Capacity Building Program on Clinical Aspects of HIV/AIDS for Nurses and other Health Workers

CASA

Face-to-face training
March 2018

HIV/AIDS Treatment and Prevention
WHO HIV Guidelines Update

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AGENZIA ITALIANA PER LA COOPERAZIONE ALLO SVILUPPO

ISTITVTO SVPERIORE DI SANITA

TIGRAY HEALTH BUREAU

First of all:

wellcome back!

Second:

what expectations do you have from this training?

Write 3 of them at the end of your notebook

Training Organization

Face-to-face training sessions
to promote active discussion on HIV/AIDS topics and clinical scenarios, and to stimulate sharing of experiences among health workers (1 full day)

Distance learning
to provide information on relevant HIV/AIDS-related topics which were introduced during the face-to-face training (video lectures and written material)

Evaluation tools:

1. Short written essay on a clinical question (individual work during the distance learning period)
2. Selection, discussion and short report on a relevant clinical case (group work during the distance learning period). Clinical cases (as above described) will be presented at the following face-to-face training session.

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TOPIC	SCHEDULE
1. HIV/AIDS Treatment and Prevention	Year 1
WHO HIV Guidelines Update	1 day face-to-face training 4 months distance learning
Clinical, immunological and virological monitoring of patients on ART	1 day face-to-face training 4 months distance learning
Retention in Care and Retention on ART	1 day face-to-face training 4 months distance learning
2. Co-infections in PLHIV	Year 2
Tuberculosis: Advanced Aspects	1 day face-to-face training 4 months distance learning
Opportunistic Infections (excluding TB): Advanced Aspects	1 day face-to-face training 4 months distance learning
Sexually Transmitted Diseases	1 day face-to-face training 4 months distance learning
3. Comorbidities in PLHIV	Year 3
Cardiovascular and Metabolic Comorbidities in PLHIV	1 day face-to-face training 4 months distance learning
Cancers in PLHIV	1 day face-to-face training 4 months distance learning
Liver and Kidney Diseases in PLHIV	1 day face-to-face training 4 months distance learning

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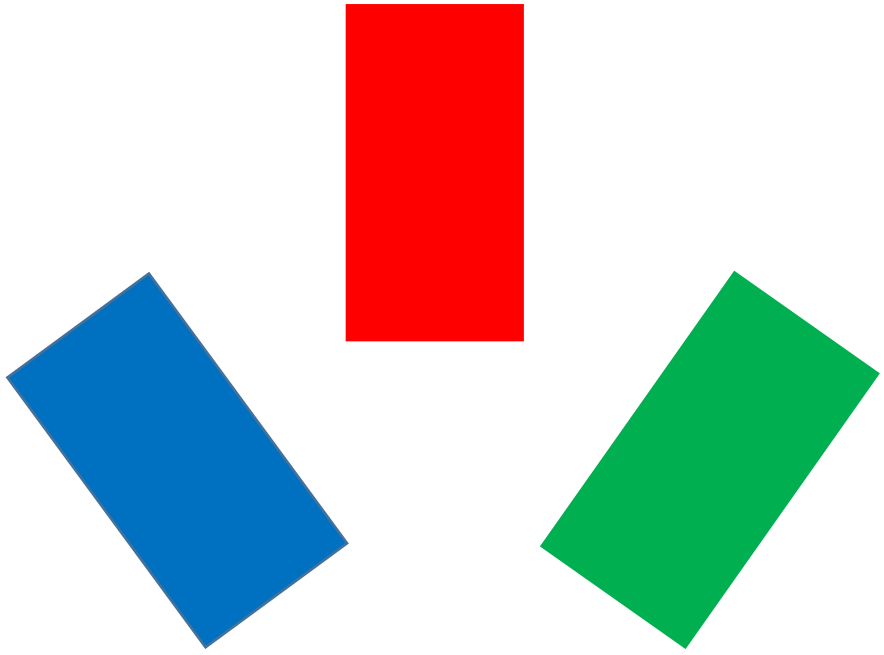
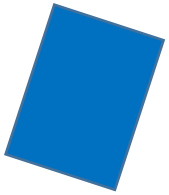
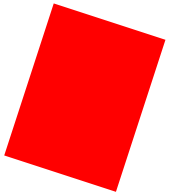
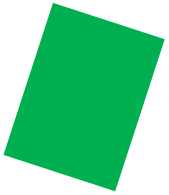
Third…

This is an Interactive Seminar!



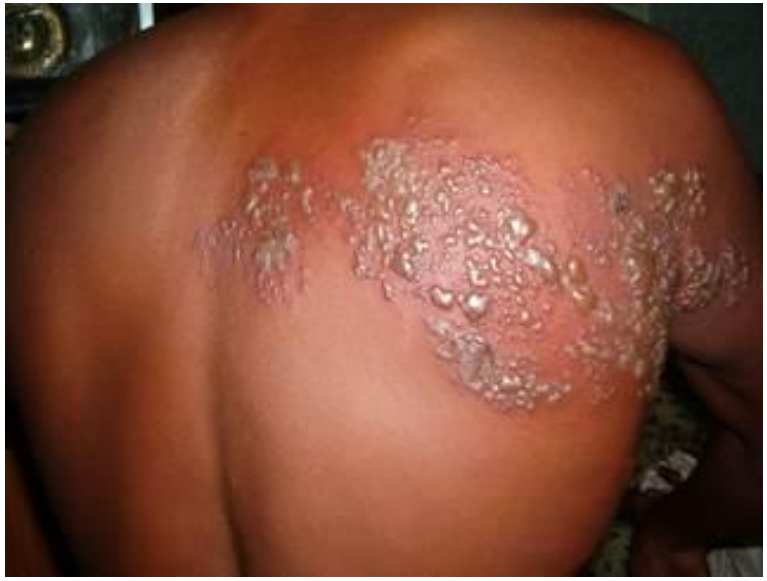
Let's try!

How do you feel in this moment?

- I'm hungry 
- I'm thirsty 
- I'm tired (actually I'm sleeping) 

Clinical Case 1: Liya

- 40 year-old woman
- New HIV diagnosis (after her husband resulted positive)
- CD4 cell count: 450 cell/mmc
- Clinical assessment: dorsal herpes zoster



Vescicles and crusts
on an erithematous base

How can you classify Liya disease according to **WHO Clinical Stage of HIV/AIDS** ?

- Stage II
- Stage III
- Stage IV

WHO Clinical Staging of HIV/AIDS

Clinical Stage	Clinical Conditions or Symptoms
Primary HIV Infection	• Asymptomatic • Acute retroviral syndrome
Clinical Stage 1	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical Stage 2	• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrheic dermatitis • Fungal nail infections
Clinical Stage 3	• Unexplained severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhea for >1 month • Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant) • Persistent oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) • Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis • Unexplained anemia (hemoglobin <8 g/dL) • Neutropenia (neutrophils <500 cells/μL) • Chronic thrombocytopenia (platelets <50,000 cells/μL)
Clinical Stage 4	• HIV wasting syndrome, as defined by the CDC (see Table 1, above) • *Pneumocystis* pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) • Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) • Extrapulmonary tuberculosis • Kaposi sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Cryptococcosis, extrapulmonary (including meningitis) • Disseminated nontuberculosis mycobacteria infection • Progressive multifocal leukoencephalopathy • Candida of the trachea, bronchi, or lungs • Chronic cryptosporidiosis (with diarrhea) • Chronic isosporiasis • Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) • Recurrent nontyphoidal *Salmonella* bacteremia • Lymphoma (cerebral or B-cell non-Hodgkin) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV-associated nephropathy • Symptomatic HIV-associated cardiomyopathy • Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

…and how can you classify Liya disease according to **CDC Classification System for HIV infection**?

- C3
- B2
- A1

CDC Classification System for HIV infection

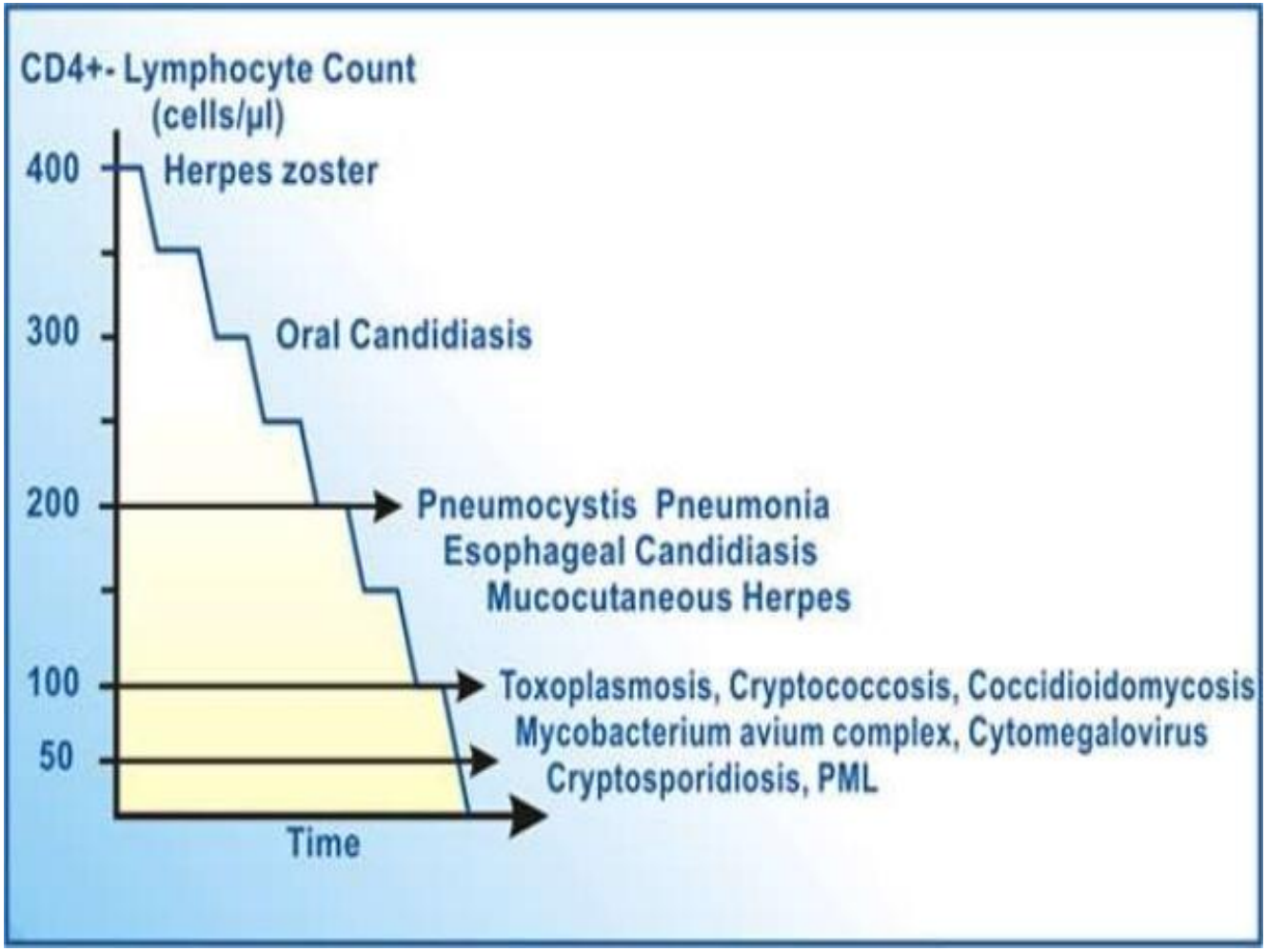
CD4 Cell Count Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	B* Symptomatic Conditions, not A or C	C# AIDS-Indicator Conditions
(1) ≥500 cells/µL	A1	B1	C1
(2) 200-499 cells/µL	A2	B2	C2
(3) <200 cells/µL	A3	B3	C3

Abbreviations: PGL = persistent generalized lymphadenopathy

Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (two or more episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month in duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month in duration), or bronchitis, pneumonitis, or esophagitis

Correlation between CD4 count and opportunistic infections (OIs)



Liya: WHO stage 2, CDC B2

Would you propose her to start ART?

- Yes
- No

"Treat all" strategy

4.3 When to start ART	
NEW 4.3.1 When to start ART in adults (>19 years old)	ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence).
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).
NEW 4.3.2 When to start ART in pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).
NEW 4.3.3 When to start ART in adolescents (10–19 years of age)	ART should be initiated in all adolescents living with HIV, regardless of WHO clinical stage and at any CD4 cell count (conditional recommendation, low-quality evidence). As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with a CD4 count ≤350 cells/mm³ (strong recommendation, moderate-quality evidence).
4.3.4 When to start ART in children younger than 10 years	NEW ART should be initiated in all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count:

2016 WHO Guidelines

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"Treat all" strategy: PROS (advantages)

Patient's point of view

Reduction of

- AIDS-related morbidity
- AIDS-related mortality
- Chronic infection -> immune activation -> organ damage = comorbidities (e.g. cardiovascular disease, tumors)

Public Health point of view

Reduction of HIV sexual transmission (treatment-as-prevention, TAsP)

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"Treat all" strategy: CONS (disadvantages)

Patient's point of view

- Drug related-toxicities
- Long-term adherence

Public Health point of view

Increased size of ART patient cohorts -> need of

- uninterrupted supply of ARV drugs
- ensuring that treatment is decentralised and easily accessible
- ensuring that routine monitoring and active tracing of all patients on ART is strengthened to reduce attrition from care and avert possible increases in HIV drug resistance

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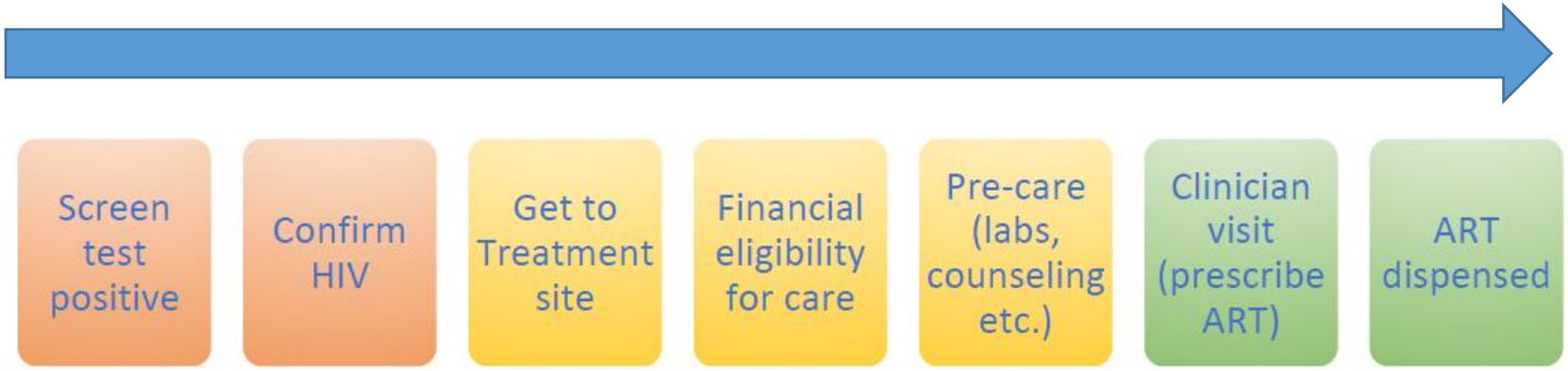
Based on your experience, usually how many days go between HIV diagnosis and ART initiation?

- Less then 14
- 14-28
- More than 28

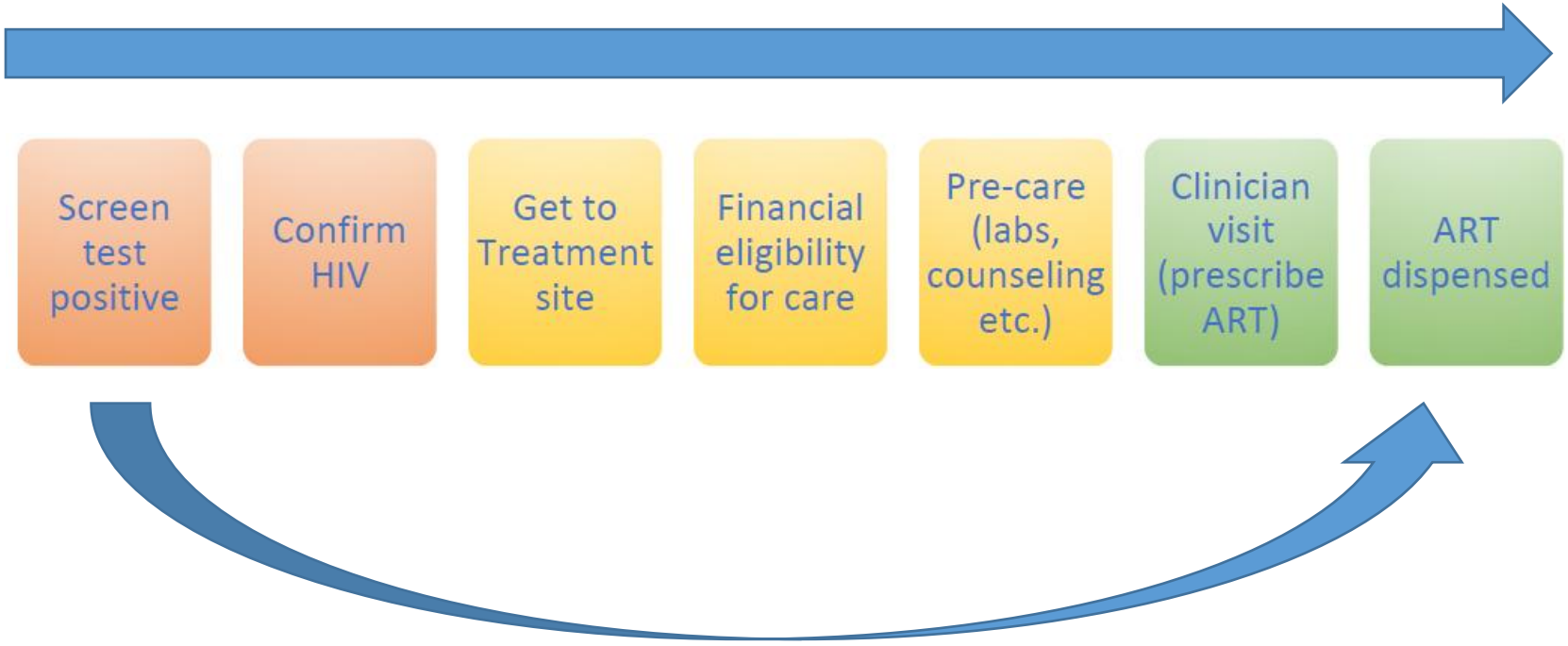
Would you propose her to start ART the same day of receiving HIV diagnosis?

- Yes
- No

Standard of Care



Standard of Care



Same-day Approach

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Why treat same day?

- Better clinical outcomes due to less time off ART (pregnant women)
- Engage people in care with ART before loss to follow-up (LTFU) -> so less LTFU
- Shorter time to treatment means less anxiety, more trust
- TAsP

Why not?

- Might treat with the wrong ART (anemia, renal disease)
- Don't want to miss tuberculosis (TB) or other OIs that require deferral of ART
- Less time to address barriers to ART and adherence
- LTFU pre-ART doesn't risk resistance; LTFU after ART does
- Insufficient time to accept HIV status and to prepare for lifelong treatment

RESEARCH ARTICLE

Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial

Serena P. Koenig et al.

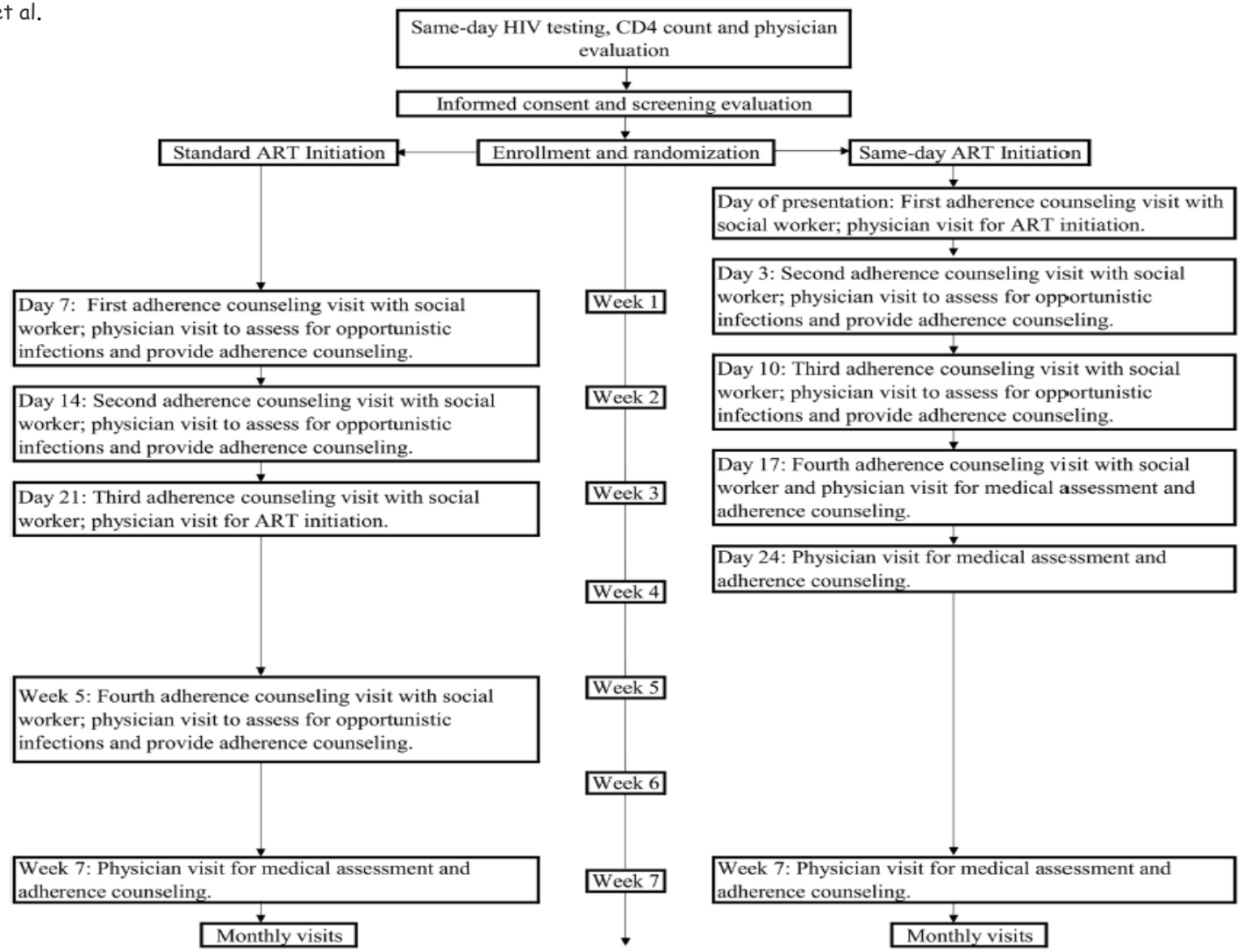

Fig 1. Study interventions for the standard ART and same-day ART groups.

RESEARCH ARTICLE

Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: A randomized unblinded trial

Serena P. Koenig et al.

- At 12 months after HIV testing, a higher proportion of participants in the same-day ART group were retained in care (80% versus 72%), and a higher proportion were retained in care with viral load <50 copies/ml (53% versus 44%) and viral load <1,000 copies/ml (61% versus 52%).

What do these findings mean?

- This study demonstrates that it is feasible to initiate ART on the day of HIV diagnosis for patients with early HIV clinical disease and that same-day treatment leads to increased ART uptake, retention in care, and viral suppression.
- Though same-day ART initiation improves outcomes, retention in care and viral suppression remain suboptimal, so further interventions to maximize long-term outcomes will be essential.

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NEW

Good practice statement

Efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of a person's readiness.

WHO 2016 Guidelines

Recommendations

Rapid ART initiation[a] should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

a Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

Goal: To improve linkage to care and reduce LTFU

WHO 2017 Guidelines

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- The introduction of the "treat all" recommendation (ART for all people living with HIV regardless of CD4 cell count) supports the rapid initiation of ART

- People with no contraindication to rapid ART initiation should be informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation

- Rapid ART start is especially important for people with very low CD4 cell count, for whom the risk of death is high

- People should not be forced to start immediately and should be supported in making an informed choice regarding when to start ART

WHO 2017 Guidelines

What's Your Experience?

What do you think about
the Same-Day Approach?

Liya: WHO stage 2, CDC B2

What ART Would you Start?

- AZT/3TC(FTC)/EFV
- TDF/3TC(FTC)/NVP
- TDF/3TC(FTC)/EFV

Do you remember EFV dosage in the TDF/3TC(FTC)/EFV co-formulation?

- No
- 600 mg
- 400 mg

4.4 What to start: first-line ART

4.4.1 First-line ART for adults

First-line ART for adults[1] should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI):

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART (strong recommendation, moderate-quality evidence).
- If TDF + 3TC (or FTC) + EFV is contraindicated or not available, one of the following alternative options is recommended:
  - AZT + 3TC + EFV
  - AZT + 3TC + NVP
  - TDF + 3TC (or FTC) + NVP

  (strong recommendation, moderate-quality evidence).

NEW

TDF + 3TC (or FTC) + DTG or TDF + 3TC (or FTC) + EFV 400 mg/day may be used as alternative options to initiate ART (conditional recommendation, moderate-quality evidence).

Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities (strong recommendation, moderate-quality evidence).

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

NEW 4.4.2 Fixed-dose combinations

Fixed-dose combinations and once-daily regimens are preferred for antiretroviral therapy (strong recommendation, moderate-quality evidence).

How Many Classes of Antiretroviral Drugs do you Know?

- 2
- 3
- 4

Classes of Antiretroviral Drugs

- NRTI
  - AZT
  - 3TC
  - FTC
  - TDF
  - …
- NNRTI
  - EFV
  - NVP
  - …
- PI
  - LPV
  - ATV
  - DRV
  - RTV
  - …
- INSTI
  - RAL
  - DTG
  - EVG
  - …
- …

Integrase Strand Transfer Inhibitors

Dolutegravir (DTG)

Dolutegravir (DTG)

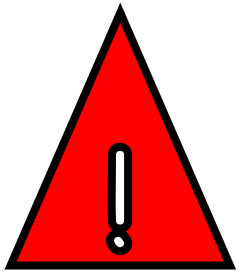
- One daily drug (50 mg/day)
- Alternative third drug for adults (in association with TDF+FTC/3TC)
- Compared to EFV, DTG enhances high viral load suppression and CD4 recovery and has a **high genetic barrier** = it maintains its antiviral effectiveness even in case of reduced treatment adherence
- Very good safety profile
- Few drug-drug interactions

This transition of first-line treatment to DTG-based regimens is supported by WHO in an effort

- to prevent the spread of HIV drug resistance
- and to improve viral suppression and quality of life for people living with HIV

The predicted price reductions announced for the fixed-dose combination of **tenofovir/lamivudine/dolutegravir (TLD)** to an average price of US$ 75 per patient per year
will make DTG-containing ARV treatment regimens affordable for many low- and middle-income countries

Dolutegravir



Main limitations: its safety and efficacy among **people taking rifampicin and in pregnancy** have not been established yet

(data are coming from ongoing studies)

400 mg Efavirenz (EFV)

- A reduced dose of EFV (**400 mg instead of 600 mg**) has been introduced, in association with TDF+FTC/3TC

- This lower dose shows a **better profile** in terms of treatment discontinuation and central nervous system adverse effects

- It is not clear if it maintains its efficacy in **pregnancy and together with rifampicin-based combinations**

400 mg EFV

- Emerging data suggest adequate therapeutic levels in pregnancy and TB treatment with rifampicin but concerns on efficacy with **rising resistance to NNRTIs** in low- and middle-income countries

Clinical Case 1: Liya
Take-home message

- Careful clinical evaluation to assess HIV/AIDS stage
- Treat-all strategy application
- Possibility of starting ART the same day after HIV diangnosis
- First-line ART: TDF/3TC(FTC)/EFV
- New treatment options are coming

Clinical Case 2:Abera

- 38 year-old man
- Fever, sore throat and weakness since 2 weeks

WHAT WOULD YOU DO?

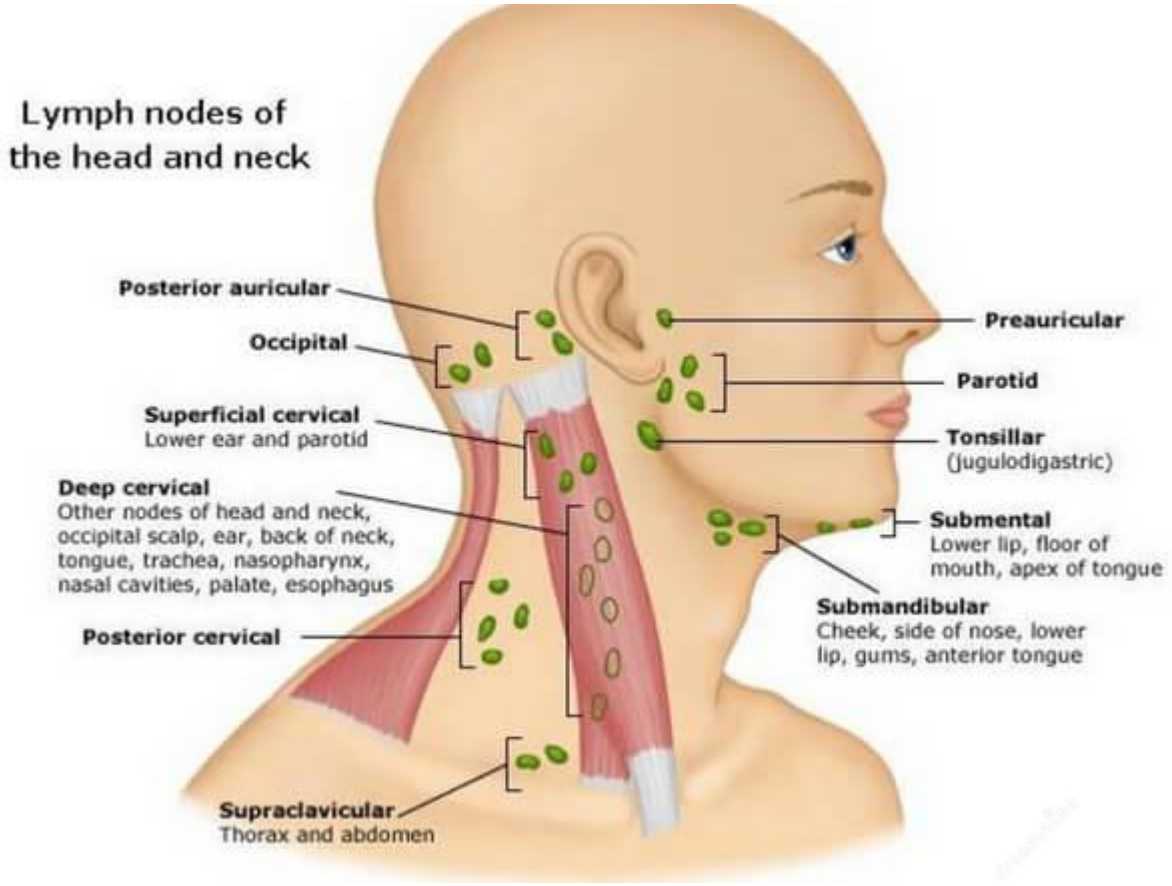
Anamnesis

(collect patient's history)

- Teacher
- Married, his wife is pregnant
- 2-year old healthy son
- No relevant comorbidities
- One month before he had a sexual intercourse with another woman

Physical Exam

- Temperature 38,5°C
- Dehydrated
- Enlarged cervical lymphonodes
- Oral ulcers
- Normal chest exam



LYMPHADENITIS

healthy lymph nodes are not visible

inflammation of the lymph nodes

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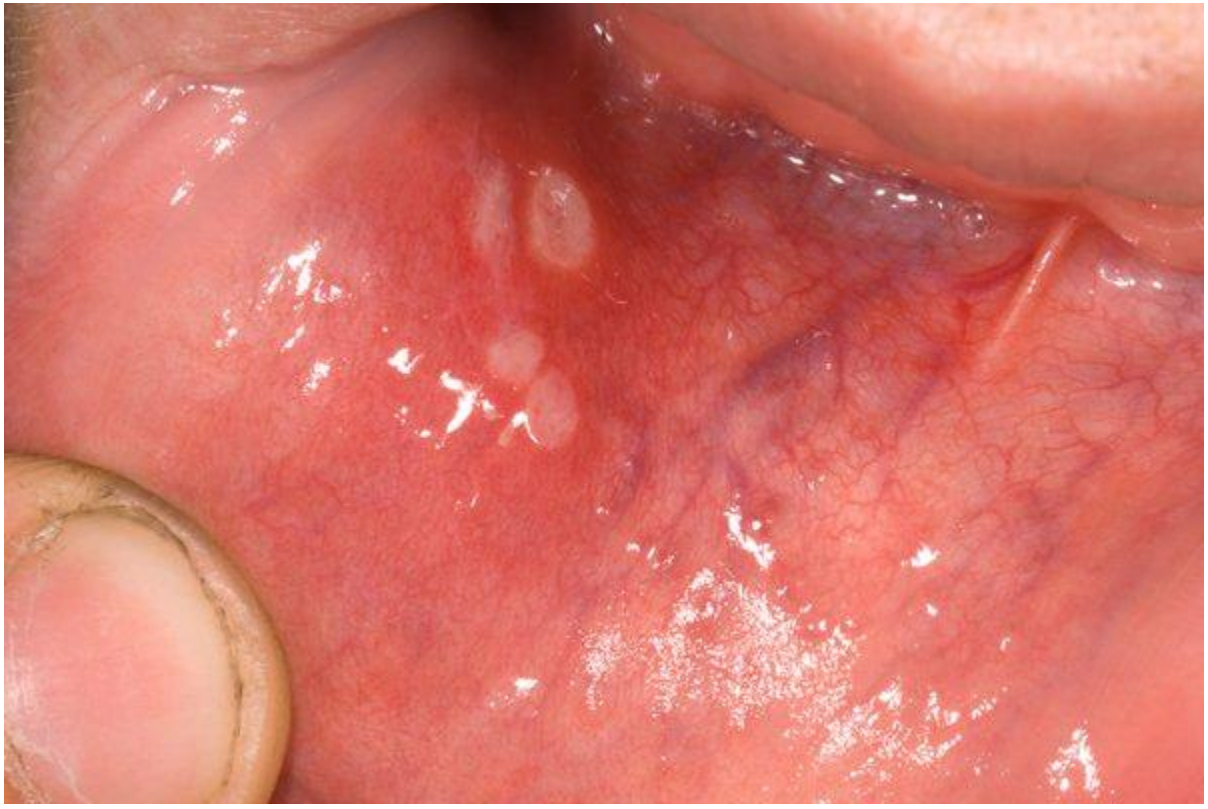
Oral ulcers



beta.nhs.uk

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WHAT WOULD YOU DO?

- Nothing, it's just a flu
- I explain the patient that he is at risk for HIV infection and I ask his consent to do the HIV test
- I admit the patient at hospital to better study his symptoms

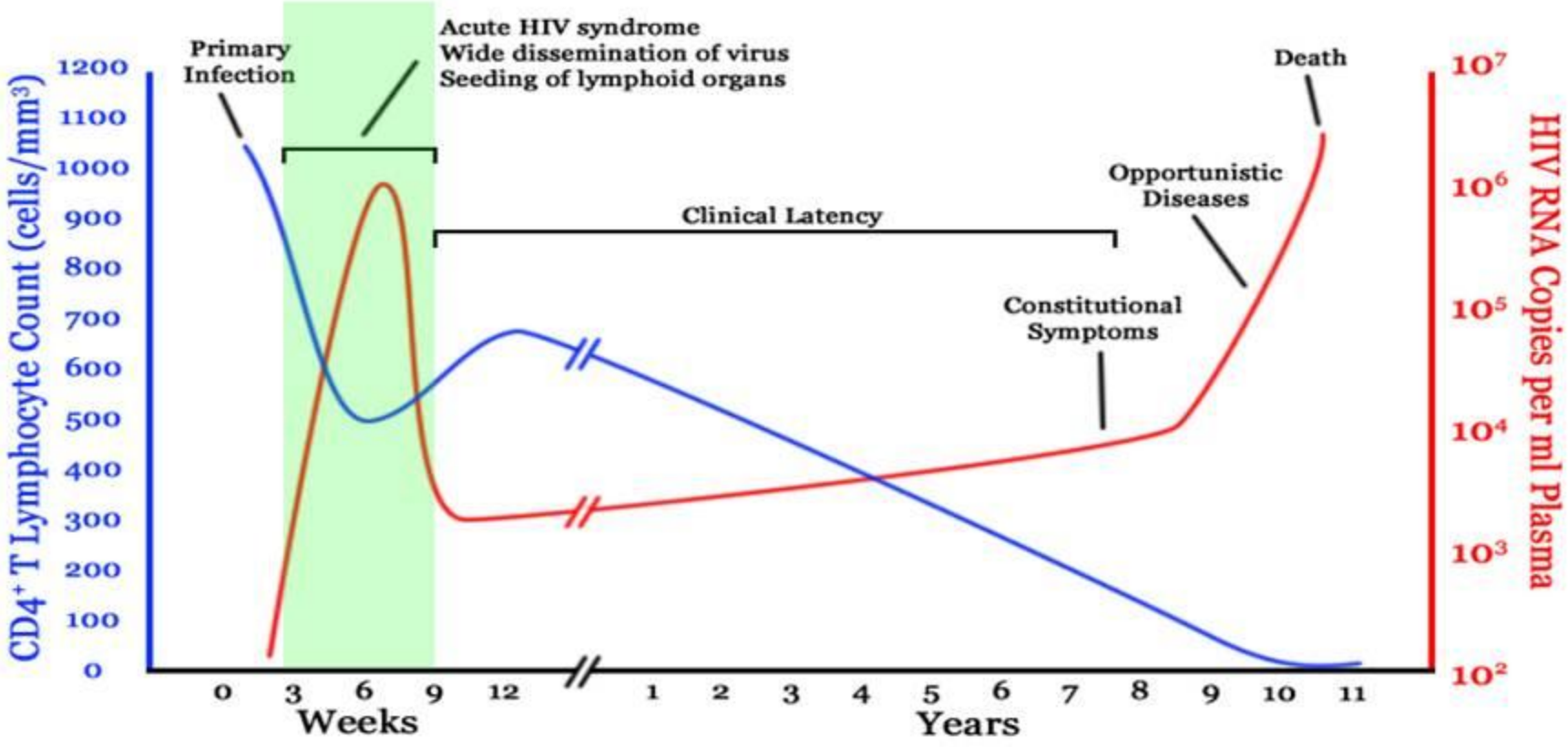
Diagnostic Tests

HIV test (antibodies): NEGATIVE

WHAT WOULD YOU DO?

- Nothing, it's just a flu (as confirmed by the negative HIV test)
- I ask the patient to repeat the HIV test after 4 weeks
- I admit the patient at hospital

Natural History of HIV Infection



Bernard Hirschel

Early HIV infection (six months after acquisition)

- Asymptomatic (10-60%) => remains undetected!
- Symptomatic = Acute HIV Infection after 2-4 weeks (incubation period)

  Fever, fatigue, myalgia, adenopathy, sore throat, rash, gastrointestinal symptoms (nausea, diarrhoea), mucocutaneous ulcers, opportunistic illness (rare)

  None of these symptoms is specific for HIV infection

  Most of symptoms are self-resolving

Without a high degree of suspicion

the diagnosis can frequently be missed by clinicians

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Please write 3 diseases
with a clinical presentation
similar to acute HIV infection

…and then put the paper in the basket!

Acute HIV infection Differential diagnosis

- Mononucleosis due to EBV or CMV
- Toxoplasmosis
- Siphylis
- Rubella
- Other viral infections (e.g. flu)
- Malaria

Public Health Implications

During early HIV infection, patients

- are **highly infectious** because of enormous viral burden in the blood and genital secretions

- may be unaware they are infected and continue to have **high risk behaviours**; pregnant women can transmit HIV perinatally

After four weeks..

The patient comes back and repeats the HIV test:
it results positive (confirmed by a second kit)

ACUTE HIV INFECTION

His CD4 cell count is 700/mmc

Would you propose him to start ART?

- Yes
- No

Clinical Relevance of the Diagnosis and Treatment of HIV Early Infection

Prompt ART initiation

- Reduces the probability of HIV trasmission
- Reduces the size of latent HIV reservoir
- Increases the chances of immune reconstitution to a normal CD4 cell count
- Improves symptoms of acute infection

Is first-line treatment for acute HIV infection different from that for chronic infection?

- Yes
- No

He starts TDF/3TC(FTC)/EFV

Nothing else to do?

Abera anamnesis

- Teacher
- Married, **his wife is pregnant**
- **2-year old healthy son**
- No relevant comorbidities
- One month before he had a sexual intercourse with another woman

Abera anamnesis

- Pregnant wife
- 2-year son

- **Counselling on serostatus disclosure**
- **Wife and son HIV test**

Clinical Case 2:Abera
Take-home message

Early/acute HIV infection

- Need of **clinical suspicion**
- Patients should be questioned about **HIV risk behaviors**, but they may be reluctant to disclose this information or may not perceive their behaviors as high risk
- Early HIV infection should be considered in patients with a recent **sexually transmitted infection**

Clinical Case 2:Abera
Take-home messages

- WHO is discussing more specific guidance on acute HIV infection.
  Anyway, **people with acute HIV infection are included in the "Treat All" strategy**
- Importance of serostatus disclosure

Clinical Case 3: Sarah

- 32 year-old woman
- Fever, weight loss, anorexia, weakness since two months
- Sporadic dry caught
- HIV test resulted positive
- Baseline CD4 cell count: 31 cell/mmc

Anamnesis

- Housekeeper
- Smoker
- Last period about 2 months ago
- No stable boyfriend
- No children
- No relevant comorbidities

Physical Examination

- Temperature 37,8°C
- Blood pressure: 110/70 mmHg
- Heart rate: 95 beats/minute
- Respiratory rate: 16 breaths/minute
- Weight 50 kg, Height 170 cm => BMI 17
- Pale mucous
- Chest exam: reduced vesicular murmur
- No palpable lymphnodes, no spleen enlargement

Vital Signs (Adults): normal range

Blood pressure	120/80 mmHg
Heart Rate	60-100 beats/minute
Respiratory rate	16-20 breaths/minute
Temperature	36.6°- 37°C 98.0°-98.6°F

Body Mass Index (kg/m^2): Indicator of Nutritional Status

BMI	Nutritional status
Below 18.5	Underweight
18.5–24.9	Normal weight
25.0–29.9	Pre-obesity
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

➡ Sarah

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BMI

Overweight and obesity are associated with premature death, cardiovascular diseases, high blood pressure, osteoarthritis, some cancers and diabetes

Underweight before starting ART is a highly significant independent predictor of mortality

-> it is comparable to a CD4 cell count <200 cell/mmc in predicting mortality within 6 months of HIV diagnosis

Sarah: symptomatic, 31 CD4 cell/mmc

Would you perform any blood test?

- Yes
- No

Blood tests

- Hb: 8.8 g/dl (n. v. 10-14 g/dl) ➡ ANEMIA
- Pregnancy test: negative

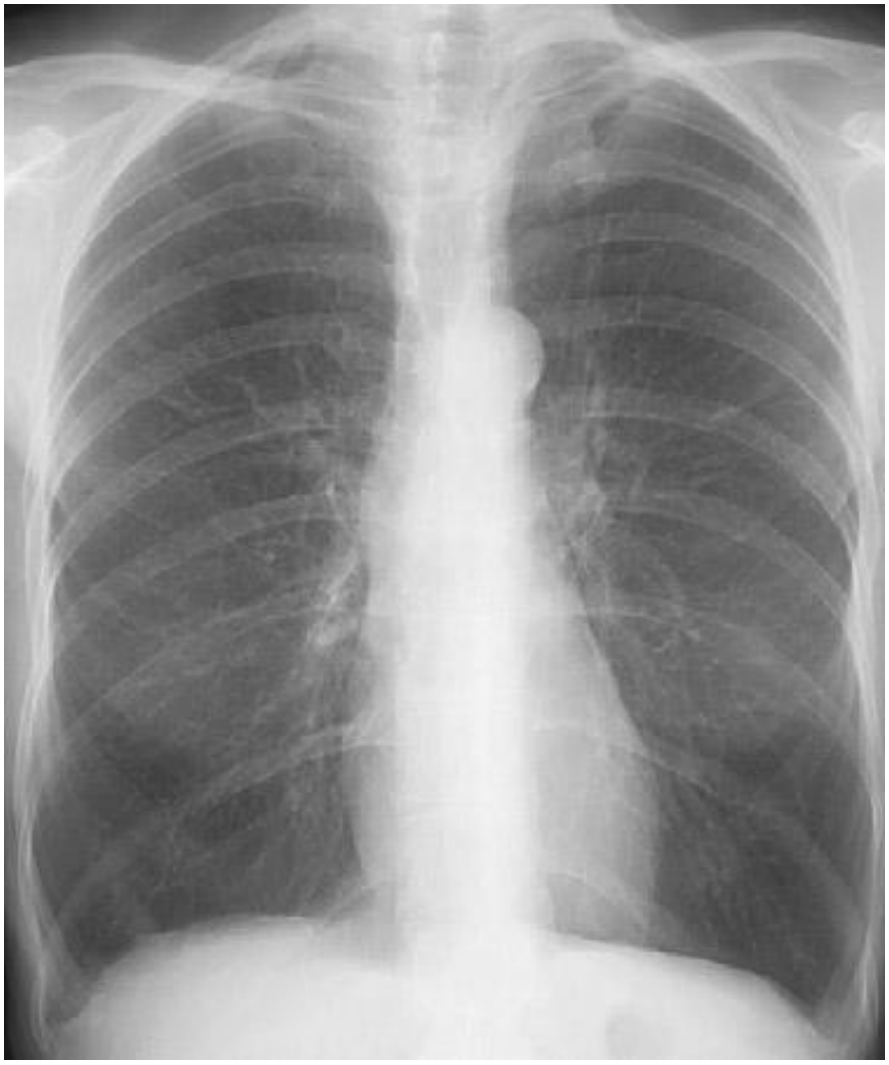
Mestrual disorders can be related to
both weight loss and HIV-infection itself

Would you perform any radiological exam?

- Yes
- No

Chest XR

Normal, except for interstitial markings slightly increased

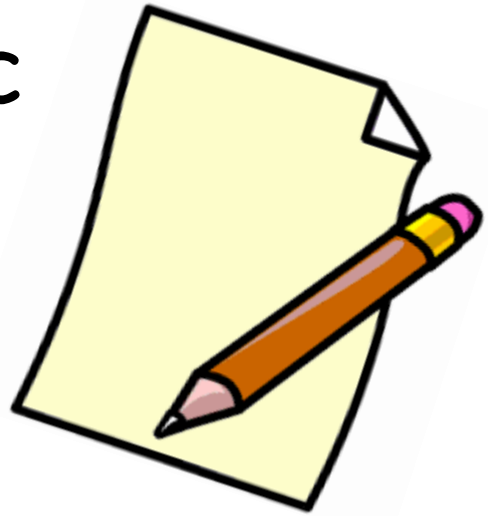


chestx-ray.com

To sum up

- HIV positive, 32 year-old women, smoker
- 31 CD4/mmc at baseline
- complains fever, anorexia, weight loss weakness and dry caught since two months; salutary dry caught
- is underweight and anaemic
- interstitial markings slightly increased at chest XR

Please write 3 diagnostic hypothesis…



…and then put the paper in the basket!

Diagnostic hypotesis

- Wasting syndrome

An involuntary loss of more than 10% of body weight plus at least 30 days of either diarrhea or weakness and fever

- Disseminated TB

No typical radiological findings
No sputum production -> no sputum mycobacterial exam

- P. jirovecii pneumonia

No dyspnoea, normal respiratory rate

- Mycobacterium Avium Complex disease

No (superficial) lymphnodes nor spleen enlargement

Diagnostic hypotesis

- Cryptococcal disease

No neurological syndrome

Search for cryptococcal serum antigen, if available

- Visceral Leishmaniasis

No spleen enlargement (but needs further exams since it is endemic in Tigray)

- Haematological disease (lymphoma)

No (superficial) lymphnodes nor spleen enlargement

Most probable diagnosis: Wasting Syndrome

Advanced Disease: having a CD4 cell count <200 cells/mm3 or a WHO clinical stage 3 or 4 disease

- People presenting with advanced HIV disease are at high risk of death, even after starting ART, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count <100 cells/mmc
- Advanced HIV disease is also associated with increased health-care costs
- For those with advanced HIV disease, more intensive follow-up and a package of interventions could reduce morbidity and mortality in this vulnerable group

WHO 2017 Guidelines

Sarah: wasting syndrome, 31 CD4 cell/mmc

What would you do?

- Start ART as soon as possible
- Defer ART initiation

Would you start Co-trimoxazole prophylaxis?

- Yes
- No

Would you start isoniazid preventive therapy?

- Yes
- No

Table 1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children
Diagnosis	Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people	Any	Yes	Yes	Yes
	LF-LAM for TB diagnosis among people with symptoms and signs of TB	≤100 cells/mm³ Or at any CD4 count if seriously ill	Yes	Yes	Yes[a]
	Cryptococcal antigen screening	≤100 cells/mm³	Yes	Yes	No
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis[b]	≤350 cells/mm³ or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes For criteria, see Annex 1
	TB preventive treatment[b]	Any	Yes	Yes	Yes[c]
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	<100 cells/mm³	Yes	Yes	Not applicable (screening not advised)

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Table 1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children
ART initiation	Rapid ART initiation (as recommended in Chapter 3)	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	<200 cells/mm^3	Yes	Yes	Yes

[a] Limited data available for children. [b] Co-trimoxazole, isoniazid and pyridoxine are available as a fixed-dose combination tablet. [c] For children younger than 12 months, only those with a history of TB contact should receive TB preventive treatment if the evaluation shows no TB disease.

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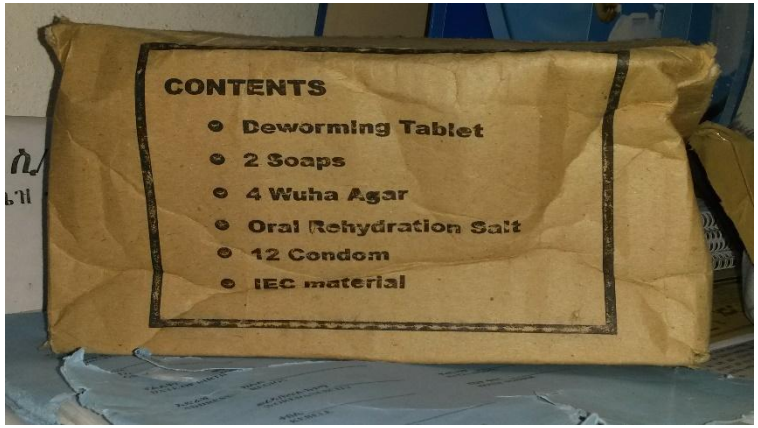
Would you start ART, co-trimoxazole prophylaxis and isoniazid preventive therapy all together the same say?

- Yes
- No

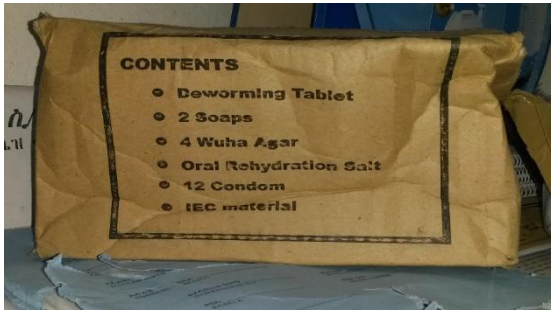
What else does Sarah need?



- Nutritional support
- Deworming treatment
- Psicological support (fear of stigma)
- Adherence support
- Close clinical follow-up

CASA

Deworming treatment



- Empiric use of anthelmintic drugs to reduce the prevalence of infection due to soil-transmitted helminths
- These infections can cause/aggravate malnutrition, and are associated with morbidity including delays in growth and cognitive development in children

Clinical Case 3: Sarah
Take-home message

- Low BMI as a predictor of mortality
- Careful clinical, haematological and radiological assessment is needed to identify AIDS defining conditions
- Patients require a multi-components package of care

Clinical Case 4: Tesfay

- 40 year-old man
- Diagnosed with HIV in 2010, WHO stage IV (TB), baseline CD4 210 cell/mmc
- On TDF/3TC/EFV since 7 years

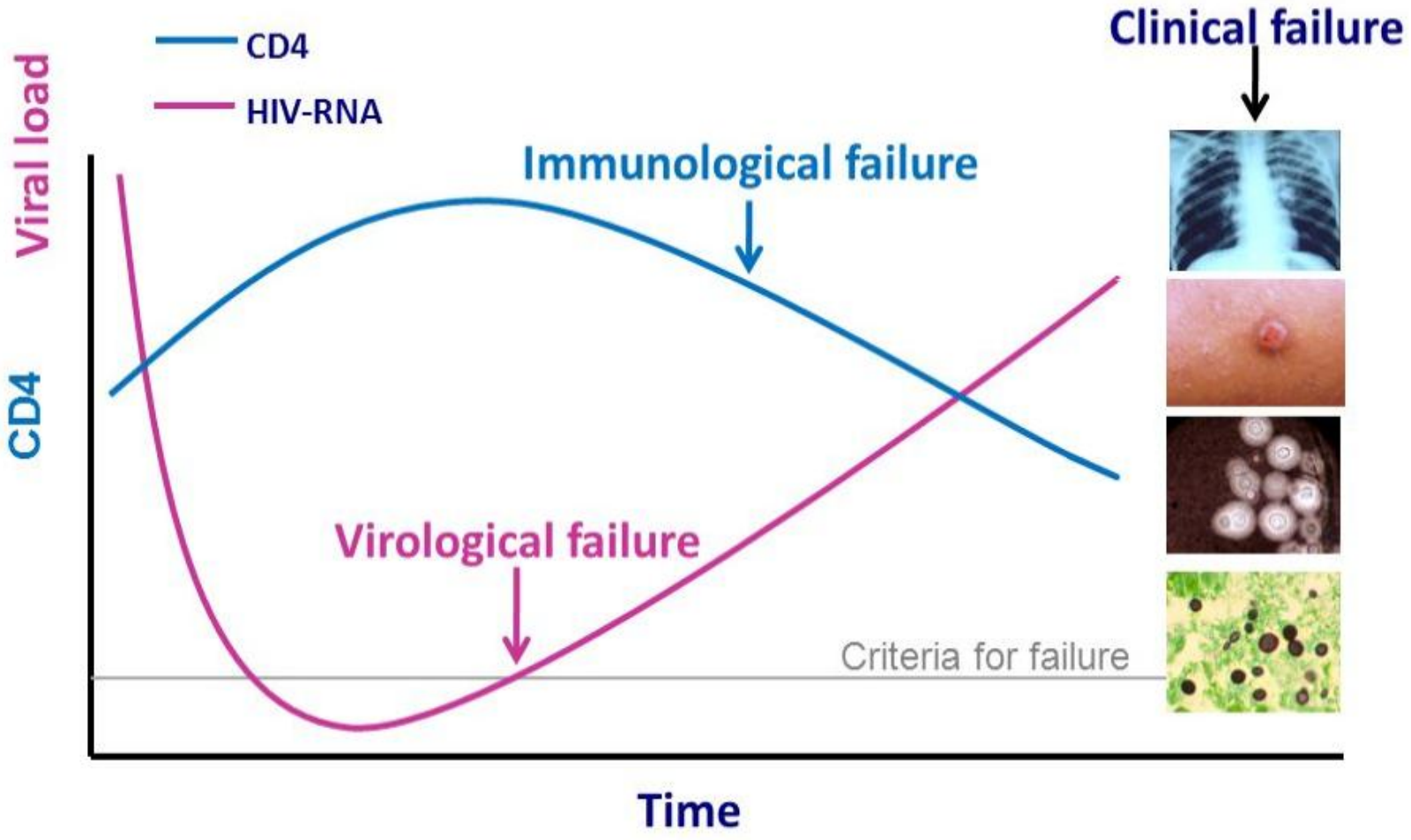
Clinical Case 4: Tesfay

- Lost to follow up in the last 12 months
- He comes back at ART clinic: in the last month he experienced dyspnoea, caught, fatigue -> you finally diagnose
  P. jirovecii pneumoniae

What are you facing with?

Treatment failure

Treatment Failure



FAILURE

VIROLOGICAL FAILURE

viral load above 1,000 copies/ml based on two consecutive viral load measurements in a 3-month interval, with adherence support following the first viral load test, after at least six months of starting a new ART regimen

IMMUNOLOGICAL FAILURE

Adults and adolescents

CD4 count at or below 250 cells/mm^3 following clinical failure or persistent CD4 levels below 100 cells/mm^3

Children

Younger than 5 years

Persistent CD4 levels below 200 cells/mm^3

Older than 5 years

Persistent CD4 levels below 100 cells/mm^3

CLINICAL FAILURE

Adults and adolescents

New or recurrent clinical event indicating severe immunodeficiency after 6 months of effective treatment

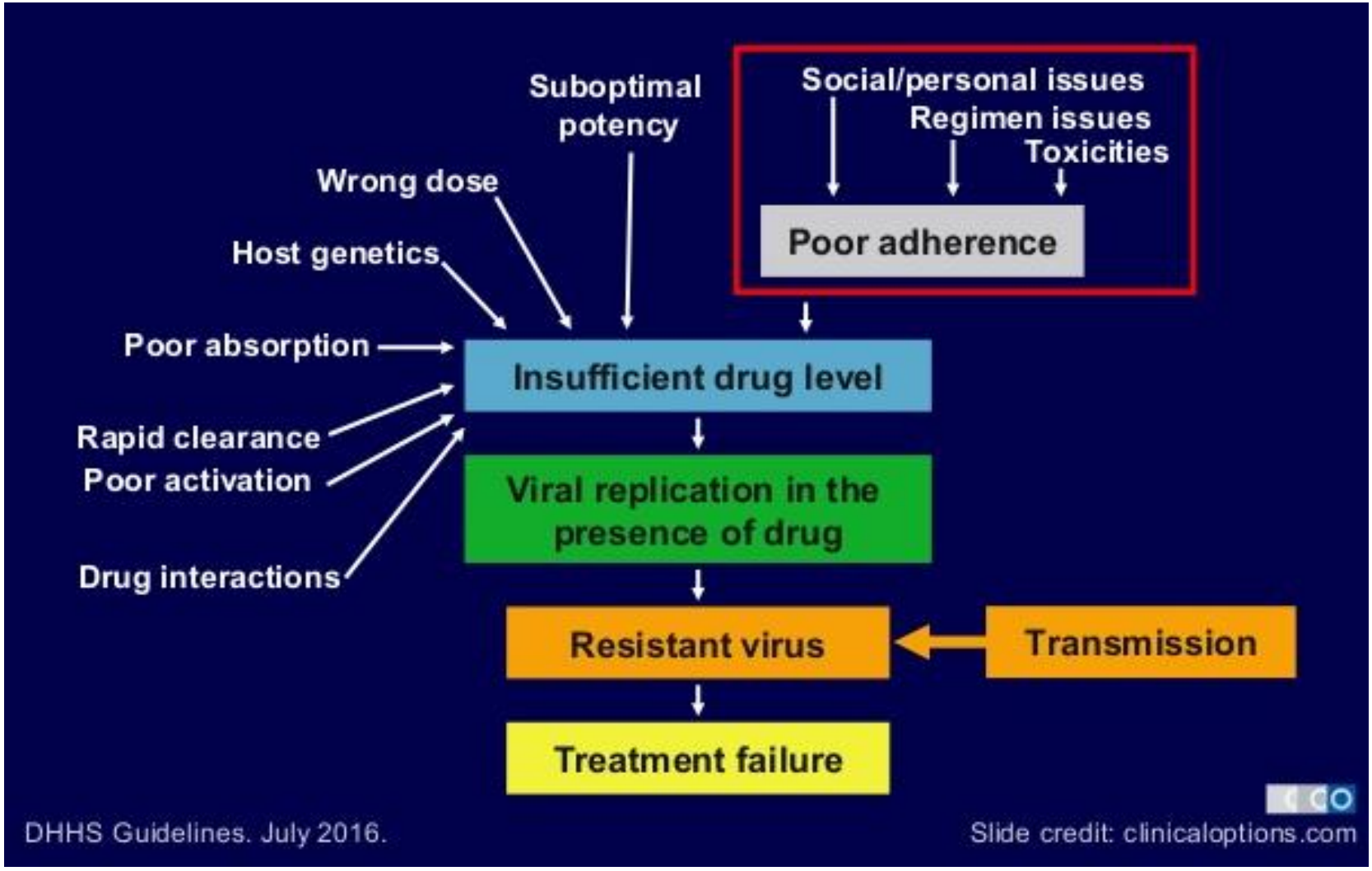
Children

New or recurrent clinical event indicating advanced or severe immunodeficiency after 6 months of effective treatment

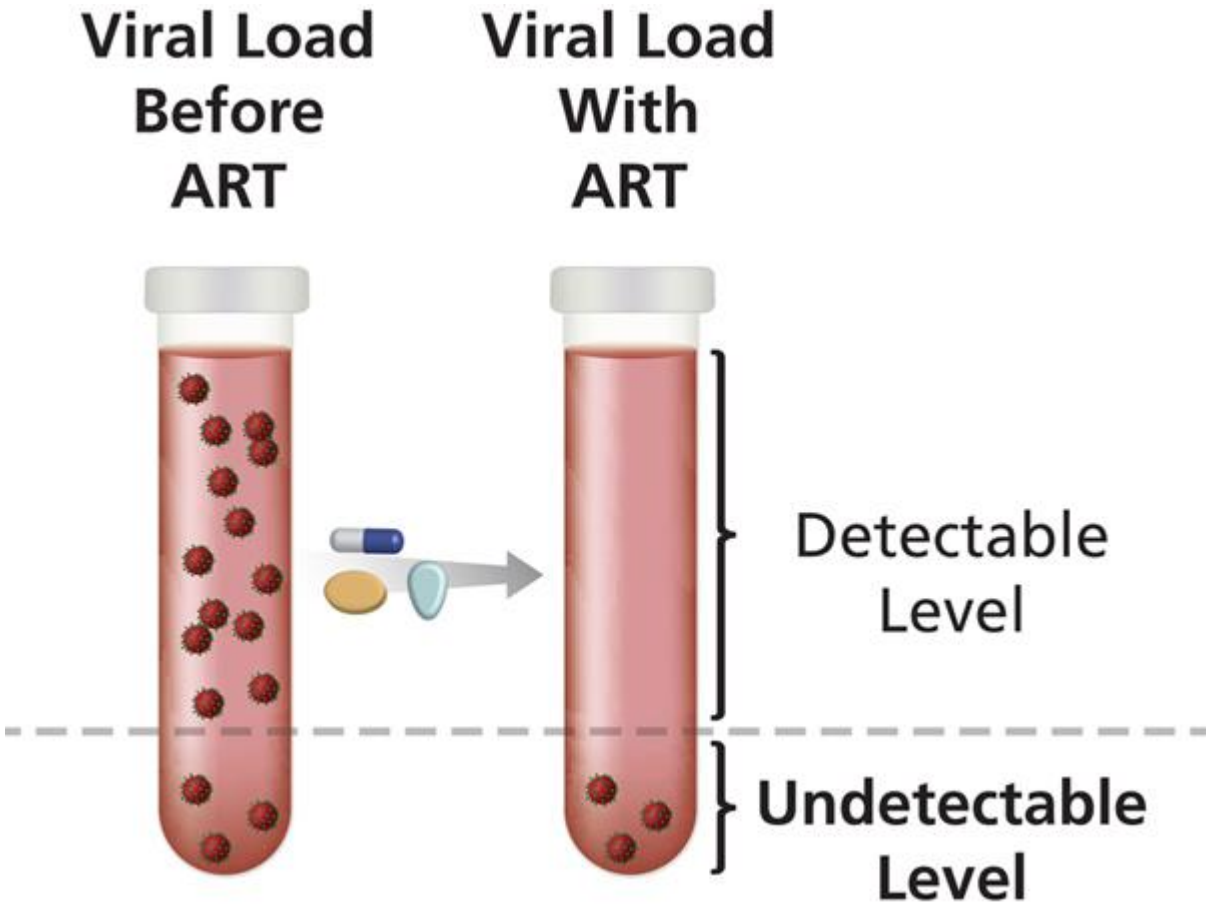
WHO 2017 Guidelines

CASA

Causes of Treatment Failure



Viral Load (VL): the amount of HIV in the blood



Viral Load

Compared to clinical or immunological monitoring, VL provides an early and more accurate indication of treatment failure and the need to switch to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes

Around 70% of patients on first-line ART who have a first high VL will resuppress following an adherence intervention, indicating non-adherence as the reason for the high VL in the majority of cases

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Viral Load

It can also serve as a
proxy measure for the risk of transmission and effectiveness of prevention interventions
at both the individual level, especially for pregnant women, and at the population level

WHO 2016 Guidelines


IAS
U=U
UNDETECTABLE
=
UNTRANSMITTABLE
A PERSON LIVING WITH HIV WHO HAS AN UNDETECTABLE VIRAL LOAD DOES NOT TRANSMIT THE VIRUS TO THEIR PARTNERS.
The International AIDS Society is proud to endorse the U=U consensus statement of the Prevention Access Campaign.

CASA

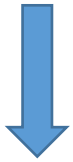
Tesfay experienced Treatment Failure
What can you do now?

1. Start ant-PCP treatment (co-trimoxazole)

Tesfay experienced Treatment Failure
What can you do now?

2. Measure his VL

It results **200.000 cp/ml**



Re-start first line ART and do counselling on ART Adherence

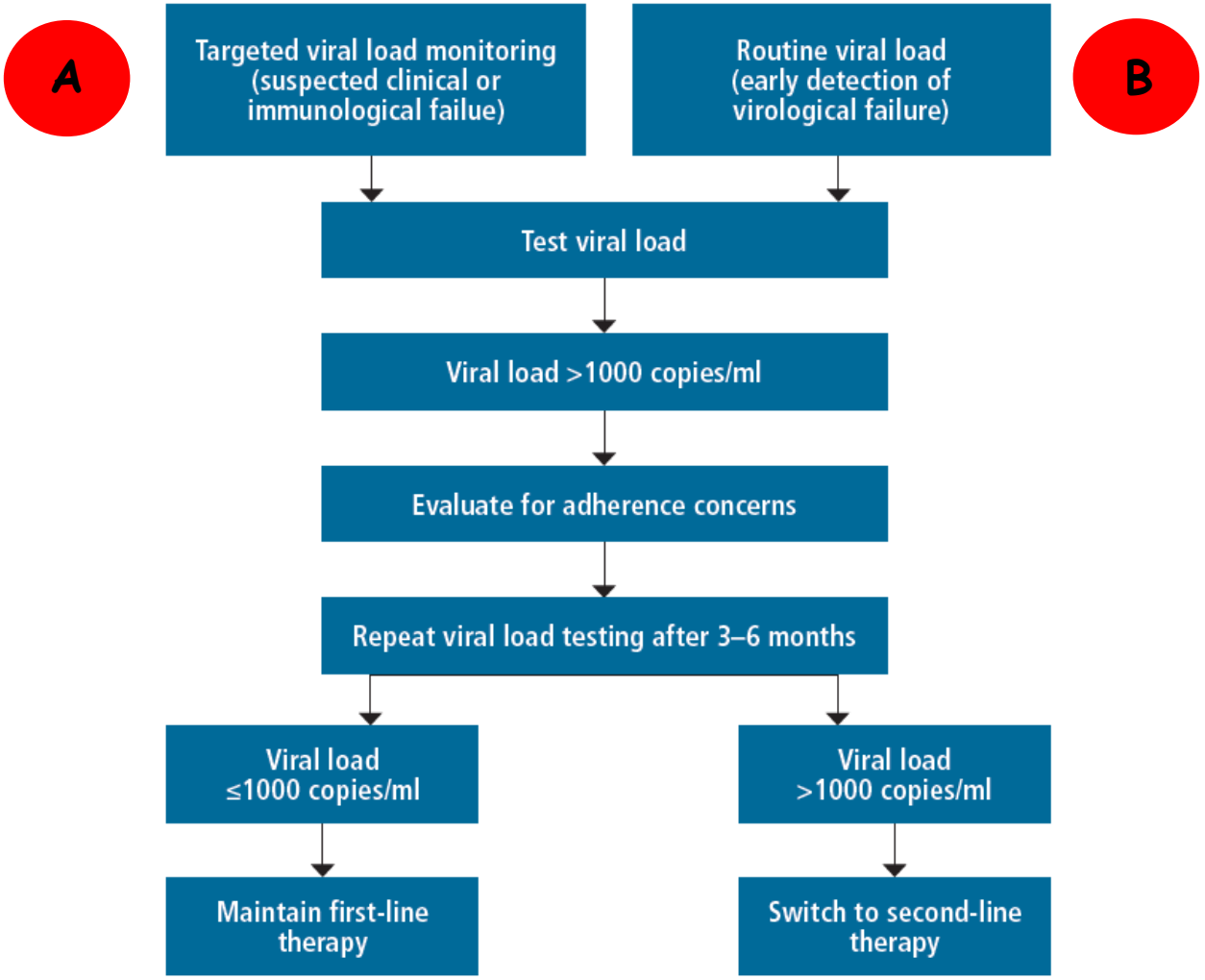
After 3 months

- Tesfay reports good ART adherence
- Repeats VL: it results **<1.000 cp/ml**

What would you do?

- Prescribe second-line ART
- Add another drug to current ART
- Maintain first-line ART

Viral Load Testing Strategy



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A Diagnosis of Treatment Failure

Recommendations for diagnosis of treatment failure

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure[a] (strong recommendation, low-quality evidence).

If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure (strong recommendation, moderate-quality evidence).

Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (that is, two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.

WHO 2017 Guidelines

CASA

B Routine Viral Load

Recommendations for routine monitoring

Routine viral load monitoring can be carried out at 6 months, at 12 months and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting[a] (conditional recommendation, very low-quality evidence).

In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed[b] (conditional recommendation, low-quality evidence).

[a] Viral load testing should be performed early after initiating ART (within 6 months), at 12 months and then at least every 12 months to detect treatment failure. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure, with targeted viral load testing to confirm viral failure where possible.

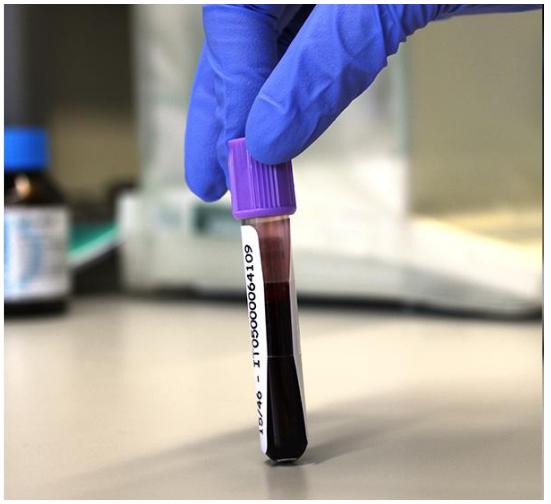
[b] WHO defines people stable on ART according to the following criteria: on ART for at least 1 year, no current illnesses or pregnancy, good understanding of lifelong adherence and evidence of treatment success (two consecutive viral load measurements below 1000 copies/mL). For service delivery recommendations in these guidelines (*see* Chapter 6 "Service delivery"), an additional criterion is that there are no adverse drug reactions requiring regular monitoring, but this is not relevant to this recommendation.

WHO 2017 Guidelines

CASA

How can you collect samples for VL?

Figure 1. Dried DBS on a 903 filter paper card



Plasma specimen

Dried blood spot specimens using venous or capillary whole blood can be used to determine the HIV viral load. A threshold of 1000 copies/mL can be used to determine viral failure when using dried blood spot samples, as defined for testing in plasma[a] (conditional recommendation, low-quality evidence).

NEW

[a] Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended for use in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

WHO 2016 Guidelines

CASA

Dried blood spot specimens

- Dried blood spot specimens using venous or capillary whole blood can be used to determine the HIV VL using a treatment failure threshold of 1,000 copies/ml

- While plasma specimens are preferred, dried blood spot specimens can be used in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens

WHO 2017 Guidelines

Dried blood spot specimens

- Dried blood spot specimens using venous or capillary whole blood can be used to determine the HIV VL using a treatment failure threshold of 1,000 copies/ml

- While plasma specimens are preferred, dried blood spot specimens can be used in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens

WHO 2017 Guidelines

Are you using VL in your daily practice?

- Yes
- No

Are you familiar with this new tool?

- Yes
- No

In your opinion, is CD4 cell count still useful?

- Yes
- No

Yes!

CD4 cell count is still useful

- At baseline remains important to determine whether the patient has advanced disease or not: relying on clinical staging alone risks missing substantial numbers of people living with HIV with severe immune suppression
- <350 CD4: start ART as a priority
- <100 CD4: criptococcal antigen, LAM

Clinical Case 4: Tesfay
Take-home message

- Connection among virological, immunological and clinical failure
- VL as the preferred monitoring approach for treatment failure
- VL is recommended both for diagnosis of treatment failure and for routine monitoring

Clinical Case 5: Layla

- 33 year-old woman
- 8th month of pregnancy
- 3 year-old son
- No relevant comorbidities
- Diagnosed with HIV
- Asymptomatic (WHO stage I), baseline CD4 600 cell/mmc

Would you prescribe her ART?

- No, because she has high CD4 cell count
- Yes
- No, because it ART could be harmful to the child

NEW

Recommendation

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong (strong recommendation, moderate-quality evidence).

Source: HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/adolescents/en).

- Improve the mother's health
- Prevent mother-to-child transmission (MTCT) of HIV
- Prevent HIV transmission from the mother to a sexual partner

WHO 2016 Guidelines

CASA

ART should be started urgently in all pregnant women, even if they are identified late in pregnancy or in the postpartum, because the most effective way to prevent MTCT is to reduce maternal viral load

Which ART would you prescribe?

- TDF/3TC(FTC)/EFV
- AZT/3TC(FTC)/EFV
- TDF/3TC(FTC)/NVP

First-line ART	Preferred first-line regimens	Alternative first-line regimens[a,b]
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP

- There was no evidence of an increased risk of congenital anomalies with TDF or EFV compared to other antiretroviral drugs
- The risk of neural tube defect associated with EFV remains low and is comparable to the general population in the United States

WHO 2016 Guidelines

CASA

What about infant prophylaxis?

- I would prescribe him a six-week course of AZT+NVP
- I would not offer him any prophylaxis
- I would prescribe him a six-week NVP course

Dual Infant Prophylaxis

Infants born to HIV-infected mothers who are **at high risk** of acquiring HIV should receive **dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life**, whether they are breastfed or formula fed.

"High risk infants" include those born to women

- who have received less than four weeks of ART at the time of delivery OR
- with viral load >1000 copies/ml in the four weeks before delivery OR
- with incident HIV infection during pregnancy or breastfeeding OR
- identified for the first time during the postpartum period, with or without a negative HIV test prenatally

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Do you usually manage HIV infection in pregnant women?

- No
- No, this task belongs to physician/midwives
- Yes

Do you usually manage HIV infection in exposed infants?

- No
- No, this task belongs to physician/midwives
- Yes

Testing high-risk newborns

No specific approach to the testing of high-risk newborns is recommended.

However, because infants who are first identified as HIV-exposed postpartum have a high cumulative risk of already having acquired HIV by the time prophylaxis is initiated, an HIV polymerase chain reaction (PCR) test should be performed around the time of initiating prophylaxis.

This will help to minimize the risk of development of resistance due to extended prophylaxis in infected infants and help to promote linkage to timely initiation of ART

WHO 2016 Guidelines

Layla is afraid about breastfeed

- I would recommend breastfeeding
- I would discourage her from breastfeeding

Recommendations

National or subnational health authorities should decide whether health services will principally counsel and support mothers known to be HIV infected to either breastfeed and receive ARV[a] interventions or avoid all breastfeeding.

In settings where national authorities have decided that maternal and child health services will principally promote and support breastfeeding and antiretroviral interventions as the strategy that will most likely give infants born to mothers known to be HIV infected the greatest chance of HIV-free survival, mothers known to be infected with HIV should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life.[b] Breastfeeding should then stop only once a nutritionally adequate and safe diet without breast milk can be provided (strong recommendation, high-quality evidence for the first 6 months; low-quality evidence for the recommendation of 12 months).

WHO guidance has been based on evidence that the maximum benefit of breastfeeding in preventing mortality from diarrhoea, pneumonia and malnutrition is in the first 12 months of life and that the risk of transmitting HIV to infants through breastfeeding is low when the mother is receiving ART

WHO 2016 Guidelines

Clinical Case 5: Layla
Take-home message

- Women diagnosed with HIV late in pregnancy are at HIV risk of HIV transmission, thus prompt ART initiation is recommended
- Dual infant prophylaxis in high risk infants is advocated
- Breastfeeding is recommended

Summary of Clinical Cases

1) Liya: "Treat all" Strategy
2) Abera: Acute HIV Infection
3) Sarah: Advanced Disease
4) Tesfay: Treatment failure
5) Layla: PMTCT

Do you think that Liya (450 CD4 at baseline) and Sarah (31 CD4 at baseline) have the same chance of obtaining and maintaining a good CD4 cell count (>500 cell/mmc)?

- Yes
- No
- I don't know

After three years on ART with virological suppression

- 15% of patients with a baseline CD4 count ≤200 cells/microL do not achieve an increase in the CD4 count to >200 cells/microL
- Overall mortality is greater among these patients without CD4 cell recovery compared with those who achieved a CD4 count >200 cells/microL

CASA

Clin Infect Dis. 2014 May;58(9):1312-21

Homework – group (health facility)

- Choose, analyze, discuss 3 clinical cases that address the themes of the first lesson/seminar, focusing on controversial points

- Present a short report at the next on site seminar (the presenting person has to change)

CASA

Next On Site Seminar

Clinical, immunological and virological monitoring of patients on ART

Focus on

- IRIS
- Treatment failure – Second line ART
- Management of side effects
- PMTCT

CASA

Brief anonymous questionare for you

Thank You!

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