Overview & History of HIV: Epidemiology, ART, 1st line treatment & monitoring

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Overview & History of HIV: Epidemiology, ART, 1st line treatment & monitoring
Hello, from a distance.
Thanks SARS-CoV-2...
Please be in contact 😊

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Flipped classroom format

Virtual interaction is hard, but let’s TRY!

Your preparation will make all the difference for your learning & the group experience

◦ Spend 20 minutes prepping prior to each session

Please “interrupt” – this is not a lecture!

I’ll ask questions and you’ll answer some post-session assessments

◦ When I don’t know an answer I’ll say so, and look it up after the session
  ◦ (we can also poll the group for wisdom)
◦ This is NOT a test
◦ I don’t grade you 😊
◦ Goal: to gauge where we are and how we can be better going forward for our patients
Overall Outline

1. HIV & ART overview
   ◦ History, Epidemiology, transmission/risk, staging
   ◦ Med Class Overview, ART initiation

2. Treatment monitoring & Failure
   ◦ 2\textsuperscript{nd} & 3\textsuperscript{rd} line ART, toxicity/complications, monitoring
   ◦ Prevention

3. Opportunistic Infections & Hepatitis B
   ◦ OIs, ART considerations, Prophylaxis
   ◦ HBV dx, tx, surveillance, & HIV-HBV co-infection

4. Special Populations:
   ◦ Pregnancy, antenatal & intrapartum, infant care & pediatric

5. HIV/HBV Case-Based Application
   1. Case Application
   2. Wrap-up/review, miscellaneous items

5 session, 2 hours each
Source Materials

Liberia Integrated Guidelines for Prevention, Testing, Care, and Treatment of HIV and AIDS
  ◦ 5th edition, August 2019

WHO HIV Diagnosis, Treatment, and Opportunistic Infection Guidelines
  ◦ 2016, 2018 ART update
  ◦ https://www.who.int/publications/guidelines/hiv_aids/en/

WHO Hepatitis B treatment guidelines (2015)

Reference Materials


HIV History

1981

AIDS identified as a clinical syndrome of immunodeficiency

1983 - 1984

HIV-1 identified as the causative agent of AIDS

Gottlieb et al 1981; Barre-Sinoussi et al 1983; Gallo et al 1984
Simian Immunodeficiency Virus (SIV)

Red-Capped Mangabeys

Greater Spot-Nosed Monkey

Chimpanzees

Southeast Cameroon

~1908

Sharp & Hahn 2011
Origin & Spread of HIV-1

Colonialism & forced labor
- Belgium & German control of Cameroon & Congo
- Ivory & Rubber industry
- Transportation Networks
  - Trails, waterways, railways

Faria et al 2011; Timberg & Halperin 2012
HIV Types

Lentivirus
- Retrovirus

HIV-1
- Groups M = 90-95% of HIV-1
  - Further subtypes & clades
    - Of little clinical relevance
  - Most recent common ancestor = 1920

HIV-2
- 30-40% homology with HIV-1 == a DIFFERENT virus
- 2-5% of global HIV infections
- Co-infection with HIV-1 is high (up to 20% rate in parts of West Africa)
- HIV-2 mono-infection is likely declining
- Found in parts of West Africa
  - Guinea-Bissau, Gambia, Senegal, Cote d’Ivoire, Mali, Nigeria, Senegal, Sierra Leone
  - Immigration distributes it more widely
- Most recent common ancestor = 1940

Kirchner 2017; Faria et al 2014
Basic Epidemiology

Liberia (2016)
- Prevalence: 39,000 (1.4%)
  - 32% do not know they are HIV +
  - 35% on ART
  - 13% with suppressed viral load
- Key Populations
  - 20% prevalence in men who have sex with men (MSM)
  - 10% prevalence in sex workers
  - 4% prevalence in people who inject drugs (PWID)
  - Reproductive age women have 60% higher prevalence than men
- Since 2010:
  - 31% decrease in incidence
  - 34% decrease in AIDS-related deaths

Prevalence
- 1.4+ %
- 0.5 - 1.4 %
- 0.2 - 0.5 %
- < 0.2 %
- No data
Your experience

What do you estimate the HIV prevalence to be in your community, in your hospital, clinic?
- What are your communities high risk or key populations?

How do your patients perceive personal risk of infection?

What are harmful & helpful beliefs of HIV common in your community?

How have societal institutions (religious, educational, governmental, local leadership) responded to HIV in your experience?
# Transmission Risk

<table>
<thead>
<tr>
<th>Activity</th>
<th>Risk per 10,000 exposures</th>
<th>Average exposures per infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Transfusion</td>
<td>9,250</td>
<td>~1</td>
</tr>
<tr>
<td>Needle Sharing during Injection Drug Use</td>
<td>63</td>
<td>159</td>
</tr>
<tr>
<td>Needle Stick Injury</td>
<td>23</td>
<td>435</td>
</tr>
<tr>
<td>Receptive Anal Intercourse</td>
<td>138</td>
<td>72</td>
</tr>
<tr>
<td>Insertive Anal Intercourse</td>
<td>11</td>
<td>909</td>
</tr>
<tr>
<td>Receptive Vaginal Intercourse</td>
<td>8</td>
<td>1,250</td>
</tr>
<tr>
<td>Insertive Vaginal Intercourse</td>
<td>4</td>
<td>2,500</td>
</tr>
<tr>
<td>Oral Intercourse</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Biting, spitting, or body fluids on intact skin</td>
<td>Very low</td>
<td></td>
</tr>
<tr>
<td>Mother-to-child transmission without ART</td>
<td>2,500 (25%)</td>
<td>4</td>
</tr>
<tr>
<td>MTCT including breastfeeding without ART</td>
<td>4,500 (45%)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*** acute HIV, high viral load, concurrent STI, and mucous membrane injury all increase risk ***

Patel et al 2014
Testing overview

HIV Enzyme Immunoassays (EIA)
- 1st gen – 1980s, high false +
- 2nd gen – 1980s, blood bank screening
- 3rd gen – 1990s, sandwiched Antibodies IgG / IgM
- 4th gen – 3rd gen Antibody & p24 Antigen combo

HIV Rapid Testing
- Determine: Ab / Ag with HIV 1/2 differentiation
- Bioline: IgG / IgM Ab with HIV 1/2 differentiation
- Uni-Gold: Ab with HIV 1/2 differentiation

HIV Nucleic Acid Amplification Test (NAAT / “viral load”)
- RNA, DNA

HIV Western Blot
- HIV lysate protein band identification in gel electrophoresis
- ~2 months until positive
Diagnosis by Rapid Testing

**Liberia:** after initial positive test > send 2 parallel confirmatory
- Confirmatory 1 & 2 positive = HIV +
- Confirmatory 1 & 2 discordant = repeat test after quality review
- Confirmatory 1 & 2 negative = Dried Blood Sample for NAAT

**WHO:** recommendation by prevalence
- If >5% prevalence in population tested:
  - Diagnosis requires 2 consecutive positive tests
    - If 1/3 assays is reactive = HIV negative
    - If assays are reactive > non-reactive > reactive == inconclusive, repeat in 14 days
- If <5% prevalence in population tested:
  - Diagnosis requires 3 consecutive positive tests
    - If Assay 1 is reactive > Assay 2 is nonreactive == HIV negative
    - If assays are reactive > reactive > nonreactive == inconclusive, repeat in 14 days
Testing

Liberia guideline – offer HIV testing to all patients at any facilities if:

- Never tested or no documentation of a test
- Tested negative > 3 months ago (if test indicated risk-assessment)
- To children under 24 mo if:
  - Mother’s HIV status is unknown
  - If the child is sick (even if documentation of prior negative maternal test)

- Index Testing:
  - Test with partner (or via Partner Referral Slip)
  - Test with family/children (or via Family Referral Slip)

- For negative tests, link to:
  - Prevention services
  - Retesting by risk assessment

Liberia HIV Testing Program Goals
1. Identify as many HIV+ people as possible
2. Identify patients early after infection
3. Start ART as soon as possible
Case

22 year old male

Negative HIV rapid test 1 year ago

Since that time has had 2 female sexual partners
  ◦ Most recent encounter was with a sex worker 2 weeks ago, unprotected vaginal intercourse

What testing scheme do you recommend, if:

1. He is asymptomatic
2. He describes fever, malaise, pharyngitis
3. He has weekly high risk sexual exposures
   1. What if monthly, twice yearly...?

What would network testing mean here?
HIV & Networks

High HIV risk networks

- Testing in high prevalence populations is high yield for:
  - Treatment as prevention
  - Case identification
- Often socially marginalized, stigmatized
  - Testing requires trust
- Social Network Strategies can identify:
  - More cases
  - The cases highest risk for transmission to others
  - Leverage social influence to encourage testing

Network analysis of HIV outbreak in USA

Alpren et al 2020
Natural History of HIV

- Primary Infection
- Acute HIV syndrome
  - Wide dissemination of virus
  - Seeding of lymphoid organs
- Clinical Latency
- Opportunistic Diseases
- Constitutional Symptoms
- Death

CD4+ T Lymphocyte Count (cells/mm³)

0 10 20 30 40 50 60 70 80 90 100 110 120

Weeks

0 1 2 3 4 5 6 7 8 9 10 11

Years

HIV RNA Copies per ml Plasma

$10^2$ $10^3$ $10^4$ $10^5$ $10^6$ $10^7$
<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
<th>Approximate CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>asymptomatic</td>
<td>Generalized lymphadenopathy</td>
</tr>
</tbody>
</table>
| 2     | Non-AIDS defining condition | <10% weight loss  
Recurrent respiratory infections  
Zoster, oral ulcers, dermatologic conditions | 200 - 500 |
| 3     | AIDS & non-AIDS | >10% weight loss  
Unexplained fever or diarrhea >1mo  
MTB (P or EP)  
Severe systemic bacterial infections  
Oral candidiasis, gingivitis  
HBV/HCV con-infection | <200 |
| 4     | AIDS-defining | OI  
HIV wasting syndrome | <200 |
**Presumed Severe HIV Disease in Infants (PSHD)**

Infant <12 months with positive rapid antibody test PLUS:

<table>
<thead>
<tr>
<th>Combination of 2:</th>
<th>At least 1:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral thrush</td>
<td>• Severe unexplained wasting / malnutrition not responding to treatment</td>
</tr>
<tr>
<td>• Severe pneumonia</td>
<td>• Pneumocystis pneumonia</td>
</tr>
<tr>
<td>• Severe sepsis</td>
<td>• Candidiasis of oesophagus, trachea, bronchi or lungs</td>
</tr>
<tr>
<td></td>
<td>• Cryptococcal meningitis</td>
</tr>
<tr>
<td></td>
<td>• Toxoplasmosis of the brain (from age 1 month)</td>
</tr>
</tbody>
</table>

START ART Immediately, do NOT wait for confirmatory PCR!
Basic Virology & Med Classes

Take out a pencil & paper!

**NNRTI**  
Non-nucleoside Reverse Transcriptase Inhibitor

**NRTI**  
Nucleoside Reverse Transcriptase Inhibitor

**INSTI**  
Integrase Strand Transfer Inhibitor

**PI**  
Protease Inhibitor
ART Regimen: Building Blocks

3 meds
- 2 fully active
- PI needs a ritonavir “booster”

Inhibits CYP 450-3A4

concentration of PI

Core

INSTI +

Backbone

NRTI +

NRTI +

NRTI +

NRTI +

PI

NNRTI

NRTI

NRTI

NRTI

NRTI

NRTI

NRTI

NRTI
Nucleoside Reverse Transcriptase Inhibitor (NRTI)

**Tenofovir [TDF]**
- Need for HIV-HBV co-infection [alternative = entecavir]
- Dose reduction for CrCl <50

**Lamivudine [3TC]**
- Well tolerated
- in all 1st & 2nd line regimens

**Abacavir [ABC]**
- Hypersensitivity reaction = absolute contraindication

**Zidovudine [AZT]**
- Q12hr dosing
- NOT if hgb <8
- Watch for anemia

**Available Combo Pills**
- ABC/3TC
- TDF/3TC
- AZT/3TC
Non-Nucleoside Reverse Transcriptase Inhibitor
NNRTI

Nevirapine [NVP]
- 1st line, but not for ART start
- SE: hypersensitivity reaction, rash, hepatitis

Efavirenz [EFV]
- 1st line, but not for ART start
- SE: neuropsych, insomnia, nightmares, dizziness, gynecomastia

Available Single Tablet Regimen
- AZT / 3TC / NVP
- TDF / 3TC / EFV – “B+”
  - Very similar to “Atripla”
Protease Inhibitor (PI)

Lopinavir / ritonavir [LPV/r – Kaletra]
- 2nd line
- diarrhea

Atazanavir / ritonavir [ATV/r]
- 2nd line
- Do NOT use with rifampicin for MTB tx
- Benign hyperbili/jaundice

Darunavir / ritonavir [DRV + r]
- 3rd line
- Must take separately

Not Available in Single Tablet Regimen
Integrase Strand Transfer Inhibitor

**INSTI**

**Dolutegravir [DTG]**
- 1st line for patients 30kg + without childbearing potential
- WHO: 1st line treatment for pregnant women
- SE mild: HA, insomnia, nausea
  - Check LFTs before/after initiation if known liver disease
  - BID with rifapentine for MTB treatment

**Available Single Tablet Regimen**
- TDF / 3TC / DTG
ART for all

Strategy of WHO & Liberia
- Established personal benefit
  - Decreased all-cause & AIDS-specific morbidity & mortality
- Likely population benefit
  - treatment as prevention
ART Start – Test and Treat

4 major trials: Ya Tsie, PopART (HPTN), SEARCH, TasP

- 3.5 / 4 had a nonsignificant impact on population incidence
- Many ecological confounders, protocol changes

### Table:

<table>
<thead>
<tr>
<th>Setting and Trial</th>
<th>No. of Participants</th>
<th>HIV Incidence per 100 person-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana (Ya Tsie)</td>
<td>12,610</td>
<td>Intervention: 31 Control: 31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.59 / 0.92</td>
</tr>
<tr>
<td>South Africa and Zambia (HPTN 071–B)</td>
<td>25,803</td>
<td>Intervention: 30 Control: 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.06 / 1.55</td>
</tr>
<tr>
<td>South Africa and Zambia (HPTN 071–A)</td>
<td>25,070</td>
<td>Intervention: 7 Control: 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.45 / 1.55</td>
</tr>
<tr>
<td>Kenya and Uganda (SEARCH)</td>
<td>150,395</td>
<td>Intervention: 5 Control: 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 / 0.27</td>
</tr>
<tr>
<td>South Africa (TasP)</td>
<td>28,419</td>
<td>Intervention: 2 Control: 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.11 / 2.27</td>
</tr>
</tbody>
</table>

![Graph showing participants with viral suppression and effectiveness](image)
Preparing for ART start

**Social Support**
- Especially for vulnerable patients

**Clinical Evaluation**
- WHO Staging
- Opportunistic Infections
  - MTB
- Chronic Conditions – HTN, DM

**Baseline labs**
- NOT required prior to ART start
- WHO Stage 3/4, inpatient ART start
  - routine urine LAM & serum CrAg

**Counseling**
- Lifelong treatment
- Individual counseling

**CONFIRM** diagnosis
### First Line ART for Initiation ("start")

<table>
<thead>
<tr>
<th>Core</th>
<th>Backbone</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>TDF / 3TC</td>
</tr>
<tr>
<td>EFV</td>
<td>TDF / 3TC</td>
</tr>
<tr>
<td>NVP</td>
<td>AZT / 3TC</td>
</tr>
</tbody>
</table>

- **Men 30kg**
- **Women 45yo +**
- **Women of childbearing potential**
- **Patients < 30kg**

"B+"
HIV-2 ART considerations

Active ART

NRTIs  INSTIs  LPV/r  DRV/r

Inactive ART

All NNRTIs  ATV/r
Case

32 year old female
- Weight loss and diarrhea for 6 months
- BMI now 18
- HIV diagnosed by rapid testing 1 month ago

How do you counsel?

What is your next step?
Monitoring Schedule

**Appointments**
- Monthly for first 6 months
- Space up to q 3 month appointments if virally suppressed & adherent
- In stable patients, 6 or even 12 months of ART may be dispensed for exceptional circumstances (ie, travel)

**Viral Load**
- 6 months after ARV start
- 12 monthly thereafter
Monitoring Treatment

Adherence
- Determine pill count & doses missed by last fill date

Nutritional Status
- Weight loss
  - Flattening of pediatric growth curve
  - BMI <17 in adult = malnutrition => Therapeutic Feeding
  - MUAC <22cm in pregnancy = malnutrition => Therapeutic Feeding
- Weight should normalize within 6-12mo on ART

Viral Load
- Dried Blood Spot (DBS) = RNA PCR

CD4
- Baseline if available
- Treatment failure suspect
  - CD4 < 200 = urine LAM & serum CrAg
  - CD4 > 200 = no action
- *may be falsely elevated in acute illness

Symptoms

Weight loss / failure to thrive
Appearance:
  - Body shape change / breast swelling (men)
  - Swollen glands
Headache / confusion / dizziness
Jaundice, Scleral icterus
Mouth sores
Cough
Shortness of breath
Fever / night sweats
Vomiting / abdominal pain
Diarrhoea
Leg pain / numbness / weakness
Rash on arms, legs or trunk

Appearance:
- Weight loss / failure to thrive
- Headache / confusion / dizziness
- Jaundice, Scleral icterus
- Mouth sores
- Cough
- Shortness of breath
- Fever / night sweats
- Vomiting / abdominal pain
- Diarrhoea
- Leg pain / numbness / weakness
- Rash on arms, legs or trunk
Case (cont)

1 months later you see her in clinic
- Reports full adherence
- Diarrhea has stopped, weight is same as on start
- Notes that she has been feeling depressed

What do you review?

What are your next steps?
Case (cont)

She returns for 2\textsuperscript{nd} month review
\begin{itemize}
  \item Nightmares developed
  \item She has stopped her ART for the past 2 weeks entirely
\end{itemize}

What is your next step?
Case (cont)

You have switched your patient to a DTG-based regimen. Her 6 month viral load returns detectable but < 1,000.

What is your next step?
Case (cont)

She discloses that her husband is a truck driver who travels a 3-day route each week. She has not disclosed to him for fear of his reaction and therefore does not take ART on days when he is home to avoid inadvertent disclosure.

How do you respond?
Adherence

“What challenges have you had taking your ARV?”

“What days / times are you most likely to forget your ARV?”

“Everyone has difficulty taking meds every day. When was the last time you were not able to take your ARV, and how many times in the past week, month were you unable?”

Root cause: there is *always* a reason (or reasons)
- Stigma & disclosure
- Socio-economic barrier
- Transportation & Work
- Psychological
- Misunderstanding
- Side effects

**Goal: >95% adherence**

**Goal: to help the patient**
- No policing
- Encourage transparency

**Practical Strategies**
- Join with daily routines (meal, cleaning)
- Cell phone alarm
- Take meds with another person
- Keep a med diary
Intensive Adherence Counseling (IAC)

for *any* sign of poor adherence
for any detectable Viral Load (even is <1k)
Patient & Treatment Supporter

Education on ART, adherence, monitoring, failure, & resistance

**Indentify Specifics**
- Travel, Work, Education
- Stigma, Privacy, Domestic Difficulties
- Substance Use
- Mental Health / Depression

**Action Plan**
- Specific
- Written on Patient Card
- Monthly appointments
  - Pill Counts
  - Action Plan review
- Viral Load in 3mo
Disclosure

An individual process based on trust

Pediatric Disclosure – a gradual & transparent process

Age 5-7
- ARV keeps their body strong to keep a germ “asleep”

Age 8-10
- Full disclosure may begin
- Physician may or may not assist

Age 11-13
- Full knowledge of HIV status
- Understand safe activities (hugging, kissing, sharing food, etc) and precautions (needles/razors)

Adolescence
- Dialogue on stigma, peer relationships, sexuality
- Family Planning, condoms
- ARV fatigue
- ART Teen Club
Primary Care of PLWHA

Family Planning
- Preventing Mother to Child Transmission (PMTCT)
- Assume all patients >14yo are sexually active
  - Offer condoms to all
  - Contraceptive Counseling
    - Long Acting Reversible Contraceptives: DPMA (Depo-Provera), hormonal implant, Copper IUD
    - Patient autonomy in decision making

Diabetes

Hypertension

Cardiovascular Risk

Malignancy
- Cervical Cancer
Preventive Treatment

Cotrimoxazole Preventive Therapy (CPT)
- HIV exposed and infected children for age > 6 weeks
  - Stop if confirm negative after breastfeeding
- HIV+ adults for life
- Contraindication: jaundice, renal failure, sulfa allergy

TB Preventive Treatment (TPT)
- All HIV+ children and adults at time of ART start
  - Rule out active TB: no cough, weight loss (or failure to thrive in children), fever, night sweat
- Isoniazid (INH) x 6 months (6H)
  - With pyridoxine
  - Visits: start & 1, 3, & 6 months
- Isoniazid (INH) + Rifapentine (RFP) weekly for 3 months (3HP)
- Poor adherence = less effective but will not cause drug-resistant TB
References


Cases (cont)

35yoM with newly diagnosed HIV ready to start treatment
  ◦ What are you next steps, recommendations
  ◦ Then your follow-up?
  ◦ What might be available to start in the “real world” in clinic?

6yoF newly diagnosed HIV
  ◦ What are your next steps?
  ◦ Then follow-up?

32yoF with history poor adherence who has failed efavirenz. What are your next steps?