Cryptococcosis in Persons with HIV: Updated Guidelines on Prevention & Treatment

Brian R. Wood, MD
Associate Professor of Medicine
University of Washington
Mountain West AETC

Last Updated: 8/12/21

Disclosures

No financial disclosures or conflicts of interest.

Reminder where to find the OI Guidelines:
https://clinicalinfo.hiv.gov/en/guidelines/

Case

- Patient with recent diagnosis of advanced HIV: CD4 count 10, HIV RNA 1 million
- No meningitis symptoms (no fever, headache, neck stiffness, etc.)
- Serum cryptococcal antigen (CrAg) **1:320**

Question: what would you do next?

A) Initiate cryptococcal meningitis therapy (amphotericin plus flucytosine)

B) Initiate cryptococcal meningitis prophylaxis (oral fluconazole)

C) Initiate ART and monitor clinically for symptoms/signs of meningitis

D) Perform LP and hold off on ART and antifungals until results available

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Cryptococcosis in Persons with HIV (PWH)
Two Major Updates to Guidelines (June 2021)

1) Treatment for patients with asymptomatic antigenemia:

- Low serum titer (<1:320 using lateral flow assay): fluconazole 400-800 mg QD
- High serum titer (≥1:640 using lateral flow assay): treat as crypto meningitis

2) Increased fluconazole dose (800 mg daily) for consolidation phase

- "…for clinically stable patients who have been started on ART and whose CSF culture results return with no growth, dose can be decreased to 400 mg daily"

OI Guidelines: https://clinicalinfo.hiv.gov/en/guidelines/

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Cryptococcal Meningitis in PWH
Screening (Asymptomatic Patient)

- Serum cryptococcal antigen (CrAg) is sensitive/specific
  - Precedes meningitis by median 22 days; in 11%, detectable >100 days before symptoms
  - Prevalence of antigenemia in US: CD4 <50: 4.3%; CD4 <100: 2.9%
  - Disseminated disease more likely if >1:160 by lateral flow assay (LFA); **with titers >1:640, assume disseminated or CNS involvement**
- So, check serum CrAg for any newly diagnosed patient with CD4 ≤100 and particularly if CD4 count ≤50 (AII)
  - Positive test should prompt CSF eval (BIII), especially if LFA titer ≥1:160 (AII)

OI Guidelines: https://clinicalinfo.hiv.gov/en/guidelines/
Wake R et al. CID 2017.
McKenney J et al. CID 2015.
Saag MS et al. CID 2000.

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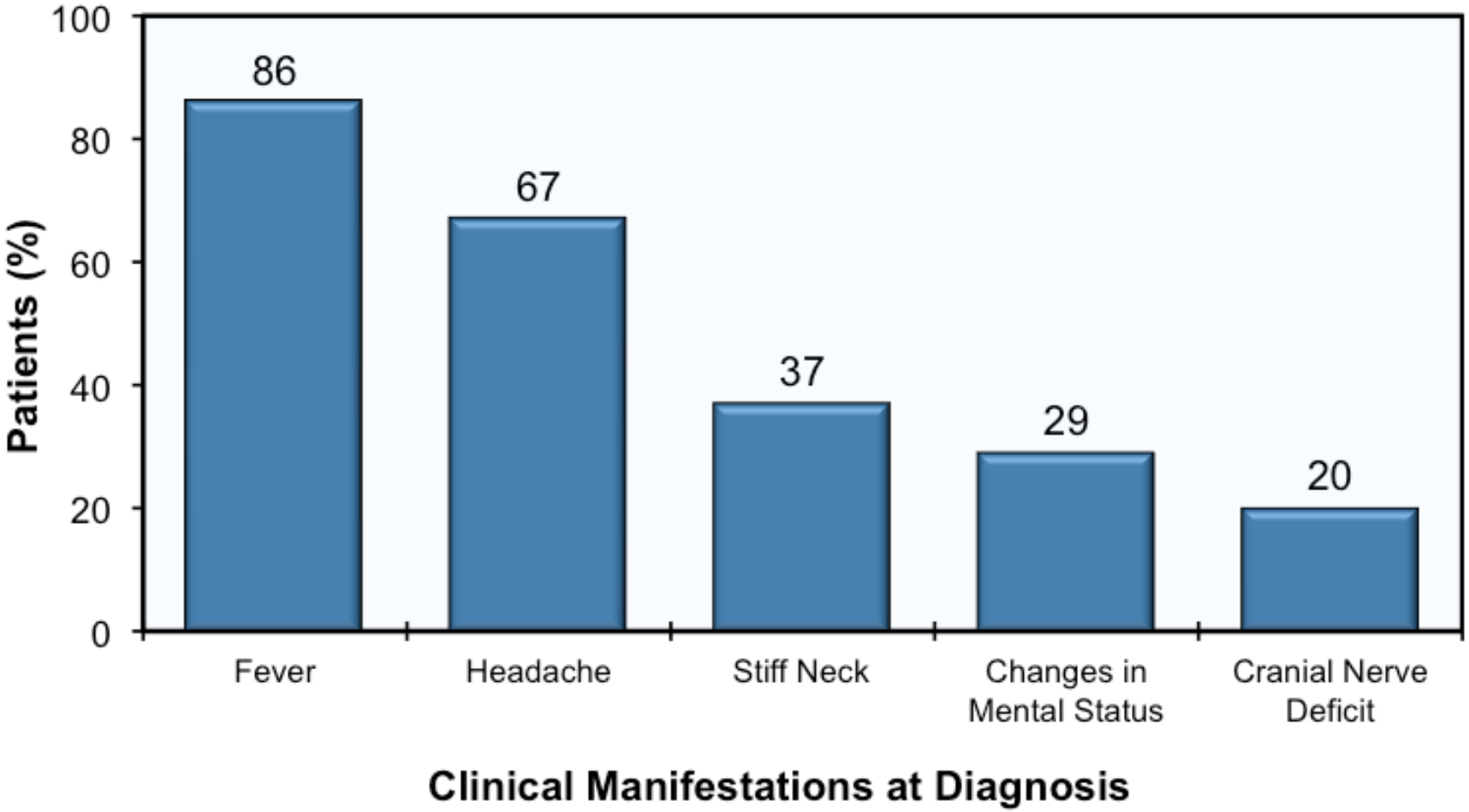
Cryptococcal Meningitis in PWH
Clinical Presentation



*Most common: subacute fever, headache, malaise

*Classic meningeal symptoms in only 25-33%

*Encephalitis symptoms can occur (from elevated ICP)

National HIV Curriculum: hiv.uw.edu
Darras-Joly C *et al* CID 1996;23:369-76

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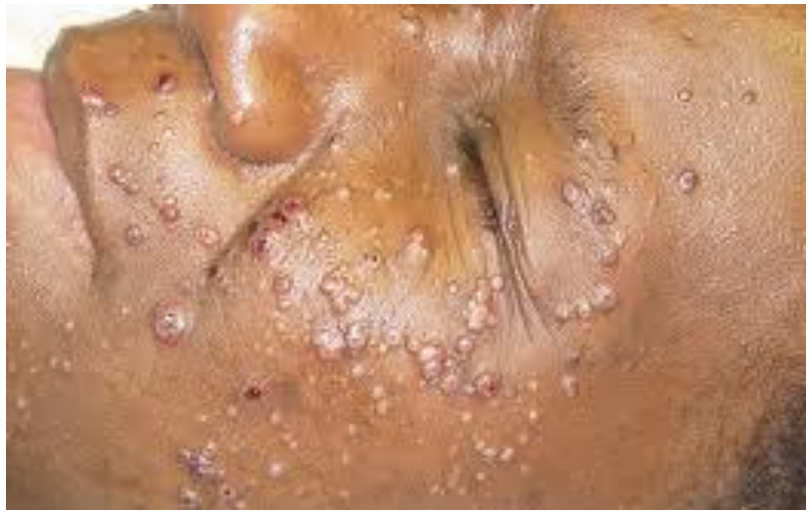
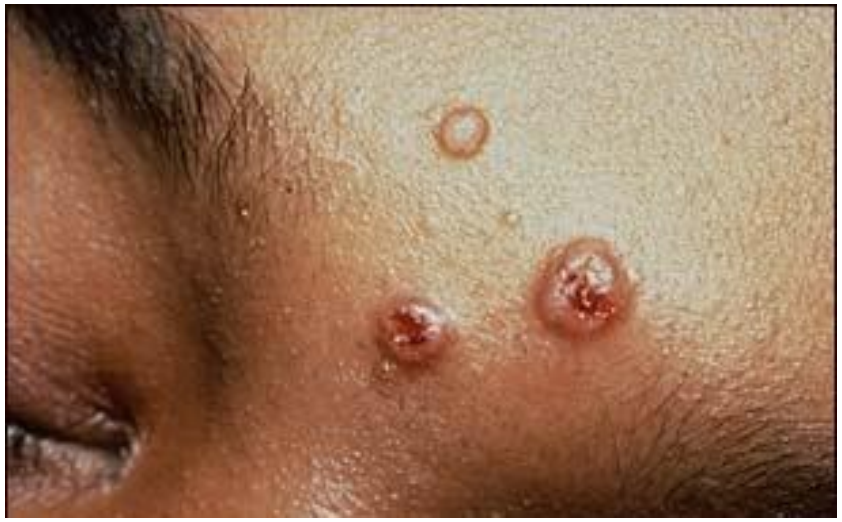
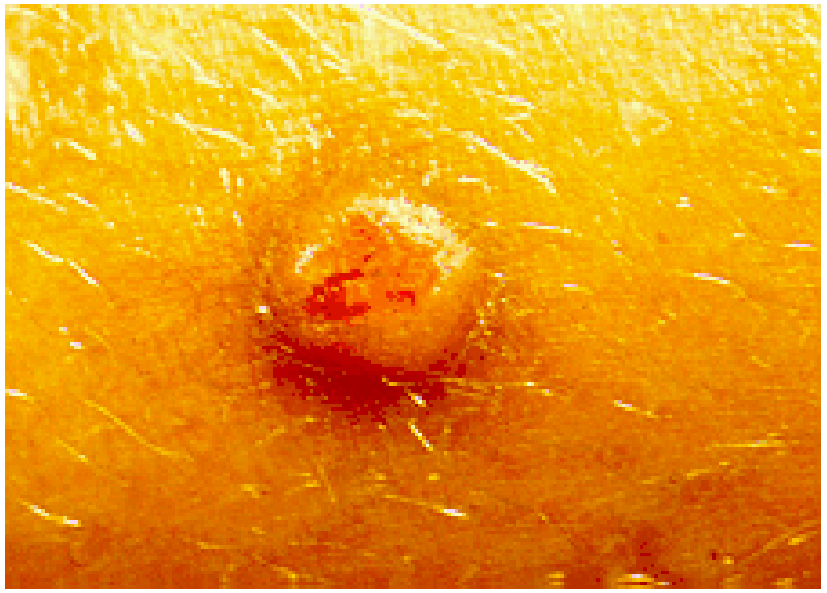
Cryptococcosis in PWH
Skin and Other Manifestations

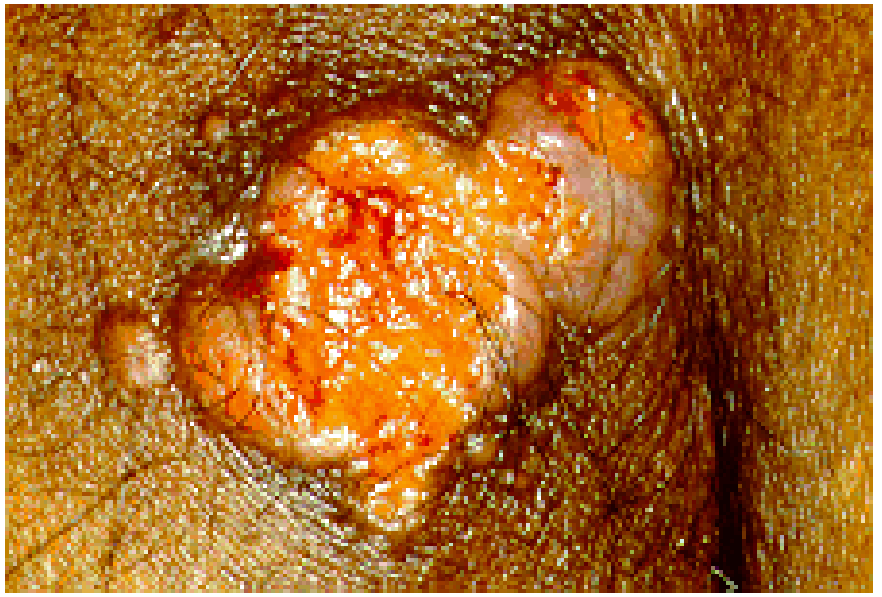
Skin lesions have molluscum-like appearance.

Crypto can also affect any organ (e.g., pulmonary disease occurs)









Pics from:
hiv.uw.edu

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Cryptococcal Meningitis in PWH
Diagnosis (Symptomatic Patient or Antigenemia)

- Brain imaging
- LP *with opening pressure* essential
  - Abnormal: >20-25 cm H_2O
- Serum & CSF cryptococcal antigen
- CSF fungal stain/culture
- Fungal blood cultures

OI Guidelines: https://clinicalinfo.hiv.gov/en/guidelines/
Saag MS et al. Practice guidelines for the management of cryptococcal disease. IDSA. Clin Infect Dis. 2000 Apr;30(4):710-8.

Cryptococcal Meningitis in PWH
Typical CSF Findings

CSF Parameter	Typical Findings	Comment
Cell type	Lymphocytes	>50% of patients will have <20 cells
Glucose	↓ or normal	
Protein	↑	
CrAg	↑↑	Positive in 95% of cases (false negatives due to post-zone effect reported but rare)
Fungal culture	Positive	Essential to document response at 2 weeks

https://clinicalinfo.hiv.gov/en/guidelines/

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Cryptococcal Meningitis in PWH
Treatment

- **General principles:**
  - #1 Induction → #2 Consolidation → #3 Maintenance
  - Aggressive management of ⇧intracranial pressure
    - Repeat LP's (to decrease opening pressure to <20 or by 50%)
    - Lumbar drain/VP shunt
    - No role for mannitol, acetazolamide, corticosteroids

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Cryptococcal Meningitis in PWH
Treatment

Phase	Preferred	Alternative	Duration
Induction	Liposomal amphotericin B 3-4 mg/kg QD + flucytosine 25 mg/kg QID	Ampho B, ampho B + fluconazole 800 mg, fluconazole + flucytosine, fluconazole 1200 mg	≥2 weeks + negative CSF culture
Consolidation	Fluconazole* (800 mg QD)	Itraconazole	8 weeks
Maintenance	Fluconazole (200 mg QD)		≥1 year + clinical improvement + CD4 ≥100 and VL suppressed x ≥3 months

*New rec: for clinically stable patients who have been started on ART and whose CSF culture results return with no growth, dose can be decreased to 400 mg daily.

OI Guidelines:
https://clinicalinfo.hiv.gov/en/guidelines/

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Clinical Infectious Diseases

MAJOR ARTICLE

Single dose liposomal ampho as part of combo therapy?

**See also: IAS 2021 Abstract OALB01LB03*

Short-course High-dose Liposomal Amphotericin B for Human Immunodeficiency Virus–associated Cryptococcal Meningitis: A Phase 2 Randomized Controlled Trial

Joseph N. Jarvis,[1,2,3,4] Tshepo B. Leeme,[1,a] Mooketsi Molefi,[4,a] Awilly A. Chofle,[5,a] Gabriella Bidwell,[5,a] Katlego Tsholo,[1] Nametso Tlhako,[1] Norah Mawoko,[1] Raju K. K. Patel,[1] Mark W. Tenforde,[1] Charles Muthoga,[1] Gregory P. Bisson,[2] Jeremiah Kidola,[5] John Changalucha,[5] David Lawrence,[3] Shabbar Jaffar,[6] William Hope,[7] Síle F. Molloy,[8] and Thomas S. Harrison[8]

[1]Botswana–University of Pennsylvania Partnership, Gaborone; [2]Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia; [3]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom; [4]University of Botswana, Gaborone; [5]National Institute of Medical Research, Mwanza, Tanzania; and [6]Department of International Public Health, Liverpool School of Tropical Medicine, and [7]Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, University of Liverpool, and [8]Centre for Global Health, Institute for Infection and Immunity, St George's University of London, United Kingdom

Background. We performed a phase 2 noninferiority trial examining the early fungicidal activity (EFA) of 3 short-course, high-dose liposomal amphotericin B (L-AmB) regimens for cryptococcal meningitis (CM) in Tanzania and Botswana.

Methods. Human immunodeficiency virus (HIV)-infected adults with CM were randomized to (*i*) L-AmB 10 mg/kg on day 1 (single dose); (*ii*) L-AmB 10 mg/kg on day 1 and 5 mg/kg on day 3 (2 doses); (*iii*) L-AmB 10 mg/kg on day 1 and 5 mg/kg on days 3 and 7 (3 doses); or (*iv*) L-AmB 3 mg/kg/day for 14 days (control). All patients also received oral fluconazole 1200 mg/day for 14 days. Primary endpoint was mean rate of clearance of cerebrospinal fluid cryptococcal infection (EFA). Noninferiority was defined as an upper limit of the 2-sided 95% confidence interval (CI) of difference in EFA between intervention and control <0.2 $\log_{10}$ colony-forming units (CFU)/mL/day.

Results. Eighty participants were enrolled. EFA for daily L-AmB was –0.41 $\log_{10}$ CFU/mL/day (standard deviation, 0.11; n = 17). Difference in mean EFA from control was –0.11 (95% CI, –.29 to .07) $\log_{10}$ CFU/mL/day faster with single dose (n = 16); –0.05 (95% CI, –.20 to .10) $\log_{10}$ CFU/mL/day faster with 2 doses (n = 18); and –0.13 (95% CI, –.35 to .09) $\log_{10}$ CFU/mL/day faster with 3 doses (n = 18). EFA in all short-course arms was noninferior to control. Ten-week mortality was 29% (n = 23) with no statistical difference between arms. All arms were well tolerated.

Conclusions. Single-dose 10 mg/kg L-AmB was well tolerated and led to noninferior EFA compared to 14 days of 3 mg/kg/day L-AmB in HIV-associated CM. Induction based on a single 10 mg/kg L-AmB dose is being taken forward to a phase 3 clinical endpoint trial.

Cryptococcal Meningitis in PWH
Attempts to Improve Outcomes

Adjunctiv[illegible]icos[illegible]roids?


ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

J. Beardsley, M. Wolbers, F.M. Kibengo, A.-B.M. Ggayi, A. Kamali, N.T.K. Cuc, T.Q. Binh, N.V.V. Chau, J. Farrar, L. Merson, L. Phuong, G. Thwaites, N. Van Kinh, P.T. Thuy, W. Chierakul, S. Siriboon, E. Thiansukhon, S. Onsanit, W. Supphamongkholchaikul, A.K. Chan, R. Heyderman, E. Mwinjiwa, J.J. van Oosterhout, D. Imran, H. Basri, M. Mayxay, D. Dance, P. Phimmasone, S. Rattanavong, D.G. Lalloo, and J.N. Day, for the CryptoDex Investigators*

CryptoDex Trial (2016):

- 6 weeks tapering dex vs. placebo
- Crypto tx: ampho B + fluc 800
- Stopped after N of 451
- At 10 weeks and 6 months:
  - Higher mortality, disability, infections, CV and renal events
  - Slower fungal clearance

[illegible]ART


ORIGINAL ARTICLE

Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis

David R. Boulware, M.D., M.P.H., David B. Meya, M.Med., Conrad Muzoora, M.Med., Melissa A. Rolfes, Ph.D., Katherine Huppler Hullsiek, Ph.D., Abdu Musubire, M.Med., Kabanda Taseera, M.Med., Henry W. Nabeta, M.B., Ch.B., Charlotte Schutz, M.B., Ch.B., M.P.H., Darlisha A. Williams, M.P.H., Radha Rajasingham, M.D., Joshua Rhein, M.D., Friedrich Thienemann, M.D., Ph.D., Melanie W. Lo, M.D., Kirsten Nielsen, Ph.D., Tracy L. Bergemann, Ph.D., Andrew Kambugu, M.Med., Yukari C. Manabe, M.D., Edward N. Janoff, M.D., Paul R. Bohjanen, M.D., Ph.D., Graeme Meintjes, M.B., Ch.B., Ph.D., for the COAT Trial Team*

COAT Trial (2014):

- ART within 1-2 weeks vs. 5 weeks
- Crypto tx: ampho B + fluc 800
- Stopped after N of 177
- Higher mortality with early ART
  - Esp. if low CSF WBC

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Cryptococcal Antigenemia in PWH
Treatment: Updated Recommendations (June 2021)

For any patient with CD4 <100 (and especially for those with CD4 <50): check serum CrAg

If positive, perform LP (with opening pressure!) for cells counts, glucose, protein, CSF CrAg, fungal stain/culture

If **serum CrAg <1:320 by LFA and no evidence of meningitis by CSF**, give fluconazole 400 to 800 mg PO daily for 10 weeks then 200 mg daily for total 6 months (same treatment as for mild or focal pulmonary disease)

If **serum CrAg ≥1:640 by LFA or if evidence of meningitis by CSF**, treat for cryptococcal meningitis (same as diffuse pulmonary disease)

OI Guidelines: https://clinicalinfo.hiv.gov/en/guidelines/

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Case

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- 30% of PWH with crypto meningitis experience IRIS after ART initiation
- More likely if: high baseline HIV RNA, less CSF inflammation on initial presentation, start ART soon after antifungal therapy
- **Crypto IRIS tx**: try to continue ART, manage elevated ICP, consider steroids
- **Recommended ART timing**:
  - OI Guidelines: 4-6 weeks
  - IAS-USA Guidelines: 4-6 weeks
  * Key: CSF cultures have sterilized

OI Guidelines: https://clinicalinfo.hiv.gov/en/guidelines/
IAS-USA Guidelines: https://www.iasusa.org/resources/guidelines/

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Acknowledgment

The Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2,886,754 with 0% financed with non-governmental sources.

AETC AIDS Education & Training Center Program Mountain West