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Amanita phalloides Mushroom Poisonings — Northern California, December 2016

Kathy T. Vo, MD[1,2]; Martha E. Montgomery, MD[3]; S. Todd Mitchell, MD[4]; Pieter H. Scheerlinck, MD[5,6]; Daniel K. Colby, MD[5,6]; Kathryn H. Meier, PharmD[2,7]; Susan Kim-Katz, PharmD[2,7]; Ilene B. Anderson, PharmD[2,7]; Steven R. Offerman, MD[8]; Kent R. Olson, MD[2]; Craig G. Smollin, MD[1,2]

Amanita phalloides, colloquially known as the "death cap," belongs to the Phalloideae section of the Amanita family of mushrooms and is responsible for most deaths following ingestion of foraged mushrooms worldwide (*1*). On November 28, 2016, members of the Bay Area Mycological Society notified personnel at the California Poison Control System (CPCS) of an unusually large *A. phalloides* bloom in the greater San Francisco Bay Area, coincident with the abundant rainfall and recent warm weather. Five days later, CPCS received notification of the first human *A. phalloides* poisoning of the season. Over the following 2 weeks, CPCS was notified of an additional 13 cases of hepatotoxicity resulting from *A. phalloides* ingestion. In the past few years before this outbreak, CPCS received reports of only a few mushroom poisoning cases per year. A summary of 14 reported cases is presented here. Data extracted from patient medical charts revealed a pattern of delayed gastrointestinal manifestations of intoxication leading to dehydration and hepatotoxicity. Three patients received liver transplants and all but one recovered completely. The morbidity and potential lethality associated with *A. phalloides* ingestion are serious public health concerns and warrant medical provider education and dissemination of information cautioning against consuming foraged wild mushrooms.

Initial case. A man aged 37 years (patient A) picked two wild mushrooms in Santa Rosa, California (Table). He cooked and ate one mushroom, and approximately 10 hours later developed nausea, vomiting, and diarrhea. He was evaluated in a local emergency department (ED) for abdominal discomfort 20.5 hours after ingestion. A mycologist identified the uncooked mushroom sample provided by the patient as *A. phalloides*. Initial laboratory findings were notable for an elevated white blood cell count with lactate elevation and elevated creatinine suggesting dehydration (Table). Liver function tests (LFTs) 6 hours later showed elevated aspartate aminotransferase (AST) (92 IU/L; normal = 15–41) and alanine aminotransferase (ALT) (95 IU/L; normal = 17–63) levels. He was treated with aggressive intravenous (IV) fluid hydration, IV octreotide,* and IV silibinin.† Two days after ingestion, the patient's LFTs peaked at AST = 6,159 IU/L, ALT = 3,084 IU/L, total bilirubin = 2.9 mg/dL (normal = 0.2–1.2), and international normalized ratio (INR) (standardized prothrombin time) 3.2 units (normal = 0.8–1.2). Gastrointestinal symptoms and laboratory values gradually improved, and the patient was discharged home on day 6.

*Octreotide, by preventing emptying of the gallbladder, might reduce recirculation of amatoxins in bile to the liver.
†Silibinin dihemisuccinate, a milk thistle extract, competitively inhibits hepatic amatoxin uptake and enterohepatic recycling, and is available in the United States through an open clinical trial.

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Household cluster. A woman aged 26 years (patient B) prepared and grilled wild mushrooms for dinner for her husband (patient C, 28 years), her daughter (patient D, 18 months), her sister (patient E, 38 years), and a female friend (patient F, 49 years). The mushrooms had been given to her by a person she did not know, who reportedly picked them earlier in the day in the mountains. The mother, father, and child ate four, three, and one-half mushroom caps, respectively; the mother's sister ate one cap and stalk, and the friend ate "pieces."

All persons who consumed the mushrooms developed nausea, vomiting, and diarrhea approximately 9 hours after ingestion. The mother, father and child (patients B, C, and D) visited the ED 20 hours after ingestion with dehydration and gastrointestinal distress. All patients had laboratory values consistent with hepatic injury (Table). The patients were treated with aggressive IV fluid hydration, IV octreotide, and IV silibinin. Two days after ingestion of the mushrooms, the mother's LFTs peaked at AST 11,427, ALT 9,693, total bilirubin 2.4 mg/dL, and INR 3.2 units. The father's LFTs peaked on hospital day 1 with AST 6,123 IU/L, ALT 4,401 IU/L, and total bilirubin 2.8 on hospital day 2. Both parents' symptoms improved, and they were discharged on hospital days 6 and 4, respectively. The child developed irreversible fulminant hepatic failure and required mechanical ventilation because of hepatic encephalopathy. She underwent a liver transplant 6 days after ingestion of the mushroom with a complicated postoperative course that included cerebral edema and permanent neurologic impairment.

The sister of the woman who prepared the meal (patient E) visited the ED before her other family members, but was discharged home after administration of IV fluids and antiemetic medications, with a diagnosis of gastroenteritis. She returned to the ED the following day with persistent nausea, vomiting, diarrhea, and abdominal cramping. At that time, her AST was 1,712 IU/L, ALT 1,025 IU/L, total bilirubin 2.0 mg/dL, and INR 1.8 units. She was treated with aggressive IV fluid hydration, IV octreotide, and IV silibinin, as well as the placement of a biliary drain, but developed irreversible fulminant hepatic failure and underwent liver transplant on hospital day 4, with subsequent improvement of her hepatic function.

The family friend (patient F) visited an ED 2 days after ingestion of the mushrooms, complaining of abdominal pain, nausea, vomiting, and diarrhea. On hospital day 1, her LFTs peaked at AST 11,940, ALT 11,350, and INR 4.5. She was treated with aggressive IV fluid hydration, IV octreotide, and IV silibinin. Her hepatic function recovered, and she was discharged home on hospital day 6.

Additional cases. In the subsequent 2 weeks, CPCS was notified of eight additional cases of acute liver injury after consumption of wild mushrooms in northern California counties (Table). One case involved a man aged 36 years who had ingested mushrooms, later confirmed to be *A. phalloides*, obtained from a friend who picked them during a hike. Another case occurred in a man aged 56 years who was evaluated at an ED 2 days after ingestion of foraged mushrooms and required a liver transplant; two cases occurred in women aged 86 and

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TABLE. Demographic and clinical data for 14 patients reported to the California Poison Control System after *Amanita phalloides* ingestion — Northern California, December 2016

Patient	Age (yr.)	Sex	Mushrooms ingested	Ingestion to symptom onset (hrs)	Ingestion to hospital admission (hrs)	Initial lactate (mmol/L)*	Initial BUN/Cr† (mg/dL)	Initial AST/ALT§ (U/L)	Peak AST/ALT, INR (units)¶	Hospitalization duration (days)	Outcome
A	37	M	1 (stalk and cap)	10	20	5.2	27/1.4	31/40	3084/6159, 3.2	6	Recovered
B**	26	F	4 caps	9	20	5.87	21/0.64	51/45	11427/9693, 3.2	6	Recovered
C**	28	M	3 caps	9	23	2.98	20/1.46	444/454	6123/4401, 1.4	6	Recovered
D**	1.5 (18 mo.)	F	½ cap	9	19	9.22	16/<0.38	70/47	14300/10200, 10.2	36	Liver transplant, permanent neurologic impairment
E**,††	38	F	1 (stalk and cap)	9	48	7.0	24/0.8	1712/1025	9573/6239, 13.3	13	Liver transplant, recovered
F**	49	F	"Pieces"	9	48	6.72	95/2.24	1038/1100	11940/11350, 4.5	6	Recovered
G	36	M	½ cap	7	12	1.5	18/0.6	32/29	1858/3526, 1.6	5	Recovered
H	56	M	Multiple 8–10 cm caps	12	64	5.4	62/2.33	1599/3200	2820/5599, >13.3	16	Liver transplant, recovered
I	86	F	Unknown	Unknown	~48	Not drawn	64/1.11	768/1084	768/1084, 1.7	3	Recovered
J	93	F	Unknown	Unknown	~48	1.4	64/2.74	765/672	1497/1994, 1.8	9	Recovered
K	19	M	4 caps	12	29	Not drawn	18/0.92	89/151	113/184, 1.2	5	Recovered
L	19	M	8 caps	9	21	1.7	23/1.95	27/29	1404/2544, 2.1	5	Recovered
M††	22	M	2 "shots" of mushroom juice and 3 (stalk and cap)	<12	64	3.2	24/1.31	887/1326	2044/3351, 5.2	9	Recovered
N	22	M	1 "shot" of mushroom juice	4	64	1.7	18/0.94	6344/6400	6344/6400, 2.5	6	Recovered

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; Cr = creatinine; F = female; INR = international normalized ratio; M = male.

* Normal lactate = 0.5–2.2 mmol/L.

† Normal BUN = 7–20 mg/dL; normal Cr = 0.8–1.2 mg/dL.

§ Normal AST = 15–41 U/L; normal ALT = 17–63 U/L.

¶ Normal INR = 0.8–1.2 units.

** Part of a single household cluster of 5 patients.

†† Discharged from initial hospital with diagnosis of gastroenteritis.

93 years who received wild-picked mushrooms from a friend; and four men aged 19–22 years who developed hepatotoxicity after ingesting what they thought were psychedelic mushrooms picked from the wild. Most of these patients had recovery of hepatic function.

Discussion

Over the course of 2 weeks in December 2016, CPCS investigated 14 suspected *A. phalloides* ingestions in five northern California counties. Eleven patients recovered, although three required liver transplants because of irreversible fulminant hepatic failure. One of those patients, a child, developed cerebral edema and suffered permanent neurologic sequelae.

Amatoxins, consisting of alpha, beta, and gamma amanitin, account for >90% of deaths related to mushroom poisoning worldwide (*1*). *A. phalloides* contains the alpha variety of amanitin, a cyclic octapeptide thought to be the primary agent of toxicity in humans (*2*). The amanitins are heat stable and are not inactivated by cooking. Once ingested, amatoxin is readily absorbed from the gastrointestinal tract into the portal circulation where it is taken up by hepatocytes, binding to DNA-dependent RNA polymerase (II) and halting intracellular protein synthesis, ultimately resulting in cell death (*3*). A lethal dose can be as low as 0.1 mg/kg, and a single mushroom can contain up to 15 mg (*1*). The clinical course of amatoxin poisoning is described in three phases: delayed gastroenteritis with significant body fluid volume loss (after a postingestion latency of 6–24 hours), symptomatic recovery (24–36 hours after ingestion), and fulminant hepatic and multiorgan failure (typically 3–5 days after the ingestion) (*4*). Patients who are evaluated early in the course of their illness might be discharged home only to return later with indications of liver failure, contributing to the relatively high case fatality rate (10%–20%) (*5*,*6*). Initial treatment emphasizes early supportive care including aggressive fluid and electrolyte replacement. In the event of irreversible fulminant liver failure, liver transplant might be required. A variety of therapies including multidose activated charcoal, high-dose penicillin, N-acetylcysteine, cimetidine, biliary drainage, and octreotide have been attempted with no definitive evidence of efficacy. Uncontrolled observational

studies of *Amanita* intoxication suggest that the early use of silibinin, a milk thistle derivative, is associated with a reduction in mortality when compared with historical controls (*7*); however, as with the other aforementioned therapies, evidence supporting efficacy is lacking because of difficulties associated with conducting randomized controlled trials. Intravenous silibinin is licensed in Europe, and a clinical trial to evaluate its efficacy in treatment of hepatic failure induced by *Amanita* mushroom poisoning is currently underway in the United States.[§] The majority of silibinin-treated patients in this report received the drug as participants of this trial.[¶] Medical providers should contact the regional poison control center or a medical toxicology consultant to assist in the management of any patient with suspected amatoxic mushroom ingestion.

In California, *A. phalloides* species grow in a symbiotic relationship with coast live oak and other hardwood trees (*8*). They can be especially abundant in the early wet winter months, though the foggy coastal climate and warmer temperatures can support mushroom growth throughout the year (*4*). In 2016, local mycologists noted an abundance of wild mushroom growth, and California county health departments reported an increase in the incidence of mushroom poisoning (*9*). Although weather conditions and increased numbers of *A. phalloides* poisonings do not prove a cause and effect relationship, early seasonal rainfall and warmer subsequent temperatures made a substantial contribution to mushroom proliferation. In addition, a general increase in naïve foraging and wildcrafting (i.e., gathering plant material from its native environment for food or medicinal purposes) activities raises risk for poisoning.

Mycologists recommend exercising caution when foraging or purchasing wild mushrooms for consumption. If wild mushrooms are to be consumed, specimens should first be examined, identified, and deemed edible by an experienced mycologist (*4*). Prompt identification of mushroom-related toxic symptoms in the ED and early, aggressive IV volume replacement are critical first steps in diminishing the significant morbidity and mortality associated with amatoxin ingestion. Antidotal therapies might also be considered in conjunction with a consultant experienced in hepatotoxic mushroom poisoning. In patients with severe poisoning, early contact with the nearest liver transplant center is recommended. Response to this outbreak included the notification of the local counties and state department of public health, which subsequently issued a widely distributed press release (*9*). Measures to disseminate information regarding the dangers of *A. phalloides* ingestion are ongoing.

Summary

What is already known about this topic?

Ingestion of *Amanita phalloides* is responsible for a majority of mushroom-related deaths worldwide. Amatoxins, the principal toxic alkaloids found in these fungi, cause cell injury by halting protein synthesis. A possible antidote licensed in most of Europe, intravenous silibinin, is undergoing evaluation by clinical trial in the United States.

What is added by this report?

In December 2016, fourteen cases of *Amanita phalloides* poisoning were identified by the California Poison Control System (CPCS) among persons who had consumed foraged wild mushrooms. In the past few years before this outbreak, CPCS only received reports of a few mushroom poisoning cases per year. All patients in this outbreak had gastrointestinal manifestations of intoxication leading to dehydration and hepatotoxicity. Three patients received liver transplants; all patients recovered, although one (a child) had permanent neurologic impairment.

What are the implications for public health practice?

Wild-picked mushrooms should be evaluated by a trained mycologist before ingestion. Inexperienced foragers should be strongly discouraged from eating any wild mushrooms. Health care providers should be aware of the potential for toxicity after wild mushroom ingestion, that gastrointestinal symptoms mimicking viral gastroenteritis can occur after ingestion and slowly progress to potentially fatal hepatotoxicity, and should contact the local poison center for reporting and assistance with management of these patients.

[§] Intravenous Milk Thistle. (Silibinin-Legalon®SIL) for Hepatic Failure Induced by Amatoxin/Amanita Mushroom Poisoning. https://clinicaltrials.gov/ct2/show/NCT00915681.

[¶] Registration identifier NCT00915681. https://clinicaltrials.gov/ct2/show/NCT00915681.

[1]Department of Emergency Medicine, University of California, San Francisco; [2]California Poison Control System, San Francisco Division; [3]Department of Emergency Medicine, Alameda County Medical Center/Highland Hospital, Oakland, California; [4]Department of Family Medicine, Dignity Health Dominican Hospital, Santa Cruz, California, [5]Department of Emergency Medicine, University of California, Davis; [6]California Poison Control System, Sacramento Division; [7]Department of Clinical Pharmacy, University of California, San Francisco; [8]Medical Toxicology Consultation Service, Kaiser Permanente Northern California.

Corresponding author: Kathy T. Vo, kathy.vo@ucsf.edu, 415-643-3243.

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Strategies for Preventing HIV Infection Among HIV-Uninfected Women Attempting Conception with HIV-Infected Men — United States

Jennifer F. Kawwass, MD[1,2]; Dawn K. Smith, MD[3]; Dmitry M. Kissin, MD[1,2]; Lisa B. Haddad, MD[1,2]; Sheree L. Boulet, DrPH[1]; Saswati Sunderam, PhD[1]; Denise J. Jamieson, MD[1,2]

By the end of 2014, a total of 955,081 persons in the United States (299.5 per 100,000 population) had received a diagnosis of human immunodeficiency virus type 1 (HIV-1) infection (*1*). The annual estimated number of HIV infections and incidence rate in the United States decreased from 2010 to 2014, and the survival rate has increased over time (*1*). Effective highly active antiretroviral therapy (HAART) is helping persons with HIV to live longer, healthier lives. Many of these persons, including an unknown percentage in discordant relationships (i.e., one partner is HIV-infected, and the other is HIV-uninfected), might wish to have their own biologic children. When the female partner is HIV-infected and the male partner is not, a discordant couple can undergo autologous sperm intrauterine inseminations to achieve conception without placing the man at risk for infection. However, for HIV-discordant couples in which the man is HIV-infected and the woman is not, strategies to minimize the risk for sexual transmission are needed. In 1988, CDC recommended against insemination with semen from HIV-infected men (*2*). Since 1988, new information has emerged regarding prevention of HIV transmission in HIV-discordant couples. This report reviews laboratory and epidemiologic information regarding the prevention of HIV transmission for HIV-discordant couples, in which the male is HIV-infected and the female is HIV-uninfected, who would like to attempt conception.

Insemination with sperm from an HIV-negative donor is the safest option for an HIV-uninfected woman to conceive with an HIV-infected male partner. However, risk-reducing approaches using sperm from an HIV-infected male partner do exist. One strategy is the use of viral suppression with HAART for the male partner, with intercourse without condom protection limited to the time around ovulation, while the female partner is taking daily oral antiretroviral preexposure prophylaxis (PrEP) (*3*). Another strategy that can be used in conjunction with HAART and PrEP is collection and washing of the male partner's sperm to remove cells infected with HIV, followed by testing to confirm the absence of HIV prior to intrauterine insemination (IUI) of the female partner or in vitro fertilization (IVF) (*4*). Each method has a unique risk profile, might confer distinctive advantages and disadvantages, and requires varying degrees of assistance from the medical community. Before attempting conception, discordant couples might wish to discuss treatment options with an experienced medical provider who can relay the risks and benefits of each treatment modality as it applies to the couple's specific situation.

Background

The American College of Obstetricians and Gynecologists, the American Society of Reproductive Medicine, and others have published guidance documents that emphasize the importance of considering HIV a chronic disease or disability, which should not result in discrimination and for which fertility treatment should be offered if it is desired (*5*,*6*). Access to treatments that require the assistance of a physician might be limited by financial and legal barriers. These barriers include state laws that preclude the use of HIV-positive sperm or fear of liability if seroconversion occurs, physician reluctance to treat discordant couples, and concerns based on previous publications, including those from CDC, that warned against use of sperm from HIV-infected men for insemination (*2*,*5*–*7*). Whereas HIV-infected men who are currently under the care of a physician are likely already receiving HAART, their sexual partners might or might not be using PrEP.

Rationale and Evidence

For HIV-discordant couples (HIV-infected male and HIV-uninfected female) who want to conceive, considerations in choosing the optimal method to achieve pregnancy include transmission risk, treatment efficacy, and affordability. Use of HIV-negative donor sperm that meets Food and Drug Administration donor eligibility criteria remains the safest option for avoiding HIV infection of the female partner (*2*,*8*). Recent evidence suggests that discordant couples who wish to have their own biologic children might consider using condomless intercourse timed to coincide with ovulation, or IUI or IVF in combination with sperm washing (*4*). Avoidance of HIV transmission is optimized when the male partner is virologically suppressed on HAART and the female partner is on PrEP (*3*). Further considerations apply when the couple has infertility issues. Many men with HIV infection have altered semen parameters that make insemination or IVF the optimal form of fertility treatment (*9*). Moreover, female infertility factors such as tubal disease might warrant a particular treatment, for example, IVF. Thus, testing for potential causes of infertility (such as tubal factors, male factors, and ovulatory dysfunction)

is a reasonable early step in treating all HIV-discordant couples who desire conception.

Condomless intercourse is associated with the highest risk for HIV transmission. The risk for male-to-female transmission in HIV-discordant couples has been estimated as approximately 1–2 per 1,000 episodes of condomless intercourse (*10*). This estimation of risk is based, however, on natural history studies of couples before routine availability of HIV viral load measurements and HAART, and might vary widely with characteristics of the man and woman, including the presence of other sexually transmitted diseases, inflammation within the genital tract, and viral load of the infected partner (*10*). Among men on HAART with undetectable seminal and plasma viral loads, the postulated risk for transmission to a female partner during condomless intercourse is low (0.16 per 10,000 exposures, 95% confidence intervals [CI] = 0.02–1.3) (*10*). However, although some studies suggest a parallel reduction in plasma and semen viral loads (*11*), other evidence suggests that plasma and semen viral loads might not correlate (*12*); men with undetectable plasma viral loads have had virus isolated from their semen (*13*). As a result, men on HAART with undetectable plasma viral loads might still be at some (albeit, very low) risk (1.2 per 100 person-years, CI = 0.9–1.7) for transmitting HIV-1 to their female partner through condomless sexual intercourse (*14*). In addition to viral suppression with HAART, the risk for sexual transmission can be further reduced by minimizing exposure frequency and limiting condomless intercourse to time of ovulation, thereby maximizing the chance of conception, and by use of PrEP by the uninfected partner (*3*).

Recent data exist on the safety of IUI following sperm washing (*4*). Sperm washing methods have evolved to include a two-step process including gradient centrifugation and separation of sperm from semen followed by use of a lymphocyte preparation medium that requires motile sperm to swim up and separate from lymphocytes, which are the largest reservoir of virus in semen (*15*). Whether HIV can infect spermatozoa is not clear; some studies suggest that HIV-1 can infect spermatozoa (*16*,*17*), whereas others refute these findings (*18*,*19*). Testing of the resultant washed specimens by polymerase chain reaction (PCR), real-time PCR (qPCR), and nucleic acid sequence based amplification for HIV RNA have suggested that 92%–99% of specimens of processed semen contain no virus measurable above the limits of detection of the test (*4*,*20*–*23*). Testing the resultant specimen for presence of residual HIV before insemination can identify 1.3%–7.7% of specimens that have been noted to be positive after appropriate washing (*4*,*20*–*24*). These 1.3%–7.7% of washed specimens that test positive even after washing would be discarded and not used for insemination.

Summary

What is already known about this topic?

For HIV-discordant couples (in which the man is HIV-infected and the woman is not HIV-infected) who wish to conceive a biological child, strategies to minimize the risk for sexual transmission are needed. In 1990, CDC recommended against insemination with semen from HIV-infected men.

What is added by this report?

Recent data regarding the safety of semen processing suggest that such processing is a viable option for HIV discordant couples attempting conception. The risk for transmission from an HIV-infected man to an HIV-negative woman is low if appropriate risk-reduction strategies, such as the use of highly active antiretroviral therapy, antiretroviral preexposure prophylaxis, and sperm washing are implemented. Recent evidence suggests that discordant couples might consider condomless intercourse timed to coincide with ovulation or intrauterine insemination of the woman or in vitro fertilization in combination with sperm washing after discussing the risks and benefits of each option with a medical provider.

What are the implications for public health practice?

As further data emerge, the risk profile for each treatment option will be further defined. HIV-discordant couples who desire to conceive might wish to discuss treatment options with a medical provider who can explain the risks and benefits of different treatment modalities as they apply to the couple's specific situation before attempting conception.

Evidence suggests that these newer methods of sperm washing significantly reduce the risk for HIV-1 transmission (*25*,*26*). Approximately 11,500 assisted conception (IUI and IVF) cycles in women without HIV infection using sperm separated from semen of their HIV-infected partners have been reported with zero HIV transmissions to the women or resultant offspring (*4*,*22*,*23*,*27*–*29*). In couples using IUI with sperm washing, risk can presumably be further reduced with the use of HAART by the infected partner and the use of PrEP by the uninfected partner (*3*).

There are some reports of women becoming HIV-infected at some point after IUI; however, the evidence suggests that the infections resulted from subsequent condomless intercourse with their infected partner (*29*). In a 1990 report describing HIV infection in a woman who underwent IUI using processed semen from her HIV-infected husband, CDC recommended against the use of sperm from an HIV-infected partner; the mechanism of sperm preparation at the time was determined to not effectively separate lymphocytes from spermatozoa (*7*). Seroconversion was also reported 4 years after IUI in a woman who was HIV-negative 1 year following the insemination and subsequently had condomless sex with her HIV-infected partner (*29*).

Because of the increased efficacy of IVF compared with IUI or natural conception (*30*), IVF might afford less cumulative risk, since the number of exposures to the infected partner's sperm is likely to be fewer. Risk for HIV transmission per IVF cycle is estimated to be similar to that with IUI (*4*). However, it is unknown whether there is a benefit to IVF compared with IUI in terms of HIV risk reduction that might offset the known surgical risk and financial cost associated with IVF if it is not being used for treatment of infertility. It is also not known whether intracytoplasmic sperm injection might further reduce the risk for transmission. As with IUI, transmission risk associated with IVF can be reduced with sperm washing, use of HAART by the infected male partner, and use of PrEP by the uninfected female partner during periods of potential exposure to HIV-infected sperm (daily while attempting conception, ideally beginning approximately 20 days before exposure) (*3*,*31*).

Conclusion

There is considerable new information about prevention of HIV transmission in HIV-discordant couples since 1990 when CDC recommended against insemination with semen from HIV-infected men (*7*). Insemination with sperm from a donor who does not have HIV infection is the safest option for an HIV-uninfected woman with an HIV-infected male partner to conceive. However, current evidence suggests that the risk for transmission from an HIV-infected male partner to an HIV-uninfected female partner is low if appropriate risk-reduction strategies are implemented. As data regarding the safety and effectiveness of semen processing emerges, the risk profile for each treatment option will be further defined. HIV-discordant couples who desire to conceive might wish to discuss treatment options with a medical provider who can explain the risks and benefits of different treatment modalities as they apply to the couple's specific situation before attempting conception.

[1]Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, CDC; [2]Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia; [3]Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC.

Corresponding author: Jennifer F. Kawwass, jennifer.kawwass@emory.edu, 404-686-3229.

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Trends in Prevalence of Advanced HIV Disease at Antiretroviral Therapy Enrollment — 10 Countries, 2004–2015

Andrew F. Auld, MBChB[1]; Ray W. Shiraishi, PhD[1]; Ikwo Oboho, MD[1]; Christine Ross, MD[1]; Moses Bateganya, MD[1]; Valerie Pelletier, MD[2]; Jacob Dee, MPH[1]; Kesner Francois, MD[3]; Nirva Duval, MD[3]; Mayer Antoine, MD[2]; Chris Delcher, PhD[4]; Gracia Desforges, MD[3]; Mark Griswold, MSc[4]; Jean Wysler Domercant, MD[2]; Nadjy Joseph, MD[3]; Varough Deyde, PhD[2]; Yrvel Desir, MSc[4]; Joelle Deas Van Onacker, MD[3]; Ermane Robin, MD[3]; Helen Chun, MD[1]; Isaac Zulu, MD[1]; Ishani Pathmanathan, MD[1]; E. Kainne Dokubo, MD[1]; Spencer Lloyd, MD[1]; Rituparna Pati, MD[1]; Jonathan Kaplan, MD[1]; Elliot Raizes, MD[1]; Thomas Spira, MD[1]; Kiren Mitruka, MD[1]; Aleny Couto, MD[5]; Eduardo Samo Gudo, MD[5]; Francisco Mbofana, MD[6]; Melissa Briggs, MD[7]; Charity Alfredo, MD[7]; Carla Xavier[7]; Alfredo Vergara, PhD[7]; Ndapewa Hamunime, MD[8]; Simon Agolory, MD[9]; Gram Mutandi, MBChB[9]; Naemi N. Shoopala, MPH[9]; Souleymane Sawadogo, MSc[9]; Andrew L. Baughman, PhD[9]; Adebobola Bashorun, MD[10]; Ibrahim Dalhatu, MD[11]; Mahesh Swaminathan, MD[11]; Dennis Onotu, MD[11]; Solomon Odafe, MD[11]; Oseni Omomo Abiri, MPH[11]; Henry H. Debem[11]; Hank Tomlinson, PhD[11]; Velephi Okello, MD[12]; Peter Preko, MD[13]; Trong Ao, ScD[14]; Caroline Ryan, MD[14]; George Bicego, PhD[1]; Peter Ehrenkranz, MD[15]; Harrison Kamiru, DrPH[16]; Harriet Nuwagaba-Biribonwoha, MBChB[16]; Gideon Kwesigabo, MD[17]; Angela A. Ramadhani, MD[18]; Kahemele Ng'wangu, MD[19]; Patrick Swai, MD[20]; Mohamed Mfaume, MD[21]; Ramadhani Gongo, MD[21]; Deborah Carpenter, MD[21]; Timothy D. Mastro, MD[22]; Carol Hamilton, MD[22]; Julie Denison, PhD[23]; Fred Wabwire-Mangen, MD[24]; Olivier Koole, MD[25]; Kwasi Torpey, PhD[26]; Seymour G. Williams, MD[27]; Robert Colebunders, MD[25]; Julius N. Kalamya, MD[28]; Alice Namale, MD[28]; Michelle R. Adler, MD[28]; Bridget Mugisa, MD[29]; Sundeep Gupta, MD[29]; Sharon Tsui, MPH[23]; Eric van Praag, MD[30]; Duc B. Nguyen, MD[31]; Sheryl Lyss, MD[31]; Yen Le, MD[31]; Abu S. Abdul-Quader, PhD[31]; Nhan T. Do, MD[32]; Modest Mulenga, MD[33]; Sebastian Hachizovu, MBChB[33]; Owen Mugurungi, MD[34]; Beth A. Tippett Barr, DrPH[35]; Elizabeth Gonese, MPH[35]; Tsitsi Mutasa-Apollo, MBChB[34]; Shirish Balachandra, MD[35]; Stephanie Behel, PhD[1]; Trista Bingham, PhD[1]; Duncan Mackellar, DrPH[1]; David Lowrance, MD[21]; Tedd V. Ellerbrock, MD[1]

Monitoring prevalence of advanced human immunodeficiency virus (HIV) disease (i.e., CD4+ T-cell count <200 cells/μL) among persons starting antiretroviral therapy (ART) is important to understand ART program outcomes, inform HIV prevention strategy, and forecast need for adjunctive therapies.*,†,§ To assess trends in prevalence of advanced disease at ART initiation in 10 high-burden countries during 2004–2015, records of 694,138 ART enrollees aged ≥15 years from 797 ART facilities were analyzed. Availability of national electronic medical record systems allowed up-to-date evaluation of trends in Haiti (2004–2015), Mozambique (2004–2014), and Namibia (2004–2012), where prevalence of advanced disease at ART initiation declined from 75% to 34% (p<0.001), 73% to 37% (p<0.001), and 80% to 41% (p<0.001), respectively. Significant declines in prevalence of advanced disease during 2004–2011 were observed in Nigeria, Swaziland, Uganda, Vietnam, and Zimbabwe. The encouraging declines in prevalence of advanced disease at ART enrollment are likely due to scale-up of testing and treatment services and ART-eligibility guidelines encouraging earlier ART initiation. However, in 2015, approximately a third of new ART patients still initiated ART with advanced HIV disease. To reduce prevalence of advanced disease at ART initiation, adoption of World Health Organization (WHO)–recommended "treat-all" guidelines and strategies to facilitate earlier HIV testing and treatment are needed to reduce HIV-related mortality and HIV incidence.

Data from 10 countries that requested and received support for ART program evaluations through CDC and agreed to participate in the analysis were included. Three approaches to sampling and analysis were employed (Table 1). In Haiti, Mozambique, and Namibia, where large, centralized, electronic ART patient monitoring systems are employed, all available data from 2004–2015 were analyzed. In each of these countries, 77%–100% of all ART patients and 67%–100% of all ART facilities were captured in the electronic system. In Nigeria, Swaziland, Vietnam, and Zimbabwe, nationally representative samples of ART facilities were selected, with probability of selection proportional to facility size. In Tanzania, Uganda, and Zambia, investigators purposively selected health facilities to represent the range of ART facilities in each country and ensure that the study remained feasible. Among the seven sample-based surveys, a sample frame of study-eligible ART patients was created at each selected facility, and simple random sampling was used to select the sample of records. Eligibility criteria included initiation of ART ≥6 months before data abstraction, during 2004–2015, and at age ≥15 years. Data were abstracted from ART records onto standardized abstraction forms by trained study personnel. Because of variations in the timing of retrospective data collection for the 10 studies (Table 1), the calendar years of ART initiation included in the analysis varied among the countries.

The CD4+ T-cell count (CD4) measured in the 6 months before ART initiation and closest to the date of ART initiation was considered the baseline CD4. For each of the 10

* World Health Organization. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. http://www.who.int/hiv/pub/guidelines/ctx/en/.

† World Health Organization. The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV. http://apps.who.int/iris/bitstream/10665/193633/1/9789241509633_eng.pdf?ua=1&ua=1.

§ World Health Organization. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. http://apps.who.int/iris/bitstream/10665/44786/1/9789241502979_eng.pdf.

TABLE 1. Summary of study designs to assess trends in prevalence of advanced disease at antiretroviral therapy enrollment — 10 countries, 2004–2015

Stage 1: selection of study sites

Region	Country	Estimated no. ART clinics (yr. of assessment)	Estimated no. adult ART enrollees at ART clinics	No. eligible clinics*	Estimated no. study-eligible adult ART enrollees at eligible clinics	Site sampling technique	No. clinics selected
Southern Africa	Mozambique	379 (2014)	582,000	254	446,379	Census	254
	Namibia	213 (2014)	165,468	213	165,468	Census	213
	Swaziland	31 (2009)	50,767	31	50,767	PPS	16
	Zimbabwe	104 (2008)	103,806	70	93,811	PPS	40
	Zambia	322 (2007)	65,383	129	58,845	Purposive	6
East Africa	Tanzania	210 (2007)	41,920	85	37,728	Purposive	6
	Uganda	286 (2007)	45,946	114	41,351	Purposive	6
West Africa	Nigeria††	178 (2009)	168,335	139	167,438	PPS	35
Caribbean	Haiti	200 (2015)	65,000	191	60,705	Census	191
Southeast Asia	Vietnam	173 (2009)	28,090	120	25,000	PPS	30
Total	—	**2,096**	**1,316,715**	**1,346**	**1,147,492**	—	**797**

Stage 2: selection of study patients

Region	Country	Age-eligibility criteria (age at ART initiation) (yrs)	ART enrollment years covered by analysis	Patient sampling technique at selected clinics	Planned sample size*	No. eligible medical records analyzed	Date of data collection
Southern Africa	Mozambique	≥15	2004–2013	Census	446,379	446,379	Dec 2014
	Namibia	≥15	2004–2012	Census	165,468	165,468	Dec 2013
	Swaziland	≥15	2004–2010	SRS	2,500	2,510	Nov 2011–Feb 2012
	Zimbabwe	≥15	2007–2009	SRS	4,000	3,896†	Jan–Jun 2010
	Zambia	≥18	2004–2009	SRS	1,500	1,214§	Apr–Jul 2010
East Africa	Tanzania	≥18	2004–2009	SRS	1,500	1,421¶	Apr–Jul 2010
	Uganda	≥18	2004–2009	SRS	1,500	1,466**	Apr–Jul 2010
West Africa	Nigeria††	≥15	2004–2011	SRS	3,500	3,496	Dec 2012–Aug 2013
Caribbean	Haiti	≥15	2004–2015	Census	60,705	60,705	Jun 2016
Southeast Asia	Vietnam	≥15	2005–2009	SRS	7,587	7,583§§	Jan–Jun 2010
Total	—	—	—	—	**694,639**	**694,138**	—

Abbreviations: ART = antiretroviral therapy; PPS = probability of selection proportional to size; SRS = simple random sampling.

* To keep sample-based studies feasible, in Zimbabwe, Nigeria, and Vietnam, only facilities with ≥50 adults on ART were eligible for sampling, whereas in Zambia, Uganda, and Tanzania, only facilities that had enrolled ≥300 adults on ART were eligible.

† In Zimbabwe, 23 of 3,919 selected patients with either missing gender (n = 12), or missing outcome (n = 11) were excluded from analysis.

§ In Zambia, among 1,457 records sampled, 243 were excluded because of noncompliance with simple random sampling procedures at one site.

¶ In Tanzania, among 1,458 records sampled, one patient was excluded because of absence of age data at ART initiation, and 36 patients enrolled in 2004 were excluded because of small sample size for 2004.

** In Uganda, among 1,472 records sampled, six patients were excluded because of absence of age data at ART initiation.

†† In Nigeria, implicit stratification was used in the sampling approach.

¶¶ In Vietnam, among 7,587 records sampled, four observations were excluded because information on gender was missing.

countries and for each calendar year, the percentages of adult patients with baseline CD4 <100, <200, and <350 cells/μL are described with percentages and 95% confidence intervals accounting for survey design. Bivariate logistic regression models accounting for survey design were used to evaluate statistical significance of changes in percentages over calendar years, with the likelihood ratio test used to assess departure from linear trend over time. Trends in median baseline CD4 at ART initiation over time are described, and a linear regression model, accounting for survey design, was used to assess statistical significance of changes.

Across the 10 countries, 694,138 adult ART patient records were analyzed from 797 ART facilities (Table 1). The overall percentage of new ART enrollees during 2004–2015 with missing baseline CD4 ranged from 9% in Swaziland to 53% in Zimbabwe. In the three countries providing more recent national electronic medical record data, prevalence of advanced disease at ART initiation declined from 73% to 37% during 2004–2014 in Mozambique, from 80% to 41% during 2004–2012 in Namibia, and from 75% to 34% during 2004–2015 in Haiti (Table 2) (supplemental figure; https://stacks.cdc.gov/view/cdc/45821). In addition, over the same periods, prevalence of CD4 <100/μL declined from 39% to 18% in Mozambique, from 39% to 16% in Namibia, and from 49% to 20% in Haiti. Prevalence of CD4 <350/μL at ART initiation also declined over time in all three countries. Over the same periods, significant increases in median CD4 count at ART initiation were observed in Mozambique (from

TABLE 2. CD4 distribution among adult antiretroviral therapy enrollees, by calendar year of ART initiation — 10 countries, 2004–2015

Country	CD4 distribution	Overall			Year (%)												p-value*
		No.	Total No.	% (95% CI)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
Southern Africa	CD4<100	66,183	282,129	23 (23–24)	39	39	34	31	29	29	28	25	21	18	18	—	<0.001
Mozambique	CD4<200	138,453	282,129	49 (49–49)	73	71	68	65	63	62	58	53	44	38	37	—	<0.001
	CD4<350	233,344	282,129	83 (83–83)	93	90	91	91	90	91	90	89	85	73	71	—	<0.001
	Missing	164,250	446,379	37	42	33	31	30	31	32	32	30	32	39	50	—	—
Namibia	CD4<100	16,724	82,774	20 (20–20)	39	35	29	26	26	22	17	13	16	—	—	—	<0.001
	CD4<200	48,555	82,774	59 (58–59)	80	76	76	75	76	71	58	36	41	—	—	—	<0.001
	CD4<350	77,351	82,774	93 (93–94)	97	95	95	95	95	95	95	91	91	—	—	—	<0.001
	Missing	82,694	165,468	50	72	78	79	76	42	38	37	34	30	—	—	—	—
Swaziland	CD4<100	770	2,296	34 (31–36)	32	50	44	41	39	36	24	—	—	—	—	—	0.035
	CD4<200	1,550	2,296	67 (63–71)	72	87	86	78	77	69	54	—	—	—	—	—	0.028
	CD4<350	2,168	2,296	95 (93–96)	90	98	98	95	97	95	92	—	—	—	—	—	0.592
	Missing	214	2,510	9	33	15	18	5	8	10	5	—	—	—	—	—	—
Zambia	CD4<100	310	849	36 (33–40)	23	36	37	38	33	35	—	—	—	—	—	—	0.792
	CD4<200	601	849	70 (67–74)	77	73	76	67	69	65	—	—	—	—	—	—	0.287
	CD4<350	810	849	96 (94–97)	100	93	95	96	96	95	—	—	—	—	—	—	0.562
	Missing	365	1,214	30	73	57	32	23	16	16	—	—	—	—	—	—	—
Zimbabwe	CD4<100	757	1,820	42 (39–45)	—	—	—	46	40	40	—	—	—	—	—	—	0.092
	CD4<200	1,424	1,820	78 (74–81)	—	—	—	84	75%	75	—	—	—	—	—	—	0.042
	CD4<350	1,767	1,820	97 (95–98)	—	—	—	97	97%	97	—	—	—	—	—	—	0.756
	Missing	2,076	3,896	53	—	—	—	55	50%	55	—	—	—	—	—	—	—
East Africa	CD4<100	432	1,085	41 (37–44)	—	40	50	40	41%	37	—	—	—	—	—	—	0.581
Tanzania	CD4<200	804	1,085	77 (74–80)	—	77	80	79	77%	77	—	—	—	—	—	—	0.994
	CD4<350	1039	1,085	97 (95–98)	—	94	99	97	95%	99	—	—	—	—	—	—	0.132
	Missing	336	1,421	24	—	24	28	22	23%	22	—	—	—	—	—	—	—
Uganda	CD4<100	438	1,166	36 (33–39)	54	50	49	30	30	28	—	—	—	—	—	—	<0.001†
	CD4<200	859	1,166	74 (71–76)	89	85	83	78	67	60	—	—	—	—	—	—	<0.001†
	CD4<350	1,127	1,166	96 (95–97)	99	96	99	95	99	95	—	—	—	—	—	—	0.122
	Missing	300	1,466	20	31	27	23	20	17	16	—	—	—	—	—	—	—
West Africa	CD4<100	884	2,876	31 (27–34)	9	36	40	31	31	32	29	25	—	—	—	—	0.001§
Nigeria	CD4<200	1,792	2,876	63 (59–67)	68	67	77	65	63	66	60	53	—	—	—	—	0.043§
	CD4<350	2,666	2,876	93 (91–94)	96	91	94	92	94	93	92	92	—	—	—	—	0.576
	Missing	620	3,496	18	33	21	20	21	18	13	16	20	—	—	—	—	—
Caribbean Haiti	CD4<100	10,835	47,209	23 (23–23)	49	51	42	32	26	21	23	22	21	19	18	20	<0.001
	CD4<200	20,578	47,209	44 (43–44)	75	79	77	68	55	46	46	42	39	36	32	34	<0.001
	CD4<350	35,306	47,209	75 (74–75)	92	94	94	90	84	86	83	76	72	70	60	59	<0.001
	Missing	25,837	60,705	43	24	36	37	33	37	30	35	31	31	32	33	53	—
Southeast Asia	CD4<100	3,015	5,228	58 (55–60)	—	74	63	58	59	52	—	—	—	—	—	—	0.007
Vietnam	CD4<200	4,384	5,228	84 (81–86)	—	91	87	84	86	80	—	—	—	—	—	—	0.046
	CD4<350	5,038	5,228	96 (95–97)	—	98	97	95	97	96	—	—	—	—	—	—	0.533
	Missing	2,355	7,583	31	—	39	42	36	28	25	—	—	—	—	—	—	—

Abbreviations: ART = antiretroviral therapy; CD4 = CD4+ T-cell count (cells/μL); CI = confidence interval.

* P-value derived from logistic regression, accounting for survey design, comparing the percentage of enrollees below the specified CD4 threshold in the most recent calendar year with the corresponding percentage in the earliest calendar year with data available.

† Specified p-values were derived from logistic regression including calendar year of ART initiation as a continuous variable because of observed linear trend.

§ In Nigeria, the p-value compares percentages in 2006 with percentages in 2011, to best capture recent declines in prevalence of advanced disease.

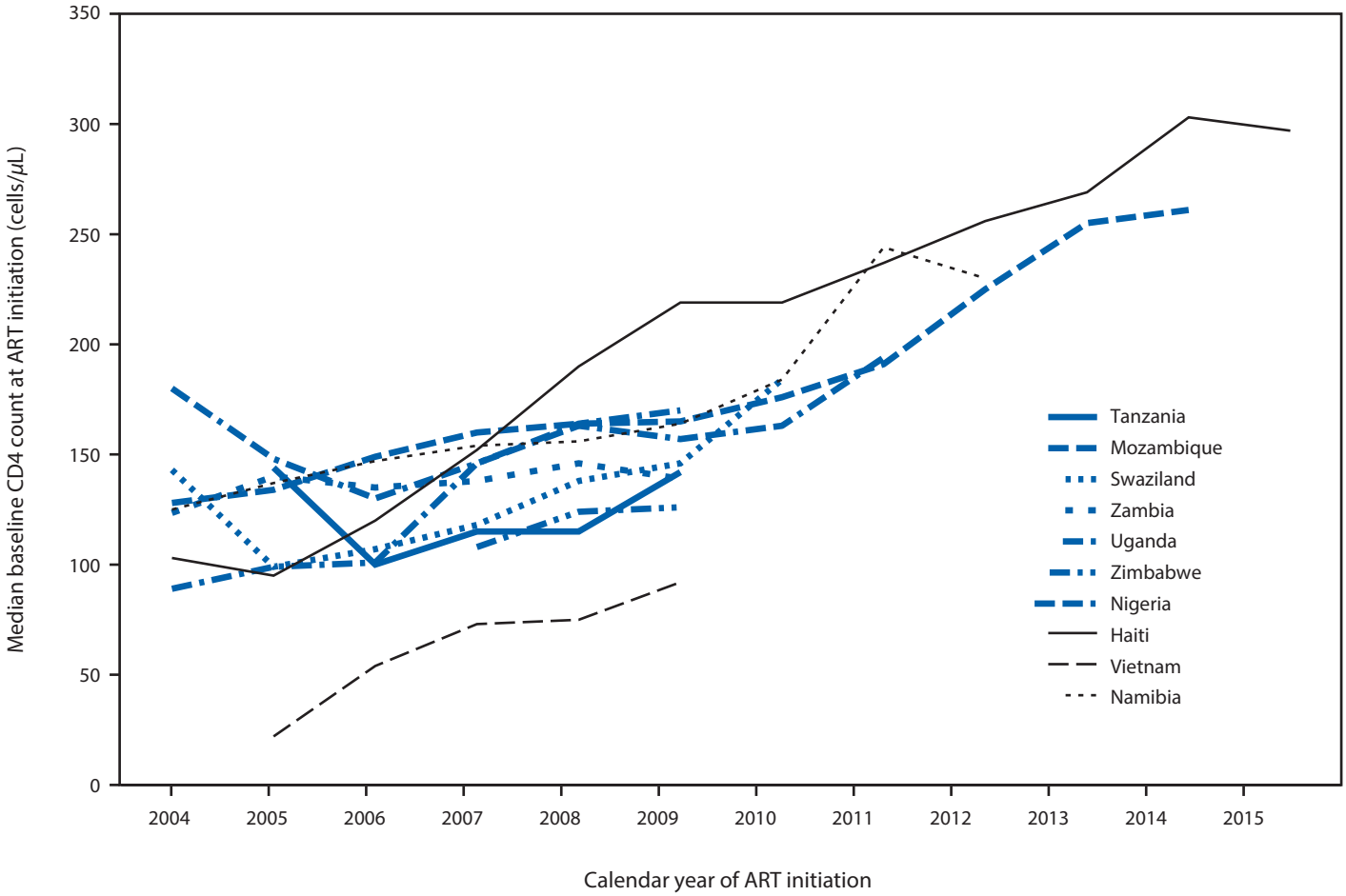
128/μL to 261/μL; p<0.001), in Namibia (from 125/μL to 230/μL; p<0.001), and in Haiti (from 103/μL to 297/μL; p<0.001) (Figure).

In the seven countries with less recent data, statistically significant declines in prevalence of advanced disease were observed in five countries (Table 2). Prevalence of advanced disease at ART initiation declined from 72% to 54% in Swaziland (2004–2010), from 84% to 75% in Zimbabwe (2007–2009), from 89% to 60% in Uganda (2004–2009), from 68% to 53% in Nigeria (2004–2011), and from 91% to 80% in Vietnam (2005–2009) (Table 2) (supplemental figure; https://stacks.cdc.gov/view/cdc/45821). Over the same periods in Swaziland, Uganda, and Vietnam, statistically significant increases in median baseline CD4 from 143/μL to 184/μL (p<0.001), 89/μL to 170/μL (p<0.001), and 22/μL to 92/μL (p = 0.014), respectively, were observed (Figure).

Discussion

This analysis of 694,138 medical records from 10 low- and middle-income countries (LMIC), contributes several findings relevant for ART programs in resource-limited settings. Observed declines in the prevalence of advanced disease at ART initiation in eight countries and increases in median baseline CD4 at ART initiation in six countries are likely due to increasing access to HIV testing and treatment (e.g., increasing numbers of facilities providing testing and treatment services), and increasingly inclusive ART eligibility guidelines (*1*). Despite this encouraging progress, however, a significant

FIGURE. Trends in median CD4+ T-cell count at antiretroviral therapy (ART) initiation — 10 countries, 2004–2015



percentage of ART enrollees still started ART with advanced disease in recent years. In Haiti, which provided the most recent data on ART enrollees for this analysis (2015), and which historically has had higher than average median CD4 at ART initiation compared with other LMIC (Table 2) (*2*,*3*), the percentage of ART enrollees with CD4 <200/μL was 34% in 2015. Similarly, in Mozambique in 2014, 37% of patients started ART with advanced disease. Although recent data from the 10 countries are limited, these data and data from a recent meta-analysis, which reported mean CD4 count at ART initiation for 27 LMIC in 2011–2013 of 186 cells/μL (*3*), suggest at least a third of ART patients in LMIC initiated ART with advanced disease in 2015. To reduce prevalence of advanced disease at ART initiation in LMIC, continued attention to programmatic strategies facilitating earlier HIV testing and linkage to care are needed, in addition to adoption of WHO-recommended universal ART eligibility ("treat-all") guidelines for persons living with HIV (*3*), which stipulate that all patients become eligible for ART on the day of HIV diagnosis, regardless of CD4 count at HIV diagnosis. Early ART for all persons living with HIV could improve ART program outcomes and HIV prevention impact (*4*,*5*). For example, in the Strategic Timing of Antiretroviral Therapy (START) trial, initiating ART for patients with CD4 >500/μL rather than deferring ART initiation until more advanced disease stages, was shown to reduce risk for a composite endpoint of any serious acquired immunodeficiency syndrome (AIDS)–related event, non-AIDS–related event, or death by 57% (*5*). In addition, early rather than deferred ART for HIV-positive persons in a serodiscordant relationship was found to reduce HIV transmission to the HIV-negative partner by approximately 96% (*4*). Among the 10 countries studied, "treat-all" guidelines have been adopted nationwide in nine (Haiti, Mozambique, Namibia, Nigeria, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe), whereas Vietnam is beginning to phase in "treat-all" guidelines with nationwide adoption planned by 2020.

Given the low median baseline CD4 from Vietnam in 2009 (92/μL), much lower than Haiti's median baseline CD4 the same year (219/μL), evaluation of more recent trends in baseline CD4 is warranted. With Vietnam's epidemic largely

involving men who inject drugs, late presentation for ART might be partly explained by suboptimal health-seeking behavior in this population (*6*). In Vietnam and similar LMIC, continued monitoring of the prevalence of advanced HIV disease at ART initiation is necessary to inform understanding of ART program access, outcomes, and prevention strategies (because baseline CD4 gives an indication of how long ART enrollees have lived with an unsuppressed viral load). Comparing prevalence of advanced disease at ART initiation among demographic groups (e.g., nonpregnant females, pregnant females, and males) or among more affected population groups (e.g., sex workers and persons who inject drugs) can inform which populations are being reached late and therefore require targeted interventions (*1*).

Recent WHO guidelines recommend a differentiated approach to treatment of persons living with HIV.[¶] This approach means that patients initiating ART with advanced HIV disease require additional specialized care to ensure optimal outcomes. For example, tuberculosis (TB) is common among patients starting ART with advanced HIV disease, and remains the most common cause of death, accounting for approximately 40% of deaths, half of which are undiagnosed before death (*7*). Based on recent evidence from a randomized trial (*8*), WHO recommends that the lateral flow urine lipoarabinomannan assay may be used to assist in the rapid diagnosis and treatment of disseminated TB among persons living with HIV admitted to hospital with CD4 <100/μL and symptoms of TB. WHO conditionally recommends the same screening approach for adult outpatients. Early identification and treatment of disseminated TB can reduce all-cause mortality (*8*). In addition, plasma screening for cryptococcal antigen (CrAg) among patients with CD4 <100/μL and consideration of preemptive treatment with fluconazole for CrAg-positive patients might reduce 12-month ART mortality (*9*). Co-trimoxazole prophylaxis for ART enrollees with CD4 <350/μL has been shown to reduce mortality (*10*). Use of these adjunctive therapies could help reduce relatively high 12-month mortality among people taking ART in LMIC (*1*).

Given the importance of baseline CD4 in determining eligibility for adjunctive therapies that have the potential to reduce mortality, it is concerning that 40% of the 694,138 medical records reviewed lacked documentation of the baseline CD4, with country-specific rates ranging from 9% in Swaziland to 53% in Zimbabwe. Quality improvement measures to ensure availability of baseline CD4 data for clinical decision-making are warranted.

[¶] World Health Organization. Guideline on when to start antiretroviral therapy and on preexposure prophylaxis for HIV. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/.

Summary

What is already known about this topic?

Monitoring prevalence of advanced human immunodeficiency virus (HIV) disease (i.e., CD4+ T-cell count <200 cells/μL) among persons initiating antiretroviral therapy (ART) is important to help understand ART program outcomes, inform HIV prevention strategies, and forecast need for adjunctive therapies.

What is added by this report?

In an analysis of 694,138 adult ART records from 10 countries, the prevalence of advanced disease at ART initiation during 2004–2015 declined in eight countries. In Mozambique (2004–2014), Namibia (2004–2012), and Haiti (2004–2015), prevalence of advanced disease at ART initiation declined from 73% to 37% (p<0.001), 80% to 41% (p<0.001), and 75% to 34% (p<0.001), respectively. In the remaining seven countries with data available for 2004–2011, significant declines in prevalence of advanced disease were observed in Nigeria, Swaziland, Uganda, Vietnam, and Zimbabwe.

What are the implications for public health practice?

Declines in the prevalence of advanced disease at ART enrollment over time in most countries are encouraging, but in 2015, approximately a third of new ART patients still initiated ART late. Adoption of World Health Organization–recommended "treat-all" guidelines and strategies to facilitate earlier HIV testing, and treatment are needed. These strategies would help reduce HIV-related mortality and HIV incidence.

The findings in this report are subject to at least three limitations. First, cohort data varied in size and generalizability; statistical significance of trends in baseline CD4 over time is more likely with larger sample sizes and more calendar years of available data. Second, missing data on CD4 at ART initiation might have introduced measurement error for summary estimates. Third, in several countries, data on more recent ART enrollees are needed to inform estimates of the current prevalence of advanced HIV disease at ART initiation.

Encouraging reductions in the prevalence of advanced disease at ART initiation were observed in eight of the 10 countries studied. This reflects the rapid scale-up of HIV testing and treatment services in LMIC since 2004 and evolution of HIV treatment guidelines encouraging earlier ART initiation. However, an estimated one third of new ART enrollees in LMIC in 2015 started ART with advanced disease, indicating that continued scale-up of interventions to facilitate earlier testing and treatment are needed. For those ART enrollees who do initiate ART late (*3*), ensuring availability of WHO-recommended adjunctive therapies could help reduce morbidity and mortality during ART.

[1]Division of Global HIV & TB, Center for Global Health, CDC; [2]Division of Global HIV & TB, Center for Global Health, CDC Haiti; [3]Programme National de Lutte contre le VIH/SIDA, Ministry of Health, Haiti; [4]National Alliance of State & Territorial AIDS Directors, Washington, DC; [5]National Institute of Health, Mozambique; [6]Ministry of Health, Mozambique; [7]Division of Global HIV & TB, Center for Global Health, CDC Mozambique; [8]Ministry of Health and Social Services, Namibia; [9]Division of Global HIV & TB, Center for Global Health, CDC Namibia; [10]Ministry of Health, Nigeria;[11]Division of Global HIV & TB, Center for Global Health, CDC Nigeria; [12]Ministry of Health, Swaziland; [13]ITECH, Malawi; [14]Division of Global HIV & TB, Center for Global Health, CDC Swaziland; [15]Gates Foundation, Seattle, Washington; [16]ICAP, New York, New York; [17]Muhimbili University of Health and Allied Sciences, Tanzania; [18]National AIDS Control Program, Tanzanian Ministry of Health; [19]U.S. Department of Defense, Tanzania; [20]USAID Tanzania; [21]Division of Global HIV & TB, Center for Global Health, CDC Tanzania; [22]Global Health, Population and Nutrition, FHI 360, Durham, North Carolina; [23]Social and Behavioral Health Sciences, FHI 360, Washington, DC; [24]Infectious Diseases Institute, Makerere University College of Health Sciences, Uganda; [25]Institute of Tropical Medicine, Department of Clinical Sciences, Belgium; [26]FHI 360, Zambia; [27]Division of Global Health Protection, Center for Global Health, CDC, South Africa; [28]Division of Global HIV & TB, Center for Global Health, CDC Uganda; [29]Division of Global HIV & TB, Center for Global Health, CDC Zambia; [30]FHI 360, Tanzania; [31]Division of Global HIV & TB, Center for Global Health, CDC Vietnam; [32]Vietnam Authority of HIV/AIDS Control, Vietnam; [33]Tropical Diseases Research Center, Zambia; [34]Ministry of Health, Zimbabwe; [35]Division of Global HIV & TB, Center for Global Health, CDC Zimbabwe.

Corresponding author: Andrew Auld, AAuld@cdc.gov, 404-639-8997.

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Notes from the Field

Veillonella Misidentified as *Francisella tularensis* — Idaho, 2016

Kris K. Carter, DVM[1,2]; Erin M. Peterson[2]; Robert L. Voermans[2]; Kenneth S. Anderson III, MSPH[3]; Tamara Cox[3]; Ahmed M. Kassem, MBBCh, PhD[2,4]; Christopher L. Ball, PhD[2], Christine G. Hahn, MD[2]

In October 2016, the Idaho Bureau of Laboratories, Division of Public Health, was notified by hospital A's clinical laboratory (a member of the Idaho Sentinel Laboratory Network) that a bacterial isolate cultured from a hospitalized patient's knee joint fluid aspirate had been identified with 96% confidence as *Francisella tularensis* (a Tier 1 select agent*) by an in-house automated microbial identification system (AMIS). The isolate was submitted to the Idaho Bureau of Laboratories for confirmatory testing using Laboratory Response Network (LRN) reference methods. Hospital A laboratory personnel reported that the isolate had been manipulated on the open bench and certain laboratory workers had potentially been exposed. The Division of Public Health, hospital A, and Eastern Idaho Public Health initiated an investigation to confirm *F. tularensis*, assess potential laboratory exposures, and determine the source of infection. The investigation determined that the infectious agent was *Veillonella* and not *F. tularensis.*

The patient, a man aged >75 years, had a multiyear history of chronic unilateral knee pain, during which time he had received a series of three intra-articular injections of hyaluronate sodium 2 years previously, and several intra-articular injections of triamcinolone with bupivacaine, the last of which occurred 15 days before he sought care at hospital A for a swollen knee. Gram staining of an intra-articular aspirate obtained that day from the affected knee showed Gram-variable cocci. The aspirate was cultured under aerobic and anaerobic conditions. Slow-growing colonies of Gram-negative cocci were observed from the anaerobic culture, with limited growth in aerobic conditions. Because an anaerobic AMIS panel was not available, isolates from the aerobic culture were processed for identification and antimicrobial susceptibility on the AMIS using a panel specific for aerobic organisms. Identification of *F. tularensis* by the AMIS triggered notification of the Division of Public Health and revision of the patient's antibiotic regimen from vancomycin, piperacillin, and tazobactam to ciprofloxacin. Eastern Idaho Public Health interviewed the patient and determined that he lived in a rural area and reported no recent exposure to potential sources of naturally occurring *F. tularensis* (e.g., ill animals, arthropod bites, contaminated water, or use of lawn mowers or string trimmers near dead animals).

The Idaho Bureau of Laboratories and Eastern Idaho Public Health provided CDC guidance on tularemia laboratory exposure (*1*) to hospital A and assisted staff members in assessing potential exposures of laboratory personnel. Among 24 employees interviewed by hospital A, 19 were considered to have potential exposure; all 19 elected to start antibiotic prophylaxis because of a high level of concern regarding risk and the approximately 48 hours required for confirmatory testing.

Using LRN real-time polymerase chain reaction methods, the Idaho Bureau of Laboratories tested the isolate for *F. tularensis* and *Brucella* spp.; no *F. tularensis* or *Brucella* spp. DNA was detected. Subsequent partial 16S ribosomal RNA (rRNA) gene sequencing identified a *Veillonella* sp. According to Clinical and Laboratory Standards Institute guidelines, *Veillonella* species-level identification could not be reported because the 16S rRNA gene fragment had a >99% sequence identity for both *V. parvula* and *V. dispar* without a <0.8% difference between them (*2*). Partial RNA polymerase subunit B gene (*rpoB*) sequencing conducted on the isolate found a >99% sequence identity to *V. parvula*, suggesting this as the most likely species of the isolate (*3*). After identification of *Veillonella* sp., the patient's antibiotic regimen was changed to piperacillin, tazobactam, and ertapenem sodium; personnel who were receiving prophylactic antibiotics for potential *F. tularensis* exposure were informed that continuation of prophylaxis was not recommended or necessary. The Division of Public Health reviewed MedWatch data† and did not identify any reports of *Veillonella* infection associated with hyaluronate sodium, triamcinolone, or bupivacaine. The source of this patient's infection was not determined.

Veillonella spp. are small, slow-growing, nonmotile anaerobic Gram-negative cocci found as part of the normal flora of gastrointestinal, respiratory, and vaginal tracts. Although *Veillonella* spp. are classified as anaerobes, anaerobic organisms (including *Veillonella* spp.) have been observed growing in aerobic conditions for a limited time after isolation before becoming nonviable (*4*). Often considered contaminants of clinical specimen collection, *Veillonella* spp. have been rarely isolated from monomicrobial cultures of invasive infections.

* Tier 1 select agents are biologic agents and toxins that present the greatest risk for deliberate misuse with significant potential for mass casualties or devastating effects to the economy, critical infrastructure, or public confidence, and pose a severe threat to public health and safety.

† https://www.fda.gov/safety/medwatch/.

Predisposing factors for invasive infection have not been fully studied, but might include local or systemic immune suppression and localized anaerobic conditions produced by tissue necrosis, diminished blood supply, or prolonged infection with aerobes (*5*).

This is the first published report of misidentification of *Veillonella* sp. as *F. tularensis* by an AMIS and of isolation of *Veillonella* sp. from a nonprosthetic knee. Hospital and public health staff members responded appropriately to the preliminary misidentification of the isolate as *F. tularensis*; however, accurate identification would have obviated the need for time-intensive response activities, use of prophylactic antibiotics by hospital staff members, and inappropriately targeted antibiotic therapy for the patient. Clinical laboratories are advised not to use a commercial AMIS if a select agent is suspected in a clinical sample (*6*) and to consult with their LRN-biologic laboratory for guidance and sample referral. Clinicians should consider *Veillonella* spp. when receiving laboratory reports of *F. tularensis* generated by AMISs. Because *Veillonella* spp. are typically resistant to recommended or alternative antibiotic therapies for tularemia (i.e., streptomycin, gentamicin, tetracyclines, ciprofloxacin, and other fluoroquinolones), antibiotic coverage for both *Veillonella* spp. and *F. tularensis* could be considered until final microbial identification is available.

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Infection control, occupational health, and laboratory staff members of Hospital A.

[1]Career Epidemiology Field Officer Program, Office of Public Health Preparedness and Response, CDC; [2]Idaho Division of Public Health; [3]Eastern Idaho Public Health, Idaho Falls; [4]Epidemic Intelligence Service, CDC.

Corresponding author: Kris K. Carter; kris.carter@dhw.idaho.gov, 208-334-5939.

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Notice to Readers

Special Podcast: "Defining Moments in *MMWR* History — *E. coli* O157:H7"

MMWR has released a special podcast that highlights the leading role that *MMWR* played in reporting on the deadly multistate *Escherichia coli* O157:H7 foodborne outbreak of 1993. "Defining Moments in *MMWR* History – *E. coli* O157:H7" features an interview with Dr. Beth Bell conducted by *MMWR* Editor-in-Chief Dr. Sonja Rasmussen. Dr. Bell, who served as director of the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) from 2010 to 2017 and as an Epidemic Intelligence Service Officer during 1992–1994, was one of the first public health responders on the scene for this landmark public health emergency.

During the outbreak, four children died, and approximately 700 persons in four states became ill with severe and often bloody diarrhea. The first reports of CDC's investigation into this outbreak were published in *MMWR* (*1*,*2*).

Additional information regarding the outbreak is available at https://www.cdc.gov/od/science/wewerethere. The podcast is available at https://www.cdc.gov/mmwr/mmwrpodcasts.html.

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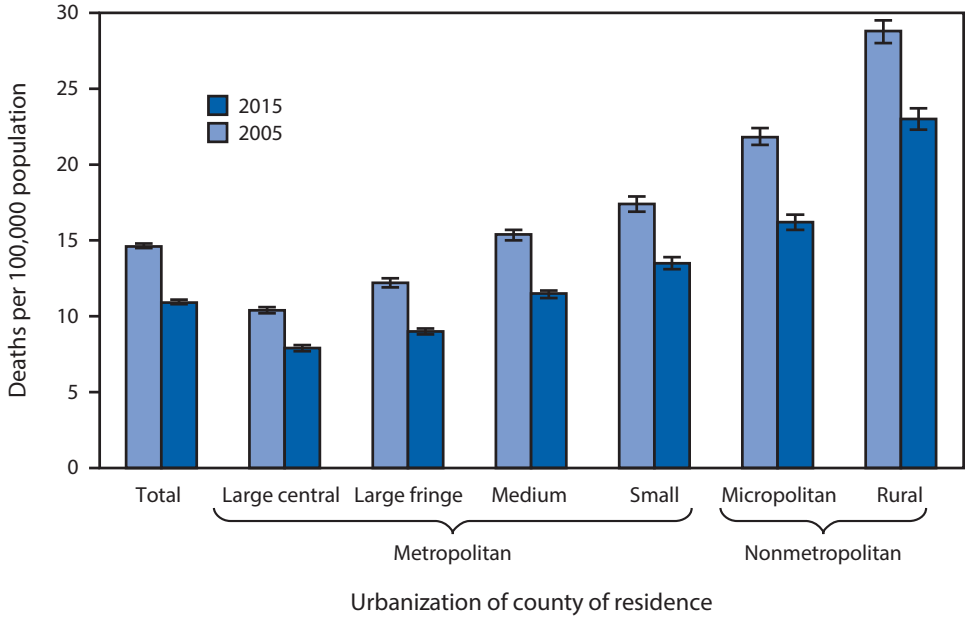
QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Age-Adjusted Rate* of Motor Vehicle Traffic Deaths,† by Urbanization of County of Residence§ — 2005 and 2015



* Age-adjusted rate per 100,000, based on the 2000 U.S. standard population, with 95% confidence intervals.
† Motor vehicle traffic deaths were identified using *International Classification of Diseases, Tenth Revision* underlying cause of death codes V02–V04[.1,.9], V09.2, V12–V14[.3–.9], V19[.4–.6], V20–V28[.3–.9], V29–V79[.4–.9], V80[.3–.5], V81.1, V82.1, V83–V86[.0–.3], V87[.0–.8], and V89.2. All motor vehicle traffic deaths were unintentional. Motor vehicle traffic decedents included motor vehicle occupants, motorcyclists, bicyclists, and pedestrians.
§ Counties were categorized into six urbanization levels based on a classification scheme that considers metropolitan/nonmetropolitan status, population, and other factors.

The overall age-adjusted rate of motor vehicle traffic deaths in the United States decreased 25% from 14.6 deaths per 100,000 population in 2005 to 10.9 in 2015. During this period, the rate declined in each of the county groupings, with the largest decline of 26% in the large fringe metropolitan and micropolitan counties and the smallest decline of 20% in rural counties. For both years, the rates for motor vehicle traffic deaths were higher in nonmetropolitan areas than in metropolitan areas. In 2015, the age-adjusted rate in rural counties was nearly three times the rate for large central metropolitan counties (23.0 compared with 7.9 per 100,000).

Sources: National Center for Health Statistics, National Vital Statistics System, Mortality File https://www.cdc.gov/nchs/nvss/deaths.htm.

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Reported by: Holly Hedegaard, MD, hdh6@cdc.gov, 301-458-4460.

For more information on this topic, CDC recommends the following link: https://www.cdc.gov/motorvehiclesafety/.

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