HIV and Opportunistic Infections
Reviews in Internal Medicine 2017

Sonnuek Sungkanuparph, M.D.
Professor of Medicine
Head, Division of Infectious Diseases, Department of Medicine
Faculty of Medicine Ramathibodi Hospital, Mahidol University

2006 Recommendations From CDC: Routine Opt-Out Testing for HIV

- Routine voluntary testing for patients aged 13-64 years in healthcare settings—not based on patient risk
- Opt-out testing
- No separate consent for HIV
- Pretest counseling not required
- Repeat HIV testing at discretion of provider, based on patient risk


Additional CDC Recommendations

- High-priority screening for
  - Patients who seek treatment for STDs
  - Patients beginning treatment for tuberculosis
- Annual screenings in patients at high risk for HIV
  - IDUs and their sex partners
  - Persons who exchange sex for money or drugs
  - Sex partners of HIV-infected persons
  - MSM or heterosexuals who have multiple sex partners

Opt-Out Testing

- HIV tests will be done routinely unless a patient explicitly refuses to take an HIV test
- Eliminate the requirements for pretest counseling, informed consent, and post-test counseling
- The CDC believes that opt-out screening for HIV:
  - Help more people find out if they have HIV
  - Help those infected with HIV find out earlier, when treatment works best
  - Further decrease the number of babies born with HIV
  - Reduce stigma associated with HIV testing
  - Enable those who are infected to take steps to protect the health of their partners


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HIV and Serological Markers

Presentations to be Suspected for Acute HIV Infection

- DHF
- Infectious mononucleosis
- Rubella
- URI with skin rash
- ITP
- Bell’s palsy
- Aseptic meningitis
- Guillain Barre syndrome
- Stroke in the young
- Peripheral neuropathy
- Acute psychosis

HIV Staging: CDC (1993)

<table>
<thead>
<tr>
<th>CD4 Cell Categories (cell/mm³)</th>
<th>Clinical Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Asymptomatic / PGL / Acute HIV Infection</td>
<td>B: Symptomatic (not A or C)</td>
</tr>
<tr>
<td>1. &gt;500 (&gt;29%)</td>
<td>A1</td>
</tr>
<tr>
<td>2. 200-499 (14-28%)</td>
<td>A2</td>
</tr>
<tr>
<td>3. &lt;200 (&lt;14%)</td>
<td>A3</td>
</tr>
</tbody>
</table>

PGL: persistent generalized lymphadenopathy

C Category: AIDS defining illnesses

- Candidiasis of the bronchi, trachea or lungs
- Oesophageal candidiasis
- Invasive cervical cancer
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptococcosis (diarrhea > 1 month)
- Cytomegalovirus, other than liver, spleen, or lymph nodes
- Cytomegalovirus retinitis, with loss of vision
- HIV encephalopathy (AIDS dementia complex)
- Herpes Simplex w/ mucocutaneous ulcer >1cm, or bronchitis, pneumonitis, esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Toxoplasmosis with diarrhea
- Kaposi’s sarcoma
- Lymphoma, Burkitt’s
- Lymphoma, Immunoblastic
- Lymphoma, primary, of the brain
- Mycobacterium tuberculosis complex
- Non-tuberculous mycobacterial disease, disseminated or extrapulmonary
- Penicilliosis
- Pneumocystis pneumonia
- Recurrent pneumonia, bacterial
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia
- Toxoplasmosis
- HIV wasting syndrome
- Nocardiosis

Changing Criteria for Antiretroviral Therapy Initiation in DHHS Guidelines

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>&gt;500</td>
<td>Offer if VL &gt; 20K</td>
<td>Offer if VL &gt; 20K</td>
<td>Consider if VL &gt; 10K</td>
<td>Consider in certain groups*</td>
<td>Consider in certain groups*</td>
<td>Treat</td>
</tr>
<tr>
<td>350-500</td>
<td>Offer if VL &gt; 20K</td>
<td>Consider if VL &gt; 55K</td>
<td>Consider if VL &gt; 10K</td>
<td>Consider in certain groups*</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>200-350</td>
<td>Offer if VL &gt; 20K</td>
<td>Offer, but controversy exists</td>
<td>Offer after discussion with patient</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>&lt;200 or asymptomatic</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
</tbody>
</table>

*Pregnant women, patients with HIV-associated nephropathy, and patients with HIV by that requires treatment.
†50% of panel members recommended starting antiretroviral therapy; 50% of members viewed treatment as optional.

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. March 2012.
Risks and Benefits of Early Initiation of ART

### Benefits
- Prevention of progressive immune dysfunction (reduced immune activation)
- Delayed progression to AIDS and prolonged survival
- Decreased risk of non-AIDS/HIV-related morbidity (e.g., malignancies, neurocognitive dysfunction, cardiovascular disease, etc.)
- Decreased risk for some ARV toxicities
- Decreased HIV transmission

### Risks
- Costs
- Reduced quality of life
- Development of drug resistance if adherence is suboptimal
- Limitation in future choices of ART if drug resistance occurs
- Uncertain long-term toxicities and duration of effectiveness for some drugs/regimens
- Possible transmitted drug resistance

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When to Start Therapy: Balance Now Favors Earlier Antiretroviral Therapy

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Treatment as Prevention

1,750 heterosexual serodiscordant couples in resource-constrained countries randomized to receive ART early (CD4 350-550) or defer until CD4 < 250 cells/µL.

Kaplan-Meier estimate for the cumulative probabilities of linked HIV-1 transmission between partners, among participants in the early-therapy and delayed-therapy groups.

96% Reduction in HIV Transmission

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Early ART in Patients With Acute OIs Reduces Risk of AIDS Progression or Death

- Randomized strategy trial of early vs deferred ART in patients with acute OIs
- Results:
  - 282 enrolled, median CD4 29;
  - OIs: PCP 63%, bacterial infection 12%
  - Early ART associated with reduced risk of new AIDS complications or death
  - Supports starting ART within 14 days of OI diagnosis

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### Early vs Delay ART Initiation during TB Treatment

<table>
<thead>
<tr>
<th>Ability to determine the cause of adverse events</th>
<th>Early ART</th>
<th>Delayed ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex because of the large number of medications started in a short time period and overlapping side effects profiles</td>
<td>Simple because the number of drugs for TB treatment is less and there has been more time to evaluate response to TB treatment</td>
<td></td>
</tr>
<tr>
<td>Drug-drug interaction</td>
<td>Problematic</td>
<td>Problematic</td>
</tr>
<tr>
<td>Severe IRIS events</td>
<td>Risk may be increased</td>
<td>Risk may be decreased</td>
</tr>
<tr>
<td>HIV disease progression (new OI or death)</td>
<td>Risk may be decreased</td>
<td>Risk may be increased</td>
</tr>
<tr>
<td>Adherence demand with use of 4-drug for TB and multidrug therapy for HIV</td>
<td>Problematic</td>
<td>Less problematic because fewer drugs necessary for TB treatment</td>
</tr>
</tbody>
</table>

### Effect of ART Timing on TB Death (CAMELIA) or Death/AIDS Progression (STRIDE, SAPIT)

- **CAMELIA**: Earlier: 2-4 weeks after TB treatment started Later: 8-12 weeks after TB treatment started
- **SAPIT**: Earlier: 2-4 weeks after TB treatment started Later: 8-12 weeks after TB treatment started

### Significant Reduction in Death/AIDS Among Those with TB and CD4 < 50 Cells/μL

- **CAMELIA**: 34% ↓ $p=0.004$
- **STRIDE**: 42% ↓ $p=0.02$
- **SAPIT**: 68% ↓ $p=0.06$

### Summary of RCTs between Early vs Delay ART

- **Study**
- **TB characteristic**
- **CD4 study arm**
- **Mortality difference**
- **Country**
- **ARV regimen**

### The New England Journal of Medicine

**Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis**

- **No. at Risk**
  - Earlier ART
  - Later ART
- **P=0.01**

### 기타

- **TB**: Tuberculosis
- **CMV**: Cytomegalovirus
- **PML**: Progressive multifocal leukoencephalopathy
- **MAC**: Mycobacterium avium complex
- **PCP**: Pneumocystis jirovecii pneumonia
- **EFV**: Efavirenz
- **AZT**: Zidovudine
- **3TC**: Lamivudine
- **TDF**: Tenofovir
- **FTC**: Emtricitabine
- **ddI**: Didanosine
- **ddC**: Zalcitabine

### References

- **STRIDE**: NEJM 2011, Trafalgar NEJM 2011
- **SAPIT 1**: Mfinanga JAIDS 2012
- **SAPIT 2**: Manosuthi W, et al. 2011
- **CAMELIA**: Abdool 2011, Abdool 2011
- **STRIDE**: NEJM 2011, D, et al. 2011
- **SAPIT 1**: Abdool 2011
- **SAPIT 2**: NEJM 2010, Abdool 2010
- **TB Study Summary of RCTs between Early vs Delay ART**
- **HAART**: Highly active antiretroviral therapy
- **D**: stavudine, didanosine, and lamivudine
- **E**: efavirenz, nevirapine, or raltegravir
- **F**: abacavir plus lamivudine or zidovudine
Factors to Consider in Choosing First-line Therapy

- Patient’s willingness to commit to therapy
- Concerns regarding adherence
- Baseline characteristics (e.g., CD4+ cell count, resistance)
- Efficacy data
- Tolerability
- Convenience
- Drug-drug or drug-food interactions
- Comorbid conditions (e.g., HBV, CV risk, renal, bone)
- Consequences of failure (resistance)
- Cost and reimbursement

Risk of NVP Hepatotoxicity by CD4 Cell Count and Sex

Adverse Effects of NNRTIs

All NNRTIs:

- rashes including Stevens-Johnson syndrome
- Hepatotoxicity (especially NVP)
- Drug-drug interactions (NVP > EFV)

Nevirapine

- Higher rate of rash
- Hepatotoxicity (may be severe and life-threatening; risk higher in patients with higher CD4 counts at the time they start NVP, and in women)

Efavirenz

- Neuropsychiatric
- Teratogenic in nonhuman primates + cases of neural tube defects in human infants after first trimester exposure
- Dyslipidemia
Efficacy of PEP

- Systematically review on the published data on PEP efficacy across animal studies
  - 25 studies (408 primates) were included for review
  - Risk of seroconversion was 89% lower among animals exposed to PEP compared with those that did not receive PEP (OR 0.11; 95% CI, 0.05-0.23)
  - In univariate meta-regression, a significant association was found
    - Timing of PEP and seroconversion (β coefficient < 0.01 [95% CI, <0.01-0.01]; P = 0.03)
    - Lower seroconversion was also associated with the use of TDF compared with other drugs (β coefficient −0.23 [95% CI, −0.42 to −0.38]; P = 0.02)

Choice of ARVs for PEP

- Effectiveness depends critically on high levels of adherence and completion of the prescribed course
- Reported completion rates are currently suboptimal for PEP in most settings

Antiretroviral Agents Generally Not Recommended for Use as PEP

Nevirapine (NVP)

• Associated with severe hepatotoxicity
• Associated with rash that can be severe and progress to Stevens-Johnson syndrome
• Differentiating between early drug rash and acute seroconversion can be difficult

Abacavir (ABC)

• Hypersensitivity reactions can occur
• Differentiating between early drug rash/hypersensitivity and acute seroconversion can be difficult

Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis

Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) Regimens

Preferred HIV PEP Regimen
Raltitivir (Isentress RAL) 400 mg PO twice daily
Plus
Truvada, 1 PO once daily
(Tenofovir DF [Viread; TDF] 300 mg + emtricitabine [Emtriva; FTC] 200 mg)

Infect Control Hosp Epidemiol 2013;34(9):875-892

EFV-containing PEP Regimen

• EFV has the major disadvantage of CNS toxicity in the first 2-3 weeks of administration
• This may be ill-advised for HCP who take treatment for 1 month and usually work in positions that require high-level cognitive function
• Choosing a well-tolerated regimen is critical since up to 75% of HCP taking PEP experience side effects and less than half complete the 1-month course
• Multivariate analysis showed that two NRTIs + EFV was the only factor significantly associated with incompletion of the 4-week course (OR 37.8; 95%CI 4.2-342.3; p=0.001)

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Wiboonchudkul et al. CAROX 2015. Abstract 977

Opportunistic Infections in Thailand

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<th>Opportunistic Infection</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tuberculosis</td>
<td>79559</td>
<td>29.61</td>
</tr>
<tr>
<td>2</td>
<td>PCP</td>
<td>57235</td>
<td>21.3</td>
</tr>
<tr>
<td>3</td>
<td>Cryptococcosis</td>
<td>43339</td>
<td>16.14</td>
</tr>
<tr>
<td>4</td>
<td>Invasive candidiasis</td>
<td>14202</td>
<td>5.29</td>
</tr>
<tr>
<td>5</td>
<td>Recurrent pneumonia</td>
<td>10070</td>
<td>3.75</td>
</tr>
<tr>
<td>6</td>
<td>Cerebral toxoplasmosis</td>
<td>8006</td>
<td>2.98</td>
</tr>
<tr>
<td>7</td>
<td>Penicillosis marneifi</td>
<td>6709</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>AIDS dementia complex</td>
<td>4155</td>
<td>1.55</td>
</tr>
<tr>
<td>9</td>
<td>MAC</td>
<td>2597</td>
<td>0.97</td>
</tr>
<tr>
<td>10</td>
<td>Chronic herpes simplex infection</td>
<td>2448</td>
<td>0.91</td>
</tr>
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Interaction of HIV and TB

- **HIV** or TB
  - Incidence of post-primary TB and TB reactivation are increased
  - TB reactivation is more common
  - TB can develop at any stage of HIV infection
    - >50% of TB occur in patients with CD4 < 200 cells/mm³

- **TB** or HIV
  - The leading cause of death for in AIDS patients
  - Higher HIV-1 viral load and more rapid disease progression
  - Enhanced immunodeficiency

Survival among HIV/Tuberculosis Co-infected Patients with and without Antiretroviral Therapy

- **Retrospective cohort study**
- **Probability of death**
- **Survival among HIV/Tuberculosis Co-infected Patients**

Clinical Manifestations

- Influenced by degree of Immunodeficiency
  - CD4 > 350 cell/mm³: similar to TB among HIV-uninfected patients
  - CD4 < 50 cells/mm³: extrapulmonary TB (bone marrow, lymph node, bone, pleura, pericardium, peritoneal, and meninges)
- Severe immunodeficiency: rapid progression and sepsis syndrome
- Could be normal chest X-ray with positive sputum and culture

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
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<tbody>
<tr>
<td>Tuberculosis</td>
<td>Usually positive</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Unusual</td>
</tr>
<tr>
<td>Pulmonary distribution</td>
<td>Upper lobe</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Often present</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>10-15% of cases</td>
</tr>
</tbody>
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Diagnosis of Active Tuberculosis

- **Sputum (pus/tissue)** for AFB smear and culture
  - Smear x 1 = 63%, x 2 = 84%, x 3 = 86% (HIV negative patients)
  - More severe immunodeficiency
    - Sputum smear/culture become less sensitive
    - Yield of smear/culture from extrapulmonary sites are higher
  - Sputum processing methods improve sensitivity
    - Centrifugation with any of several chemical methods (NaOH, N-acetyl cysteine)
    - Overnight sedimentation preceded by chemical processing is more sensitive but specificity is similar
    - Insufficient data in HIV-infected patients
- **Nucleic acid amplification**
  - Identify M. tuberculosis in new cases with smear positive, especially high incidence of NTM (HIV, TB lymphadenitis in children)

Anti-TB Drug Sensitivities in HIV-infected Thai Patients

<table>
<thead>
<tr>
<th>Anti-TB drug sensitivities</th>
<th>N = 212</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH resistance</td>
<td>17%</td>
</tr>
<tr>
<td>Rifampicin resistance</td>
<td>9%</td>
</tr>
<tr>
<td>Ethambutol resistance</td>
<td>5%</td>
</tr>
<tr>
<td>Streptomycin resistance</td>
<td>13%</td>
</tr>
<tr>
<td>MDR</td>
<td>7%</td>
</tr>
</tbody>
</table>

Thai HIV Guidelines 2014: Diagnosis

- Patients with abnormal chest X-ray must have been tested for sputum AFB
  - Sputum AFB at least 2 times: the first day, and the next day after wake up the morning
  - Send sputum cultures to confirm the diagnosis of TB, exclusion of NTM, and sensitivity test before starting treatment
  - In case of abnormal chest X-ray but sputum AFB negative, should detect abnormalities of other organs, i.e. lymph node, to consider needle aspiration and tissue culture
  - Blood culture for TB should be performed in HIV-infected patients with prolonged fever

Survival among HIV/Tuberculosis Co-infected Patients with and without Antiretroviral Therapy

- **Retrospective cohort study**
- **Probability of death**
- **Survival among HIV/Tuberculosis Co-infected Patients**
Treatment of Tuberculosis

- 6 months: 2 IRZE/4 IR
- Bone and joint infection: 6-9 months
- CNS including meningitis: 9-12 months
- DOTs should be implemented especially during first 2 months
- Prolonged treatment (up to 9 months) if
  - delayed clinical response
  - delayed microbiological response


Thai HIV Guidelines 2014: Treatment

- Considered TB treatment for 6-9 months.
  - In the case of slow response, with cavity in chest x-ray, sputum AFB positive at 2 months of treatment, anti-TB should be administered for a total of 9 months
- Treatment extra-pulmonary TB similarly to pulmonary TB
  - Some extra-pulmonary TB require treatment for a longer time
  - CNS TB: for 12 months.
  - TB of bones and joints: 9-12 months.
- IRZE during the first 2 months, then HR for another 4-7 months if susceptible to H and R

Paradoxical TB-associated IRIS

- Signs:
  - Fever, increased in size and inflammation of involved LN, new lymphadenopathy, expanding CNS lesions, and worsening of chest X-ray
- Manifestations may be as subtle as fever and minor lymph node enlargement, or as dramatic as respiratory failure or neurological deterioration
- Risk factors: 1-6
  - Rapid increased CD4 cells
  - Higher baseline plasma HIV RNA
  - Rapid fall in initial HIV RNA
  - Short duration between TB treatment and initiation of ART
  - Extrapulmonary TB or disseminated TB


INSHI Definition of Paradoxical TB-IRIS

(A) Antecedent requirements
- Diagnosis of TB, and
- Initial response to TB treatment

(B) Clinical criteria
- Onset of TB-IRIS should be within 3 months of ART, and
- Plus at least 1 major criterion or 2 minor clinical criteria

(C) Alternative explanations must be excluded if possible
- Anti-TB drug resistance
- Poor adherence
- Another OI or neoplasm
- Drug toxicity or reaction

Major criteria
- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement e.g. tuberculous arthritis
- New or worsening radiological features of tuberculosis
- New or worsening CNS tuberculosis
- New or worsening serositis

Minor criteria
- New or worsening constitutional symptoms such as fever, night sweats, or weight loss
- New or worsening respiratory symptoms such as cough, dyspnea
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

Paradoxical TB-associated IRIS: Treatment

1. Supportive treatment
2. Immune modulation
   - Steroid
   - NSAIDS
   - Thalidomide, azathioprine and tumor necrosis factor α blockers (such as adalimumab)
3. Surgical intervention
   - drainage

Biliary Cryptosporidiosis

- Less frequently recognized than the diarrheal illness
- Higher infectious burden
- Cholecystitis was first recognized in 1983
- Typically present with clinical symptoms consistent with acalculous cholecystitis or sclerosing cholangitis
- Fever, RUQ pain, and nausea and vomiting are common clinical complaints
- Diarrhea may or may not be present simultaneously
- Laboratory findings: elevated alkaline phosphatase and bilirubin levels consistent with anicteric cholestasis
- Liver transaminase levels are generally only modestly elevated

Bacillary Angiomatosis (BA)

- Unique vascular lesions caused by infection with small, gram-negative organisms of the genus Bartonella
- Causative agents: B. quintana or B. henselae
- Skin lesions: smooth surface or eroded surface of red papules
- Occurs primarily in immunocompromised persons
- Second-most-common cause of angiomatous skin lesions in HIV
- Histology: vascular proliferation with neutrophils adjacent to the blood vessels and masses of bacteria in Warthin-Starry silver stain
- Treatment: Erythromycin or doxycycline

Kaposi Sarcoma (KS)

- Neoplasm of endothelial cells involving skin & other internal organs
- Common among HIV esp. MSM with advanced HIV disease
- KS may affect any portion of cutaneous surface
- Initially, it appears as red-to-brown flat macules, papules, or nodules
- Lesions tend to arise along the lines of cleavage, forming oval papules
- Numbering from 1 to 100+, range in size from mm to >10 cm and may be widespread, grouped, or zosteriform
- Visceral involvement occurs in 72% of patients with advanced HIV disease: GI tract (50%), lymph nodes (50%), and lungs (37%)

Kaposi Sarcoma (KS)

- Therapy aims at controlling symptoms, reducing edema, eliminating pain, and clearing lesions, but it is not curative
- If treatment is necessary or elected, use radiation and systemic alpha-interferon or chemotherapy
- Cutaneous lesions may be improved with local cryotherapy or intralesional injections of vinblastine

How to Discriminate Common Disseminated Fungal Infection in HIV/AIDS

- Penicillium
- Histoplasma
- Cryptococcus

Secondary Syphilis

- Non-itchy skin rash that covers the entire body or in a few areas
- More commonly found on the palms, and soles of the feet
- Rash contains reddish brown, small, solid, flat or raised skin sores
- This stage of syphilis is highly contagious as well
- Disappear without treatment during a period of 2-12 weeks
- Without treatment the bacteria will go on to the next stage of syphilis
- There may be recurrences of secondary syphilis for a 1-2 year period

CMV Diseases

- Cytomegalovirus (CMV) causes multiple organ dysfunction in the immunocompromised host
- Hepatitis, pneumonitis, ulceration of the oesophagus or colon, retinitis, or encephalitis
- Organ involvement is routinely diagnosed by biopsy, with visualization of owl's eye intranuclear inclusions in stained tissue sections

“Only the unknown frightens men. But once a man has faced the unknown, that terror becomes the known.”

Antoine de Saint-Exupery
“The Little Prince”