.e., self-resolving first-stage infections) and trypano-tolerance (i.e., the long-term persistence of parasites [e.g., in the skin] without clinical features of disease) have been reported for T. b. gambiense. Concomitant HIV co-infection does not seem to pre dispose individuals to an increased risk of HAT, and the impact of the virus on the clinical presentation of HAT is not known. T. b. gambiense The occurrence of trypanosomal chancre is reported in a sizeable proportion of travelers, but very rarely in patients living in endemic areas, where the nonpurulent, painful, and itchy nodule can easily be confused with a lesion caused by the bite of another arthro pod. The chancre spontaneously disappears in 1–3 weeks. SYSTEMIC FEATURES After an asymptomatic incubation period that usually lasts for weeks or months but occasionally lasts for years, patients may present with irregular and remittent fever, sometimes accompanied by fatigue, malaise, and myalgia. Fever is more frequent among travelers than among natives, but the absence of fever in no way rules out the disease. Circinate or serpiginous rashes, commonly called trypanids, can occur on the trunk and on proximal parts of the extremities. Trypanids are almost impossible to detect on dark skin and have been reported only in Caucasians. Pruritus is a common but non specific symptom that affects up to half of patients during the second stage. Painless edema of the face and extremities occasionally occurs during the first phase. Enlarged lymph nodes—a classic sign of HAT—are detected in 38–85% of patients at both disease stages. Cervical palpation is essen tial in patients with suspected HAT. The lateroposterior cervical group (Winterbottom sign) and the supraclavicular group are most commonly

affected. Lymph nodes are movable, soft initially, harder later, and pain less. A variable proportion of patients present with mild to moderate hepatomegaly and splenomegaly. Signs of myocarditis and pericarditis are occasionally detected by ECG and echocardiography but are usu ally clinically silent. Symptoms of HAT may mimic hypothyroidism or adrenal insufficiency, but thyroid and adrenal function tests yield normal results. Loss of libido, impotence, and amenorrhea, with decreased levels of testosterone and estradiol, are common in second-stage patients and are most likely caused by dysfunction of the hypothalamic–pituitary axis. NEUROPSYCHIATRIC FEATURES Most patients with second-stage ill ness have no or only mild specific neuropsychiatric symptoms and signs, which, when they develop, tend to do so late in the disease course. In contrast, some nonspecific features, such as headaches and mood and behavioral changes, are present in both disease stages but become more permanent and severe during the second stage. As mentioned earlier, HAT is commonly called “sleeping sickness” because of various sleep disturbances (daytime somnolence, nocturnal insomnia) that are more pronounced late in the second stage. Dysregulation of the daily sleep/ wake cycle and fragmentation of sleeping patterns are characteristic. Depending on the area of the brain affected, various neurologic syn dromes also can develop, including disorders that are pyramidal-related (e.g., motor weakness, rare instances of hemiplegia), extrapyramidalrelated (e.g., rigidity, paratonia), and cerebellar-related (e.g., ataxia, abnormal gait). Fine tremor, resting myoclonus, and abnormal (athetoid or choreic) movements also have been reported. Mental disorder is a key feature of HAT and can easily be misdiagnosed as primary psychiatric ill ness. Common presentations are antisocial or aggressive behavior, mood disorders (e.g., irritability, indifference), apathy or hyperactivity, and depression or psychosis (e.g., delirium, hallucinations). In the final stage of illness, decreased consciousness, dementia, and sometimes epilepsy are present, leading to coma, bed sores, aspiration pneumonia, or other bacterial infections and ultimately to death. T. b. rhodesiense The clinical presentation of T. b. rhodesiense HAT can be similar to that of T. b. gambiense HAT in areas (e.g., Zambia, Malawi) that characteristically harbor specific parasite genotypes and host factors. The typical acute form with an incubation period of <3 weeks generally occurs in the northern range of the disease’s distribution (e.g., Tanzania, Uganda) and in travelers. The initial try panosomal chancre is clinically similar to that seen in T. b. gambiense HAT but is more common, especially among travelers. SYSTEMIC FEATURES Fever can be high and occurs in both first- and second-stage patients, often in association with headaches and with diffuse myalgia and arthralgia. Pruritus and edema of the face and legs can be present. Lymphadenopathies have been reported in variable proportions in both disease stages and predominately affect the submandibular, axillary, and inguinal regions. Mild to moderate hepatomegaly and splenomegaly are documented in a minority of patients. Myocarditis and pericarditis appear to influence clinical course and outcome, even though clinical features of cardiac fail ure or arrhythmia have not been prominent findings in large case series. In contrast, conduction abnormalities, with various degrees of atrioventricular block, have been reported in travelers. Sepsis-like features, with disseminated intravascular coagulation and multipleorgan failure, can occur in the terminal stage. NEUROPSYCHIATRIC FEATURES Neuropsychiatric symptoms and signs in T. b. rhodesiense HAT are reported with varying frequency but overall are similar to those described above for T. b. gambiense HAT. The notable exception in T. b. rhodesiense disease is a more rapid evolu tion toward coma and death. ■ ■DIAGNOSIS The clinical and biologic features of T. b. gambiense and T. b. rhodesiense HAT—anemia, thrombocytopenia, elevated levels of C-reactive protein and IgM—are not sufficiently specific, and current drug regimens are not sufficiently practical to allow the initiation of treatment solely on the basis of suspicion. Diagnostic confirmation is therefore required in all patients.

T. b. gambiense The diagnosis of T. b. gambiense HAT is based on a three-step approach: screening, diagnostic confirmation, and staging. SCREENING Immunologic (serologic) methods constitute the pre ferred screening tool. The card agglutination test for trypanosomiasis (CATT) has been used in most endemic areas for several decades. The test reagent contains stained, freeze-dried trypanosomes of selected variable-antigen types. If specific antibodies are present in the patient's blood or serum, agglutination can be seen with the naked eye. The sensitivity of the CATT on undiluted blood or serum is 69–100% (>90% in most studies), with some regional variation; its specificity is 84–99%. The CATT and associated equipment (e.g., a rotator) are manufactured and distributed by the Institute of Tropical Medicine in Antwerp, Belgium, but are not widely available outside endemic areas. In recent years, lateral flow tests have been developed and commercial ized, first based on whole parasites and later on recombinant antigens. Their diagnostic performance is comparable to that of the CATT. Other serologic test formats (ELISA, immunofluorescence, indirect hemagglutination) are available in some reference laboratories in both endemic and nonendemic countries. DIAGNOSTIC CONFIRMATION The microscopic observation of try panosomes in the lymph, blood, skin, or CSF confirms the diagnosis. Direct observation of motile trypanosomes on a wet preparation of lymph obtained by cervical lymph node puncture is simple and cheap but has limited sensitivity (50–65% in most studies). Trypanosomes can be found in the blood but often occur at low densities. Therefore, stained thin and thick blood smears have very low sensitivity. Sensitiv ity is improved (to 40–60% in most studies) with the microhematocrit centrifugation technique, which is based on microscopic examination of the buffy coat after centrifugation of four to six microhematocrit tubes. The most sensitive method (~90%) is the miniature anionexchange centrifugation technique, which is based on the visualization of trypanosomes in eluate after the passage of a large volume (500 µL) of blood through an anion-exchange column and subsequent centrifu gation. Trypanosomes can also be visualized on microscopic examina tion of skin biopsies, even when parasites have not been visualized in the blood or lymph node. STAGING Staging is based on the examination of CSF obtained by lum bar puncture. Second-stage HAT is defined by the presence in CSF of a raised leukocyte count (>5/µL) and/or of trypanosomes. The latter can be detected in the cell-counting chamber or, preferably, after centrifuga tion of the CSF. Staging is no longer an obligatory step in settings where fexinidazole is used as first-line treatment for both first- and secondstage HAT patients, except for young children (<6 years or weighing <20 kg) and for patients with neuropsychiatric symptoms and signs consistent with severe HAT, i.e., mental confusion, abnormal behavior, logorrhea, anxiety, ataxia, tremor, motor weakness, speech impairment, abnormal gait or movements, or seizures (see "Treatment," below). Several molecular methods based on PCR or loop-mediated isother mal amplification have been developed, mostly based on the detection of multiple-copy DNA targets of the Trypanozoon group (to which T. brucei belongs) or the single-copy TgsGP gene of T. b. gambiense. None of these methods has been fully validated for diagnostic pur poses, and a positive result of their application to blood should be interpreted as suspected rather than confirmed HAT. Molecular meth ods applied to CSF (to detect biomarkers) have not proved more accu rate than classic methods for staging and have yielded false-positive results in a substantial proportion of cases. T. b. rhodesiense The diagnosis of T. b. rhodesiense HAT is usually simpler because parasites are more numerous in body fluids. They can occasionally be visualized in a chancre aspirate. In light of the lack of available serologic tests and the high sensitivity of parasite detection methods in blood, wet mounts, thin/thick smears (Fig. 234-4), and the microhematocrit or other concentration techniques are used for both screening and confirmation. Because the modalities of treatment of T. b. rhodesiense are stage dependent, staging remains an

obligatory step, and the definition and methods used are the same as for T. b. gambiense HAT.

FIGURE 234-4 Trypanosoma brucei rhodesiense in blood (thin smear, Giemsa stain). (Credit to the DPDx team, U.S. Centers for Disease Control and Prevention, Atlanta.) TREATMENT Human African Trypanosomiasis The management of HAT is based on general supportive therapy (e.g., rehydration, pain management), treatment of concomitant infections (e.g., malaria, pneumonia), and antiparasitic treatment. The modalities of antitrypanosomal treatment depend on the Trypanosoma species, the stage of illness, and the presence of

contraindications (Table 234-4). T. B. GAMBIENSE Fexinidazole, a nitroimidazole compound, is the first effective oral treatment against HAT. It is administered with food for 10 days, divided into a 4-day loading phase and a 6-day maintenance phase. It is highly effective (>95% cure rate) in patients with firststage and nonsevere second-stage HAT, the latter being defined as

<100 leukocytes/μL in the CSF. Fexinidazole is associated with a lower cure rate (87%) in patients with severe second-stage (≥100 leukocytes/μL in the CSF) HAT. The most relevant adverse reactions reported in clinical trials are vomiting, headache, and neuropsychiatric disorders (e.g., insomnia, anxiety, agitation). Fexi nidazole is contraindicated in patients with hepatic insufficiency or at increased risk of QT interval prolongation. In the absence of safety and efficacy data, it remains contraindicated in small children (<6 years and/or weighing <20 kg). CHAPTER 234 Chagas Disease and African Trypanosomiasis Pentamidine isethionate is highly effective (>95%) against firststage T. b. gambiense HAT and is an excellent alternative to fexi nidazole when the latter is contraindicated or not available. It is generally well tolerated and can therefore be administered in peripheral health care centers in endemic countries (Fig. 234-5). Hypotension after injection is common but generally mild. Hypo glycemia or hyperglycemia occasionally occurs, but permanent dia betes is very rare. Severe adverse events, such as acute pancreatitis and anaphylaxis, occur extremely rarely. Nifurtimox–eflornithine combination therapy is very effective (>95% cure rate) and safe in patients with second-stage HAT, including patients with severe (≥100 leukocytes/μL in the CSF) illness. Common adverse reactions include gastrointestinal distur bances (nausea, vomiting, abdominal pain), headache, anorexia, and reversible bone marrow toxicity (anemia, leukopenia). Convul sions and psychosis are reported in <5% of patients. Acoziborole, administered orally as a single-dose treatment (three tablets), cured >95% of 208 patients age >15 years with first- and second-stage HAT. Provided that its efficacy and safety is confirmed in a higher number of individuals, acoziborole could become the preferred treatment for T. b. gambiense HAT in the future.

TABLE 234-4 Treatment of Human African Trypanosomiasis (HAT) FIRST-LINE TREATMENT DISEASE AND STAGE ALTERNATIVE TREATMENT DRUG(S) AND ROUTE DOSE AND DURATION T. b. gambiense HAT First stage Fexinidazole PO ≥35 kg: 1800 mg for 4 days, followed by 1200 mg for 6 days 20–34 kg: 1200 mg for 4 days, followed by 600 mg for 6 daysa Nonsevere second stage (6–99 leukocytes/μL in the cerebrospinal fluid [CSF]) Fexinidazole PO ≥35 kg: 1800 mg for 4 days, followed by 1200 mg for 6 days 20–34 kg: 1200 mg for 4 days, followed by 600 mg for 6 daysa Severe second stage (≥100 leukocytes/μL in the CSF) Eflornithine IV + nifurtimox PO Eflornithine: 200 mg/kg bid for 7 days Nifurtimox: 5 mg/kg tid for 10 days T. b. rhodesiense HAT First stage Suramin IV 4–5 mg/kg on day 1 followed by 5 weekly injections of 20 mg/kg (e.g., days 3, 10, 17, 24, 31)c Pentamidine isethionate IM or IVb: 4 mg/kg per day for 7 days Second stage Melarsoprol IV 2.2 mg/kg per day

for 10 days — aFexinidazole should not be administered in children <6 years and weighing <20 kg. bFor IV administration, slow infusion (60–120 min) should be used. cThe maximal dose is 1 g per injection; the drug should be diluted in distilled water. Sources: Control and surveillance of human African trypanosomiasis: Report of a WHO Expert Committee. WHO Technical Report Series 984, 2013; WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. August 2019; https://www.who.int/publications/i/item/9789241550567. T. B. RHODESIENSE Suramin has been used for >90 years and remains the first-line treatment for first-stage T. b. rhodesiense HAT. Common adverse events are pyrexia and nephrotoxicity, which is usually mild and reversible but necessitates surveillance of albuminuria and renal function before each dose. PART 5 Infectious Diseases Because eflornithine is ineffective against T. b. rhodesiense, melar soprol, an arsenic-based derivative, remains in use for second-stage T. b. rhodesiense HAT. Reactive encephalopathy is a life-threatening adverse event that occurs in 5–18% of patients, with an associated mortality rate of 10–70%. The efficacy of concomitant high-dose prednisolone to prevent reactive encephalopathy in patients with T. b. rhodesiense HAT is not known. Other severe but less frequent adverse reactions to melarsoprol include exfoliative dermatitis, FIGURE 234-5 Intramuscular injection of pentamidine by a nurse in a village health center, Province Orientale, Democratic Republic of the Congo.

Pentamidine isethionate IM or IVb: 4 mg/kg per day for 7 days Eflornithine: 200 mg/kg bid for 7 days plus Nifurtimox: 5 mg/kg tid for 10 days Fexinidazole: ≥35 kg: 1800 mg for 4 days, followed by 1200 mg for 6 days 20–34 kg: 1200 mg for 4 days, followed by 600 mg for 6 daysa bloody diarrhea, peripheral neuropathy, renal dysfunction, and liver toxicity. Phlebitis is common, as is soft tissue necrosis if the drug is accidentally given paravenously. The 10-day fexinidazole oral treatment regimen (see above for T. b. gambiense HAT) was recently studied as an alternative to suramin and melarsoprol in Malawi and Uganda. Fexinidazole was administered in 45 patients with first-stage (n = 10) and secondstage (n = 35) patients and cured 43 (96%). ■ ■PROGNOSIS Provided that treatment guidelines are properly followed, >95% of patients with first-stage and second-stage T. b. gambiense HAT are definitively cured with fexinidazole, pentamidine, and nifurtimox– eflornithine combination therapy. The overall case–fatality rate is <1% except in very advanced cases. Because relapses can occur long after completion of treatment, follow-up visits are advised every 6 months for at least 2 years. If clinical features of HAT are present, both blood and CSF examinations are indicated. Patients with second-stage T. b. rhodesiense HAT are at a 5–10% risk of dying during or after melarsoprol treatment, but relapses are very rare. ■ ■GLOBAL CONSIDERATIONS The elimination of sleeping sickness as a public health problem has been achieved, thanks to increased control activities run by national control programs and nongovernmental medical organiza tions, improved funding, and the end of several civil wars (e.g., in Angola) in the past 20 years. Funding for research, development, and implementation of improved diagnostic (e.g., rapid diagnostic tests), therapeutic (e.g., oral drugs), and vector control tools remains crucial to sustain recent achievements and to move on to the next objective, i.e., the global elimination of transmission by 2030. ■ ■FURTHER READING Bern C et al: Chagas disease in the United States: A public health approach. Clin Microbiol Rev 33:e00023-19, 2019. Büscher P et al: Human African trypanosomiasis. Lancet 390:2397, 2017. de Sousa AS et al: Chagas disease. Lancet 403:203, 2024. Lindner AK et al: New WHO guidelines for treatment of gambiense human African trypanosomiasis including fexinidazole: Substantial changes for clinical practice. Lancet Infect Dis 20:e38, 2020. Urech K et al: Sleeping sickness in travelers—Do they really sleep? PLoS Negl Trop Dis 5:e1358, 2011.

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