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Human Immunodeficiency Virus-Tuberculosis Coinfection: Challenges

AA Mumtaz, ZA Mumtaz

Abstract

Human immunodeficiency virus (HIV)-tuberculosis (TB) coinfection is a growing concern, both nationally and internationally. TB-related complications accounts for >25% of deaths in people living with HIV (PLHIV). Delay in diagnosis of HIV-TB coinfection could lead to emergence of MDR/XDR TB. Manifestations depend on the stage of disease and can have varied presentation. There has been significant progress made in both diagnosis and treatment of the condition. Knowledge of drug interactions, overlapping drug toxicities, as well as timing of initiation of ART following ATT administration is important. Proper ART and ATT therapy selection and dose adjustment are imperative.

Introduction

Human immunodeficiency virus (HIV)-tuberculosis (TB) coinfection is global health problem, and continues to pose challenges. World Health Organization (WHO) in 2018 estimated that, almost 8,62,000 people living with HIV (PLHIV) were coinfected with TB worldwide. TB is one of the leading causes of death, among patients with HIV, and accounts for almost one-third of the deaths. PLHIV are 19 times more likely to develop tuberculosis, than those without HIV. A vast majority of death (84%) due to HIV-TB coinfecion were reported from Africa. Delay in diagnosis of HIV-TB coinfection can lead to emergence of MDR/XDR TB. TB continues to be a top killer among infectious diseases, with WHO report estimating that about 1.5 million people died of tuberculosis alone in 2018, including the 2,51,000 people with HIV-TB coinfection. The worldwide incidence of TB for 2018 was estimated to be 10 million, amongst which only 7 million have access to antituberculosis therapy (ATT) (R1), and about 0.5 million people developed drug resistant TB. The prevalence for HIV at the end of 2018 was 37.9 million, amongst which 23.3 million (62%) patients received antiretroviral treatment (ART), and 0.77 million died from HIV-related illnesses. The number of patients receiving ART increased to 24.5 million, by June 2019. TB is among the most common illnesses, among PLHIV, and is fatal, if undertreated/untreated. So early detection of TB and prompt linkage to ATT and ART can prevent or delay these deaths.

Presentation and Diagnosis of HIV

The clinical manifestation depends upon staging of HIV disease, and presence of opportunistic infections (OIs). Presentation can range from being asymptomatic, to experiencing fever, headache, rash, or sore throat. As the immune system gradually weakens, patients may develop cough, diarrhea, weight loss, or generalized lymphadenopathy. If treatment is delayed, patients can develop severe illness like tuberculosis, cryptococcal meningitis, bacterial pneumonia, pneumocystis jiroveci pneumonia, kaposi’s sarcoma, and lymphoma.

Diagnosis of HIV infection: Diagnosis of HIV infection is based on following tests:
**SECTION 13**  

Human Immunodeficiency Virus

- HIV-ELISA (Enzyme-linked immunosorbent assay)—It is 50% sensitive after 22 days of HIV infection and 95% positive within 6 weeks. Sensitivity is 99.9%.
- Western Blot Test—It is confirmatory test for HIV. It is highly specific test and is based on antibody to core protein (p24) and envelope glycoprotein (gp41).
- HIV Rapid Antibody Test—It provides result within 16–20 minutes, easy to perform and is a screening test.
- Absolute CD4 Lymphocyte Count—It is predictor of HIV progression, so risk of progression to AIDS, OI, or malignancy is high with CD4 < 200 cell/µL.
- CD4 Lymphocyte Percentage—It is more reliable than CD4 Count. If less than 14%, risk of progression to AIDS to OI or malignancy is high in absence of treatment.
- HIV Viral Load—It indicates the amount of active replication of HIV, indicating disease progression and response to antiretroviral drugs.
- P24 Antigen—It indicates replication and is positive even before seroconversion.

**Antiretroviral Therapy**  

Usually three drugs from two different groups of ARV drugs are given (Tables 1 and 2).

**Presentation and Diagnosis Tuberculosis**

Tuberculosis is caused by infection with mycobacterium tuberculosis. The infection may be active TB or latent tuberculosis infection (LTBI). Active TB may be pulmonary TB or extra pulmonary TB. LTBI is presence of mycobacterium tuberculosis organism without symptoms or radiographic evidence of TB disease.

**Diagnosis of TB in HIV-infected Persons**

Screening of TB should be done using clinical algorithm, that is, cough, fever, weight loss, or night sweats and should be evaluated for TB.

- **Radiological findings:** It may show diffuse micronodular infiltrations, as in miliary tuberculosis, or show

**TABLE 1** NACO (National AIDS Control Organization) recommended first-line ART regimen

<table>
<thead>
<tr>
<th>ART regimen</th>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir + Lamivudine + Efavirenz</td>
<td>First-line ART regimen for all ARV naive PLHIV patients with HIV-1 infection, age &gt;10 years and body weight &gt;30 kg</td>
</tr>
<tr>
<td>Abacavir + Lamivudine + Efavirenz</td>
<td>First-line ARV regimen for all patient with abnormal serum creatinine. All adults and adolescents with body weight &lt;30 kg</td>
</tr>
<tr>
<td>Tenofovir + Lamivudine + Lopinavir/ritonavir</td>
<td>First-line ART regimen for all women with single dose NVP exposure in past pregnancy, all confirmed HIV-2 or HIV-1 and HIV-2 coinfection</td>
</tr>
<tr>
<td>Zidovudine + Lamivudine + Nevirapine</td>
<td></td>
</tr>
<tr>
<td>Zidovudine + Lamivudine + Efavirenz</td>
<td>All patients who are on either of these first-line regimens initiated earlier, need to be continued on same regimen unless failing</td>
</tr>
</tbody>
</table>

**TABLE 2** WHO 2018 recommended first-line antiretroviral therapy regimen

<table>
<thead>
<tr>
<th>Population</th>
<th>Preferred</th>
<th>Alternatives</th>
<th>Special situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult men and adolescent boys</td>
<td>TDL</td>
<td>TLE600 TLE400</td>
<td>AZT + 3TC + EFV600 TDF + 3TC (or FTC) + PI/r</td>
</tr>
<tr>
<td>Pregnant (&gt;8 weeks) and breast feeding women and adolescent girls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women and adolescent girls with effective contraceptive or not of childbearing potential</td>
<td>TLE600</td>
<td>TDF + 3TC (or FTC) + PI/r</td>
<td></td>
</tr>
<tr>
<td>Women and adolescent girls of childbearing potential who want to become pregnant and have no effective contraception</td>
<td>TLE600</td>
<td>TDF + 3TC (or FTC) + PI/r</td>
<td></td>
</tr>
</tbody>
</table>

TDL = TDF + 3TC + DTG, TLE = TDF + 3TC (or FTC) + EFV  

TDF, Tenofovir; 3TC, Lamivudine; DTG, Dolutegravir; FTC, Emtricitabine; EFV, Efavirenz; PI/r, Protease inhibitors/ritonavir; AZT, Zidovudine; RAL, Raltegravir
pleural effusion, pericardial effusion, or tuberculous pulmonary lesions.

- **Sputum smear microscopy:** It is easy to perform and is inexpensive. There is direct microscopic examination of sputum for AFB (acid fast bacilli) after Ziehl-Neelsen staining.

- **Sputum culture:** Culture of sputum or other samples is the cornerstone in definitive diagnosis of tuberculosis. Culture can be done in egg-based solid medium such as Lowenstein-Jensen or Agar based Middlebrook medium. These are sensitive but slow as it may take 6–8 weeks of incubation. It may also be cultured in liquid medium detecting growth of mycobacteria in 1–2 weeks time using carbon dioxide production or O2 consumption with radiometric sensors = BACTEC 460, florescent sensors = BACTEC MGIT 960, calorimetric sensors = MB/BacT system, pressure sensors = ESP culture system, or Redox Reagent, such as Alamar blue.

- **Molecular assays:** Xpert MTB/RIF is diagnostic method of choice in HIV positive people. Its sensitivity in positive smear patient is 98.2% and in patients with sputum smear negative is 68%. It is more than 99% specific. It is done by nucleic acid amplification method (NAAT, real time polymerase chain reaction = RT-PCR). It detects mycobacterium tuberculosis quickly (<2 hours). In TB/HIV coinfection, its sensitivity is 79%. Some of the modified versions of NAAT are:
  - **LAMP—Loop Mediated Isothermal Amplification.**
  - **FISH—Fluorescence In Situ Hybridization.**
  - **LPAs—Line Probe Assays.** LPA is more than 75% sensitive and 100% specific. It detects MTB.
  - **Gene Xpert/RIF—It is cartridge-based nucleic acid amplification assay, is TB specific, and detects RIF resistance with 99.1% sensitivity and exclude resistance by 100% specificity.**2,3

- **Serological tests:**
  - **Antibody detections—There is negative recommendations by WHO.**
  - **Antigen detection by ELISA-based assay—LAM—Lipoarabinomannan assay in urine is better in HIV infected than HIV uninfected HIV patients.**

- **Other tests:** IGRA—Interferon gamma release assay. This is useful in diagnosing latent TB.

- **Quantiferon:** TB Gold Test—It is in vitro test for detecting latent TB.

### Treatment of TB

All PLHIV diagnosed with TB should be started with antituberculous treatment (Table 3).

### Challenges in HIV-TB Coinfection

In management of HIV-TB coinfection, the main challenges are:

- Immune reconstitution inflammatory syndrome (IRIS).
- Drug interaction in patient on antiretroviral therapy.
- Overlapping drug toxicity.

### Timing of Initiation of Antiretroviral Treatment

A number of trials have shown that providing early ART to HIV-TB coinfected persons during antituberculosis treatment reduces mortality.4 It is now recommended by Health and Human Services and Infections Disease Society of America, that ART should be started 2 weeks after initiation of antituberculosis treatment in most patients, with CD4 count less than 50 cells/mm3. For those with CD4 count more than 50 cells/mm3 ART should be started after 2–8 weeks time. It is reasonable to give ATT for 6 months duration; however, some guidelines favor 9 months rifamycin based therapy.

### Immune Reconstitution Inflammatory Syndrome

It is an inflammatory reaction, following the initiation of effective ART, due to improvement in immune system of HIV patient, leading to paradoxical worsening of symptoms and signs, of untreated or partially treated OIs.

### Table 3: Antituberculous treatment schedule

<table>
<thead>
<tr>
<th>Type of TB case</th>
<th>Treatment regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>New: A TB patient who has never had treatment with anti TB drugs or has taken it for &lt;1 month</td>
<td>2H7RZ7E7 + 4H7RZ7E7</td>
</tr>
<tr>
<td>Previously treated: A TB patient who has received 1 month or more of any TB drugs in the past</td>
<td>2H7RZ7E7S7 + 1H7RZ7E7 + 5H7RZ7E7</td>
</tr>
</tbody>
</table>

E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide
or neoplasm (paradoxical IRIS) and undiagnosed cases (unmasking IRIS). Signs and symptom may appear 2–12 weeks after initiation of ART, and is most commonly seen, when ART is started with CD4 count less than 50/mm³, and close to diagnosis of OI. IRIS occurs in 10% of all cases put on ART, and 25% of those who have CD4 lymphocyte count less than 50/mm³. It manifests as fever, increase in size of lymph glands, and pulmonary infiltrates. Severe cases may be fatal. It is treated by antimicrobials for OI, corticosteroids, and continuation of ART.5

Drugs Interactions in Patients on Antiretroviral Therapy

Rifampicin induces Cytochrome P450, and leads to increased metabolism of HIV drugs, resulting in its decreased concentration in serum, to subtherapeutic levels, that may lead to HIV treatment failure and antiretroviral drug resistance.

- **Rifampicin and NNRTIs:** Drug interaction between rifampicin and NNRTIs are important, because first line ART includes NRTIs with NNRTIs like Efavirenz or Nevirapine. Multiple cohort studies and randomized controlled trial have shown that standard adult dose of efavirenz (600 mg/day) with two NRTIs is well tolerated and highly efficacious in achieving complete viral suppression along with rifampicin-based antituberculous treatment.6,7 Efavirenz should not be used in first trimester of pregnancy, those intolerant to efavirenz or NNRTIs, resistant strains of HIV, or children less than 3 years of age.

- **Rifampicin and Nevirapine:** Rifampicin reduces serum concentration of nevirapine by 20–55%.8 In India in a randomized trial nevirapine 200 mg/day for 2 weeks than 200 mg/bd or efavirenz 600 mg/day with rifampicin based ATT, those on nevirapine showed more virological failure and severe toxicity.8 So efavirenz is more effective, and less toxic than nevirapine for HIV-TB coinfection.

- **Rifampicin and Protease inhibitors:** It has been found that when protease inhibitor based ART is given with rifampicin in HIV-TB coinfected persons, concentration of protease inhibitor may be diminished by more than 90%.9 Studies have shown adequate serum concentration of PI can be achieved by super boosting (standard those of PI + higher dose of ritonavir), or doubling the dose (doubling dose of both PI and ritonavir), that is, 400 mg/100 mg twice daily to 800 mg/200 mg twice daily (double dose), along with rifampicin 600 mg/day, but there is possibility of increased risk hepatotoxicity with the regimen.

- **Rifampicin and Triple nucleos(t)ide:** Because of lack of evaluation nucleosides or nucleotides alone are not recommended for treatment of HIV-TB coinfection.

- **Rifampicin and Integrase inhibitors:** Raltegravir when used with rifampicin, it is recommended to double the dose of raltegravir to 800 mg twice daily, because concentration of raltagravir is reduced by almost 55%. Dose of the dolutegravir should also be doubled, that is, 50 mg bd when used with rifampicin.

| TABLE 4 | Drug interactions between ATT and ART |
|---|---|---|---|
| ATT drugs | ART drugs | Drug interaction | Action to be taken |
| Rifampicin | NRTIs | No | Given in usual dose |
| | NNRTIs | Yes | Avoid nevirapine. Use efavirenz in usual dose |
| | Booted PI | Yes | Replace rifampicin with rifabutin (150 mg od) |
| | Integrase inhibitors | Yes | Double dose of integrase inhibitor |

Dolutegravir 50 mg bd
Raltegravir 800 mg bd

| TABLE 5 | Overlapping adverse reactions of ATT and ART |
|---|---|---|
| ATT | ART | Adverse reactions |
| RIF/INH/PZA | NEV/EFV | Rashes |
| PZA/ETB | ZDV/TDF/PIs/DTG | GIT intolerance |
| RIF/PZA | TDF/EFV/PIs | Hepatitis |
| INH/RIF/LZD | ZDV | Anemia |
| INH/CYS | EFV/DTG | CNS toxicity |
| STM/KANA/Capreomycin | TDF | Renal dysfunction |

NACO: CYS, cycloserine; DTG, dolutegravir; ETB, ethambutol; INH, isoniazid; LZD, linezolid; PZA, pyrazinamide; RIF, rifampicin
- **Rifabutin and Protease inhibitors:** Rifabutin has less effect in comparison to rifampicin on metabolism of drugs mediated by cytochrome P450 3a enzyme. Rifabutin 150 mg daily (instead of 300 mg/day) is recommended when used with ritonavir boosted lopinavir (as ritonavir also influences CYP3a metabolizing enzyme, so increases concentration of rifabutin leading to rifabutin toxicity-uveitis).

- **Rifampicin,** if used with nevirapine, causes concentration of nevirapine to reduce, so rifabutin should be preferred instead of rifampicin.

- **Efavirenz** reduces the concentration of rifabutin, so rifampicin should be preferred ATT with efavirenz.

### Latent TB Treatment

LTBI should be treated in cases of HIV coinfection. INH 300 mg daily for 9 months or Rifampicin 600 mg/day for 4 months, as per recommendations. No dose adjustment of ART is needed when INH is used (Tables 4 and 5).

ATT and antiretrovirals produce several overlapping toxicities, so treating clinicians should monitor for these overlapping adverse reactions.

### Conclusion

HIV-TB coinfection is a curable but potentially lethal combination. Timely diagnosis and early institution of treatment in HIV-TB coinfection reduces morbidity and mortality. Both HIV and TB have the potential to exacerbate and worsen each other. ATT in proper dose along with ART is corner stone of the treatment. HIV-TB coinfection poses many challenges because of management of both diseases, and is complicated by drug interactions between ATT and ART, risk of IRIS, and overlapping drug toxicity. So ATT should be started immediately and ART should be initiated as soon as the ATT is tolerated (2–8 weeks). Proper selection and dose adjustment of both antiretroviral drugs and antituberculous drugs for HIV-TB coinfected patients are important components of patient management.

### References


CHAPTER

Advanced HIV Disease: Prioritizing the Most Vulnerable among PLHIV

S Anuradha

Abstract

Although the mortality among PLHIV has shown a significant reduction with effective ART, the decline in the number of deaths has plateaued during the past few years. This is due to the persistent burden of HIV associated mortality and morbidity in a significant section of PLHIV who still present to health-care systems with "advanced HIV disease (AHD)." It has been estimated recently that nearly 30–40% PLHIV initiating ART in resource limited countries have CD4 cell count <200 cells/mm and almost 20% have CD4 <100 cells/mm. The risk of death among PLHIV with AHD is high. This risk increases with declining CD4 cell counts, particularly with CD4 <100 cells/mm. AHD also contributes to increased health-care expenditure. Hence, it is important to identify PLHIV with advanced disease early and deliver a specialized package of interventions that will prevent the morbidity and mortality.

Introduction

It is estimated that 37.9 million people globally had Human Immunodeficiency Virus (HIV) infection in 2018 and new HIV infections had decreased to 1.7 million. Out of these, 24.5 million people living with HIV (PLHIV) received Antiretroviral Treatment (ART). In India, there are 2.1 million PLHIV of which 88,000 are newly infected and 1.18 million are receiving ART (56% coverage).

The number of PLHIV dying annually from AIDS-related causes has diminished by 48% in 2018 from 2003. This decline in mortality is chiefly due to increased access to ART and early initiation of ART according to the World Health Organization (WHO) 2016 guidelines on "universal use of ART," recommending "life-long ART to all children, adolescents and adults including all pregnant and breast feeding women living with HIV regardless of CD4 count or clinical stage." However, the decline in the number of deaths has plateaued during the past few years. This is due to the persistent burden of HIV associated mortality and morbidity in a significant section of PLHIV who still present to health-care systems with "advanced HIV disease (AHD)."

Advanced HIV Disease

After the WHO recommended "universal ART for all PLHIV irrespective of clinical or immune status," national programs of most countries have implemented it. Earlier initiation of ART, along with enhanced availability of HIV testing, has resulted in a betterment in overall condition at ART initiation, as evidenced by an increase in the average CD4 cell count globally at the commencement of treatment.

Notwithstanding this improvement, nearly half of PLHIV present with AHD to health-care systems. The WHO has developed a consensus definition for PLHIV with advanced disease at entry to the health system and those patients who are "stable on ART."
According to WHO guidelines for management of AHD, July 2017, advanced HIV disease is defined as—
- "having a CD4 cell count less than 200 cells/mm³ or
- A WHO clinical stage 3 or 4 event
- Any child younger than age 5 years with HIV is considered to have advanced HIV disease”

The risk of death among PLHIV with AHD is high. This risk increases with declining CD4 cell counts, particularly with CD4 <100 cells/mm³. AHD also contributes to increased health care expenditure.

Erstwhile the distinct definition of AHD, there was lack of clarity and confusion regarding the designation of the term. The term “late presenters” was used often. The patients with CD4 count <350 cells/mm³ at presentation or those with an AIDS-defining illness (irrespective of CD4 count) were considered to be late presenters of HIV, as per the European Late Presenter Consensus definition. Varying cut-offs of CD4 counts <200/mm³ or <100/mm³ have been used to classify PLHIV presenting late. The WHO definition has helped evolve a uniform standard definition that makes analysis and comparisons easier.

**Prevalence of AHD and Risk Factors Associated with It**

It has been estimated recently that nearly 30–40% PLHIV initiating ART in resource limited countries have CD4 cell count <200 cells/mm³ and almost 20% have CD4 <100 cells/mm³. In some reports almost half of all PLHIV have AHD.

The International epidemiology Databases to Evaluate AIDS (IeDEA), along with Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) examined the CD4 cell counts of PLHIV at start of ART globally. This evaluation included nearly 1 million PLHIV across North America, South America, Asia-Pacific, Sub-Saharan Africa, and Europe. Countries were classified as per the World Bank classification in 2015 as low income countries (LICs), lower middle income countries (LMICs), upper middle income countries (UMICs), and high income countries (HICs). Overall, the median CD4 count at presentation improved across the globe: from 78 cells/mm³ in 2002 to 287 cells/mm³ in 2015 in LICs, from 99 cells/mm³ to 234 cells/mm³ in LMICs, from 71 cells/mm³ to 311 cells/mm³ in UMICs, and from 161 cells/mm³ to 327 cells/mm³ in HICs. Although the median CD4 cell count continued to remain below 350. The increases in LICs and UMICs were more than that in LMICs or HICs. This increase was more noticeable in women compared to men, except in the HICs.

The proportion of people starting ART with AHD in Africa is about 55%, varying from 31% in Swaziland to almost 77% in Senegal. A study from four high burden countries in Sub-Saharan Africa Cameroon, Mozambique, Uganda, and Zimbabwe demonstrated that the fraction of PLHIV presenting with AHD persisted to be steady: 19.4% in 2012 to 16.1% in 2016. It ranged from 14.5% within Uganda to 29.8% in Cameroon.

A nationwide longitudinal cohort in the Netherlands by Eline LM et al., revealed that among the HIV patients registered into care between 1996 and 2014, 53% presented late and 35% had advanced HIV disease. Among late presenters and advanced disease, the median CD4 was 150 cells/mm³ and 80 cells/mm³ respectively. Late presentation was more commonly associated with being a heterosexual male (OR-1.59), injecting drug use (OR 2.0), age ≥50 years, region of origin, and location of HIV diagnosis.

A cross sectional study from South-Western China by Xi Hu et al, including 46000 newly diagnosed PLHIV from 2012-2016 demonstrated 70% PLHIV were late presenters while 45.1% presented with advanced HIV disease. Higher prevalence of AHD was found among male gender, heterosexuals, older age-group, lower education, and divorced/widowed persons.

Data on the precise prevalence of AHD is lacking from India. A single center study from Delhi has reported that 83.7% of PLHIV were late presenters while 33% of PLHIV had AHD with 9.5% having CD4 cell count below 50 cells/mm³ at presentation. The median CD4 cell count was determined to be 242 cells/mm³.

This emphasizes that late presentation among PLHIV remains a major challenge all over the world.

**Impact of AHD on Mortality and Morbidity**

PLHIV who have AHD are prone to greater risk of mortality and morbidity due to multiple factors such as lower CD4 response after ART, increased risk of OIs and their complications, polypharmacy, non-adherence, and suboptimal virological suppression.

Morbidity and mortality are even higher in initial 3 months particularly in first 4-8 weeks. In a meta-analysis
by Alana T. Brennan et al. to determine early mortality in lower- and middle-income countries of Sub-Saharan Africa, Asia, and Caribbean it was revealed that early mortality was 6% (5.5–6.3%). When mortality estimate was calculated assuming that PLHIV who were lost to follow-up had died, the overall estimate increased to 10%.17

A study from Uganda and Zimbabwe by Walker AS et al. to assess mortality during first year of ART demonstrated that 5.4% PLHIV died, with half of the deaths reported in the initial 3 months. Mortality risk was highest between 30–50 days and, it reduced rapidly thereafter till about day 180. Further, it continued to decline slowly over time. One-year mortality in PLHIV was: 9.4% in CD4 <50 cells/mm³, 4.5% in CD4 between 50–99 cells/mm³ and 2.9% in CD4 >100 cells/mm³.8

Tuberculosis, severe bacterial infections, chronic diarrhea, cryptococcal meningitis, cerebral toxoplasmosis, *Pneumocystis jiroveci* pneumonia, and anemia were the chief causes of mortality in adult PLHIV with AHD. Among children, tuberculosis, severe bacterial infections, pneumonia, diarrheal diseases, malnutrition, and wasting are the leading causes of death.8,18,19

A landmark study, REALITY, was conducted across Zimbabwe, Uganda, Malawi, and Kenya in ART naïve PLHIV with CD4 <100 cells/mm³. It was found that mortality rates were highest during first 4 weeks of starting ART, decreasing through week 8 and substantially dropping further through 24 and 48 weeks. The leading causes of death were opportunistic infections: tuberculosis cryptococcal meningitis, severe bacterial infections, and immune reconstitution inflammatory syndrome (IRIS). This study also highlighted that patients with the greatest risk of dying had a high burden of symptoms, weight loss, lower CD4 count, low albumin and hemoglobin levels.20

Another crucial observation was that loss to follow-up is more likely among those with AHD. This increases the risk of mortality in these patients and adds to the threat of transmission of HIV.

With such life-threatening events and adverse outcomes, patients with advanced disease remain the most vulnerable among the PLHIV. It is imperative that these patients be brought into the health-care systems early. It is also crucial to initiate ART at the earliest in these patients, even on the same day as presentation. This will prevent missed opportunities for initiating treatment.

It is due to these concerns that the WHO recognized that the people with AHD are a specially vulnerable group who need a specific and specialized package of interventions for them.

### Package of Interventions for PLHIV with AHD

In July 2017, the WHO released comprehensive guidelines for the management of AHD and rapid initiation of ART. The guidelines provide suggestions for a public-health-approach for managing PLHIV with AHD including timing of ART initiation.5

The “package of interventions” recommended include the:

- Co-trimoxazole prophylaxis,
- Tuberculosis preventive treatment,
- Use of Xpert MTB/RIF for tuberculosis diagnosis among symptomatic PLHIV,
- Using the lateral flow lipoarabinomannan (LF-LAM) antigen test for people with symptoms suggesting TB with CD4 count ≤100 cells/mm³ or who are seriously ill,
- Cryptococcal antigen screening in all with CD4 cell count ≤100 and pre-emptive antifungal treatment for those with positive blood cryptococcal antigen.2

This is summarized in Table 1.

Two large randomized trials instituting packaged interventions among PLHIV presenting with AHD were done. The first one named REMSTART, was conducted in Zambia and the United Republic of Tanzania, and compared ART-naïve PLHIV with CD4 count <200 cells/mm³ receiving a specialized package of care versus standard care. ART initiation was done around 2 weeks (delayed beyond 2 weeks only in those with TB). A 28% reduction in mortality and a trend toward better adherence was observed in the intervention group compared to the group receiving standard care at 6 months.21

In the second trial, REALITY, PLHIV with CD4 <100 cells/mm³ were enrolled from Kenya, Malawi, Uganda, and Zimbabwe. Study subjects were randomized to receive either the standard care (as per existing respective national guidelines) or an enhanced prophylaxis package of 12 weeks of fluconazole (100 mg once daily), 12 weeks fixed-dose combination of co-trimoxazole (800 + 160 mg) + isoniazid (300 mg) + pyridoxine (25 mg), 5 days of 500 mg of azithromycin once daily and albendazole (400 mg single dose). ART was started simultaneously with all drugs. In the enhanced prophylaxis package arm, there was a
TABLE 1  Diagnosis and prophylaxis components of package of care interventions for advanced HIV disease (WHO)$^5$

<table>
<thead>
<tr>
<th>Areas for the package</th>
<th>Intervention</th>
<th>CD4 cell count</th>
<th>Adults and adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening and diagnosis</td>
<td>Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Urine LF-LAM$^*$ for TB diagnosis in patients with symptoms and signs of TB</td>
<td>≤100 cells/mm$^3$</td>
<td>Yes</td>
<td>Yes$^*$</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal antigen (CrAg) screening$^{**}$</td>
<td>≤100 cells/mm$^3$</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prophylaxis and pre-emptive treatment</td>
<td>Co-trimoxazole prophylaxis</td>
<td>≤350 cells/mm$^3$ or WHO clinical stage 3 or 4 event. Any CD4 cell count value in settings with high prevalence of malaria and/or severe bacterial infections</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>TB preventive treatment$^§$</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis</td>
<td>≤200 cells/mm$^3$</td>
<td>Yes</td>
<td>Not applicable (Screening not advised)</td>
</tr>
<tr>
<td>ART initiation</td>
<td>Rapid ART initiation</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adapted adherence support</td>
<td>Tailored counseling to ensure optimal adherence to advance disease care package, including home visits if feasible</td>
<td>&lt;200 cells/mm$^3$</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

$^*$Urine LF-LAM: lateral flow urine lipoarabinomannan assay.
$^{**}$Limited data for children.
$^{**}$CrAg screening and pre-emptive therapy is strongly recommended at CD4 <100 cells/mm$^3$ and conditionally recommended at CD4 <200 cells/mm$^3$.
$^{****}$When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm$^3$ (strong recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of < 200 cells/mm$^3$ (conditional recommendation; moderate-certainty evidence).
$^§$Co-trimoxazole, isoniazid, and pyridoxine are now available as a fixed-dose combination tablet.
$^#$For children <12 months of age, only those with a history of TB contact should receive TB preventive treatment, if the evaluation shows no active TB disease.

Reduction in mortality by 27% over 24 weeks. Mortality due cryptococcal infections significantly decreased (1.5% to 0.4%), and mortality due undetermined causes decreased from 6.0% to 3.8%. The incidence of OI also reduced: TB by 28%, cryptococcal meningitis 62%, and admissions to hospitals by 17%. Majority of deaths occurred within the initial 3 weeks of the study, emphasizing the need for early prophylaxis among PLHIV with AHD.$^{22}$

Both these large studies in patients with advanced HIV disease have demonstrated the benefits of delivering a specialized and specific package of interventions to this extremely vulnerable subset of PLHIV.
Conclusion

The world has committed toward ending AIDS as a significant public health problem by 2030. However, without rapid escalation of services, the HIV epidemic will outrun the global response. To prevent this, The UNAIDS Fast-Track strategy sets out 90-90-90 targets for prevention and treatment. This includes, reducing new annual HIV infections to fewer than 500,000 by 2020 and to fewer than 200,000 by 2030, and AIDS related deaths by 90% by 2030, in comparison to 2010 levels.

Hence, it is necessary to identify PLHIV with advanced disease and deliver a package of interventions consisting of screening, prophylaxis and treatment of OIs, early ART initiation and enhanced adherence support. This will mitigate the high, early mortality seen in advanced HIV disease and also reduce the AIDS-related mortality rate overall. At the same time this will reduce the health-care costs and reduce community transmission. It requires an effort and commitment on part of programs and governments to develop strategies for advanced HIV care in their own country's context. The National AIDS Control Organization of the Govt. of India is also developing a specialized package of interventions to be delivered to this population. These are the most vulnerable among the PLHIV. Additional and special support to this population will have far reaching implications for the country and the world.

References

ANTIRETROVIRAL THERAPY IN 2020

BB Rewari, Priyanka Ojha

Abstract

ART has changed the outlook of HIV from a virtual death sentence to a chronic manageable disease. The current guidelines are to provide ART initiation to all those infected with HIV regardless of their CD count of WHO clinical stage. The standard of care is a triple drug combination (Tenofovir + Lamivudine + Dolutegravir) in a single pill once daily and is a lifelong therapy. Adherence to therapy is most crucial for good outcomes of therapy and to reduce chances of resistance, hence patient counseling is an important component of HIV care. Availability of high-quality generic drugs helped increase the coverage of ART significantly, thereby reducing the chances of transmission from those with HIV. Besides ART, antiretroviral drugs are also used for post exposure prophylaxis (PEP) after accidental exposure and pre-exposure prophylaxis (PrEP) for those at high risk of HIV.

Introduction

Antiretroviral therapy (ART) is seen as a panacea for People Living with HIV (PLHIV) and has helped save millions of lives in addition to improving quality of life. In addition, this has saved many countries from catastrophic economic consequences of the disease.

Zidovudine, being used for some malignancies, was the first drug shown to be effective against HIV in 1985. Soon it was felt that virus developed resistance quickly and drug becomes ineffective in less than a year with Zidovudine monotherapy. By 1995, many studies had demonstrated the clinical benefits of using a two-drug combination of Zidovudine or Stavudine in combination with Lamivudine. The year 1996 was a landmark in ART journey when results of using a triple drug combination using protease inhibitors were revealed at the International AIDS Society (IAS) conference in Vancouver. These drugs over the years have transformed lives of millions of people and have changed outlook of HIV from that of a virtual death sentence to a chronic manageable condition. The Figure 1 shows the development of various antiretroviral (ARV) drugs over last three decades.

Besides treating those with HIV, ARV drugs are also used for preventing mother to child transmission of HIV (PMTCT), for preventing acquiring HIV infection in case of accidental exposure to the virus (post-exposure prophylaxis, PEP) and for preventing HIV infection in HIV negative individuals with substantial risk of being infected (pre-exposure prophylaxis, PrEP).

What are Options Available for ART

Highly Active Antiretroviral Therapy (HAART) or simply ART is a combination of three ARV drugs from different groups in a fixed dose combination (FDC). The “one pill a day” therapy has potential for good adherence as ART is a lifelong therapy. Production of generic formulations of these drugs have helped reduced its costs from USD 10,000 to less than USD 80 now making it affordable for most people. In addition, roll out of free ART program in countries have helped increase coverage of ART resulting
in individual patient benefits, as well as, prevention of transmission of HIV due to reduction in viral load. Presently available ARV drugs cannot cure HIV as the virus remains dormant in resting states in some cells like spleen, brain, bone marrow, etc. It starts replicating again if the ART is stopped. Hence, ART is a lifelong therapy.

The ARV drugs broadly act at various steps in life cycle of virus either by blocking enzymes (reverse transcriptase, protease, integrase) needed for replication or by blocking entry of HIV into CD4 cells (Fusion inhibitors) or by blocking maturation of virions and their budding out from CD4 cells. Based on the site of action, these drugs are broadly divided into six classes (Table 1). There are over 26 drugs/combinations. The drugs commonly used in India are listed in the following table.

The combinations of antiretroviral drugs inhibit the replication of HIV leading to slowing of disease progression, while reduced CD4 cell destruction leads to better immunity and fewer opportunistic infections. Over the years, the drugs have been evolving toward better efficacy, fewer toxicities, better pharmacokinetics, fewer drug-drug interactions, and lesser chances of resistance. This has led to optimization of ART, and WHO has released updated ART guidelines in July 2019.

**When to Start ART is No Longer a Question or Discussion Point**

In the early days when HAART was just being introduced, it was considered that a “hit hard, hit early” would be adopted. However, evidence that emerged in those years questioned the advantages of early HAART. Till about 3 years ago, treatment for HIV infected person was based largely on the CD4 count levels and clinical stage of the infection. The CD4 count cut-off point for ART initiation was less than 200 cells/cmm in 2004 and later moved to less than 350 cells/cmm in 2010. The cut-off was advanced to less than 500 cells/cmm in 2013 while in 2016, the recommendation came to TREAT ALL, regardless of clinical stage or CD4 count. The basis for these changes has been evolving evidence from various randomized clinical trials (RCTs) and large observational cohorts.
TABLE 1 Classes of ARV drugs currently in use in India

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors (NsRTIs)</td>
<td>Zidovudine (AZT/ZDV) Lamivudine (3TC)</td>
</tr>
<tr>
<td></td>
<td>Abacavir (ABC) Emtricitabine (FTC)</td>
</tr>
<tr>
<td>Nucleotide reverse transcriptase inhibitors (NtRTIs)</td>
<td>Tenofovir (TDF)</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</td>
<td>Nevirapine (NVP)* Efavirenz (EFV)</td>
</tr>
<tr>
<td>Protease inhibitors (PIs)</td>
<td>Lopinavir (LPV) Ritonavir(RTV)</td>
</tr>
<tr>
<td></td>
<td>Atazanavir (ATV) Darunavir (DRV)</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>Raltegravir (RGV) Dolutegravir (DTG)</td>
</tr>
<tr>
<td>CCR5 entry inhibitor</td>
<td>Maraviroc**</td>
</tr>
</tbody>
</table>

*Being phased out
**Used sometimes in private sector

What is Latest WHO Recommendations on which Drugs to Start in ART

As described earlier, ART comprises of using at least three drugs from two different groups of ARV drugs in a combination, preferably in single pill, to improve adherence to therapy. The most commonly used combination is using two drugs from NRTI and one from NNRTI. So far most developing countries have been following a combination of Tenofovir (TDF 300 mg) + Lamivudine (3TC 300 mg) + Efavirenz (EFV 600 mg) in a single pill, as standard of care. In 2018 ART update, WHO recommended use of Dolutegravir (DTG) in the first-line ART based on evidence that with DTG:

- Viral suppression is faster than with EFV (Avg. 4 weeks for DTG vs. 12 weeks for EFV),
- DTG has fewer side effects,
- Fewer drug-drug interaction, and
- Patients on DTG have a higher threshold for developing resistance.

The SINGLE study compared the efficacy and safety of DTG as compared to current standard of care (Tenofovir plus Lamivudine plus efavirenz). A total of 833 participants who had an HIV-1 RNA level of >1,000 copies/mL were chosen and randomly assigned to DTG-ABC-3TC group or EFV-TDF-FTC group. The key findings from study revealed that at week 48, the proportion of participants with an HIV-1 RNA level of <50 copies/mL was significantly higher in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (88% vs. 81%, P=0.003). It was also seen that DTG-ABC-3TC group had a shorter median time to viral suppression.

which have revealed that with earlier ART initiation, there was a significant delay in progression to AIDS and reduction in incidence of TB. These studies are briefly summarized in Figure 2.

Hence, the current recommendation (since 2016) is to initiate ART for all those who present with HIV infection regardless of CD4 count or WHO clinical staging.
than EFV-TDF-FTC group (28 vs. 84 days, P<0.001), as well as greater increases in CD4+ T-cell count (267 vs. 208/ cubic mL, P<0.001). The proportion of participants who discontinued therapy owing to adverse events was lower in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (2% vs. 10%).

The results from some other studies like FLAMINGO, SPRING2, and SAILING showed that DTG achieves viral suppression much faster than EFV (Avg. 4 weeks for DTG vs. 12 weeks for EFV). There are very few discontinuations on DTG regimen due to drug toxicity (<2%), less than with DRV/r and EFV. Main clinical adverse events seen are rash (2% vs. 13%) and neuropsychiatric events (including dizziness). These were significantly more with common with EFV (5% vs. 35%), while insomnia was reported more frequent in DTG (13% vs. 7%) (SINGLE study). DTG has a strong resistance barrier. No known treatment-emergent resistance were seen across trials. This was a very significant finding as it is well known that EFV has a very week genetic barrier to resistance.

Accordingly, the WHO guidelines on what to start were updated in 2018 to include DTG as preferred first-line drug along with Tenofovir and Lamivudine. However, an ongoing observational Tsepamo study in Botswana identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. Interim analysis identified four neural tube defects out of 426 women taking DTG at the time of conception, for a rate of 0.9% (0.37–2.4%). So, 2018 guidelines specified that women and adolescents of child bearing potential who wants to become pregnant and have no effective contraception should not use DTG and continue to be provided an Efavirenz based regimen.

As new evidences from Tsepamo study became available it showed that the risk NTDs associated with use of DTG at the time of conception is less than originally signaled. The updated prevalence in the study has declined from 0.94% to 0.30%. The difference remains statistically significant compared to EFV, but the overall risk remains low. This new data presented in IAS 2020 (abstract #11299) includes 39,200 births surveyed from March 2019 to April 2020. Neural tube defects were identified in 0.19% of infants born to women on Dolutegravir at the time of conception and in 0.04% of infants born to women who started taking Dolutegravir during pregnancy. The risk-benefit models suggest that the benefits of DTG for women of childbearing potential (WCP) newly initiating ART are likely to outweigh the risks. According to WHO, the benefits of DTG outweigh the risks. Women of childbearing age or potential should be provided informed choice about the benefits and risks for the use of DTG. DTG has been found to be in breast milk of women on DTG, resulting in significant plasma concentration in infants, and thus a potential important tool to reduce the mother-to-child transmission of HIV infection.

The ART guidelines released by WHO in July 2019 recommend that a Fixed Dose Combination (FDC) of Tenofovir, Lamivudine (or Emtricitabine) and Dolutegravir (TLD) should the preferred first-line regimen for all adults including women and upgraded the recommendation from "conditional" to a "strong" recommendation. It also recommended to adopt a woman-centered approach to health care should be taken that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect women’s autonomy in decision-making and provide information and options to enable women to make informed choices.

**Tables 2 and 3** summarize the WHO 2019 ART guidelines.

In line with these guidelines, National AIDS Control Organization has also revised its ART guidelines on 17th September, 2020, and TLD based regimen is now the preferred regimen for ART initiation in new patients, DTG is also preferred for second-line ART for those failing on NNRTI and also to be used for PEP.

**Initiating and Monitoring ART**

Before starting ART, a full examination of person should be done to rule out any active opportunistic infection. He should undergo basic investigations like complete hemogram, routine biochemistry, CD4 count, and viral load (if available) as per guidelines. ART should not be started in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART. A proper counseling of person needs to be done highlighting the need for high levels of adherence to therapy and person must understand it is a lifelong therapy. A nutritional assessment and required supplementation are essential part of the counseling. A caregiver should be identified for each person to provide adequate support. Caregivers must be counseled and trained to support treatment adherence, follow-up visits, and shared decision-making.
TABLE 2  
WHO ART initiation guidelines (July 2019)

<table>
<thead>
<tr>
<th>2019 WHO guidance: preferred and alternative 1L regimens for adults and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred 1L regimen</strong></td>
</tr>
<tr>
<td>TDF + 3TC (or FTC) + DTG&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
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</tbody>
</table>

a. Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy.

b. EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher. DTG-based ART is preferred, and if DTG is unavailable, a boosted PI-based regimen should be used. The choice of PI/r depends on programmatic characteristics.

c. NRTI backbone to be changed to unused NRTI (lamivudine can be retained as any resistance to it will make virus less fit).

TABLE 3  
WHO ART guidelines for those with failure to first-line ART (July 2019)

<table>
<thead>
<tr>
<th>Population</th>
<th>First-line regimens</th>
<th>Preferred second-line regimens</th>
<th>Alternate second-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥30 kg)</td>
<td>2 NRTIs&lt;sup&gt;*&lt;/sup&gt; + DTG</td>
<td>2 NRTIs&lt;sup&gt;*&lt;/sup&gt; + ATV/r or LPV/r</td>
<td>• 1–2 NRTIs&lt;sup&gt;*&lt;/sup&gt; + DRV/r</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs&lt;sup&gt;*&lt;/sup&gt; + EFV</td>
<td>2 NRTIs&lt;sup&gt;*&lt;/sup&gt; + DTG</td>
<td>• 1–2 NRTIs&lt;sup&gt;*&lt;/sup&gt; + DTG</td>
</tr>
</tbody>
</table>

Fig. 3: Evolution of ART guidelines 2002–2020
Once a patient has been started on ART, patient needs to be monitored for signs of improvement due to ART as well as any new symptoms/signs which may indicate a side effect of a drug. It is recommended that in the initial phase of ART, patient needs to be monitored more frequently, preferably once in 2 weeks for initial 4–6 weeks, and then can be evaluated monthly.

The signs of improvement are weight gain, feeling of wellbeing, better appetite, better sleep, improvement in nutritional status, hemoglobin, etc., but more specifically increase in CD4 count and decrease in viral load at 6 months after ART initiation. Ideally the viral load should become undetectable 6 months after ART initiation. Once it becomes undetectable the viral load can be done annually and CD4 count monitoring can be stopped. It is also important to monitor lab parameters like Hb, renal functions periodically while on ART.

**Conclusion**

ART has been evolving rapidly toward earlier initiation with more robust and less toxic regimen. The Figure 3 summarizes this evolution of guidelines till now.

It will continue to evolve as more evidences become available on long-term safety and efficacy of drugs. Recently US FDA has approved a two-drug therapy using only Dolutegravir and Lamivudine and many new drugs are under trial including once a month injectable option. Simultaneously lot of research is ongoing on finding a cure for HIV. Vaccine trials have been partially successful, but the best vaccine available is prevention and for those infected early diagnosis and linkage to treatment remains crucial.

**Suggested Readings**

Abstract

With many new classes of drugs and molecules and changes in strategies, HIV-AIDS has become a chronic manageable infection. Various international and national agencies have adopted mechanisms to ensure that these are translated to reach the affected people. 90-90-90 target, which was supposed to be achieved by 2020 has been delayed due to the effect of Covid on health scenario. However, it’s not just the numbers only, but also various benefits to the society that matters. The outlook toward persons living with HIV has changed, but lot more needs to be done to ensure access, adherence, and persistence. Uniform practices will lead to them becoming undetectable as far as viral suppression is concerned and untransmittable for the rest of the society.

Introduction

HIV/AIDS has been with human kind for many decades now. From 1981 to 2020, the management of HIV infected persons has taken many turns. Introduction of Antiretroviral Therapy has radically changed the quality of life for all. However, there are wide variations among populations in different continents. UNAIDS launched the Fast Track strategy in 2014 aimed at enabling all HIV infected persons for a long-term survival. The motto of 90-90-90 aimed at reducing the deaths by 90% by 2030 is being actively chased in all countries. This not only means a reduction in the numbers getting listed and in the number of survivors but also improvements in the quality of life among the surviving population. The decrease in the number and severity of opportunistic infections, ability to lead a normal life, and decreased quantum of infective persons in the world are other benefits of this strategy. This will also lead to significant reduction in hospitalizations and near normal socioeconomic status for the infected. While many countries have reached this target, many others are lagging behind and the gaps are getting reduced fast.

Antiretroviral Therapy

The list of drugs effective against human immunodeficiency that began with azidothymidine (AZT, zidovudine) is expanding fast. With the advent of the drugs that act on various phases of HIV replication, viz. fusion inhibitors, reverse transcriptase inhibitors, integration inhibitors, protease inhibitors, coreceptor antagonists, etc. it has become clear that viral load can be controlled. This will enable the person to lead a longer, symptom-free survival with reduced chance for opportunistic infections, malignancies. The most important prerequisites for this advantage to be transferred to the infected persons involve the triad of early detection, quick initiation, and strict adherence with regular monitoring. A detailed description of Antiretroviral Therapy is beyond the scope of this article.
The 90-90-90 Strategy

The Millennium Development Goals were established following the Millennium Summit of the United Nations in 2000, following the adoption of the United Nations Millennium Declaration. MDG 6 was to combat HIV/AIDS, malaria, and other diseases. The year 2015 was the target at that time. In 2015, they were replaced by 17 Sustainable Development Goals. Specific targets were described to be achieved by 2030.

SDG 3 (to ensure healthy lives and promote well being for all at all ages) contains the two targets:
- **Target 3.3:** End AIDS as a public health threat by 2030.
- **Target 3.8:** Achieve universal health coverage, access to quality health-care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all.

In addition, the following statements also are important for HIV related activities.

- **SDG 4:** Quality education, including targets on comprehensive sexual and reproductive health (SRH) education and life skills.
- **SDG 5:** Gender equality, including targets on sexual and reproductive health and rights (SRHR) and the elimination of violence, harmful gender norms, and practices.
- **SDG 10:** Reduced inequalities, including targets on protection against discrimination, and the empowerment of people to claim their rights and enhance access to HIV services.
- **SDG 16:** Peace, justice, and strong institutions, including reduced violence against key populations and people living with HIV.

In 2014, UNAIDS announced the Fast Track strategy aimed at stepping up the responses in HIV prevention, control, and care particularly in low- and middle-income countries (LMIC). This was aimed at meeting the SDC-3 target to “end AIDS by 2030.” This strategy aims to catch up with the expanding infected pool by providing care including antiretroviral therapy to reducing new HIV infections and AIDS related deaths by 90% in relation to the 2010 values. The targets include reduction of new HIV infections to fewer than 500,000 per year by the year 2020 and to 200,000 or less by the year 2030—equivalent to ending AIDS as threat to public health. Once this is achieved by the treatment cascade upgradation, HIV transmission will be reduced, HIV infection may not affect the health of a person and deaths from HIV-related issues will be minimum. This is also supported by the WHO recommendation for starting ART in all HIV infected persons at all CD4 counts.

The 90-90-90 targets include aims to reach the following targets:1,2
- 90% of infected persons being identified,
- 90% of identified (infected) persons being started on antiretroviral therapy, and
- 90% of persons on ART achieving sufficient viral suppression (Fig. 1).

UNAIDS has put forth the idea of five pillars for this project. It is actually a people centered, rights-based approach. These include:
- Reduce new infections among women and girls to under 100,000 (current rates are approximately 700,000 per year globally),
- Ensure that 90% of people at risk of HIV can access preventive services,
- Make 20 billion condoms available annually in LMIC,
- Provide 25 million more with voluntary male medical circumcision, and
- Provide PrEP (pre-Exposure Prophylaxis) to 3 million people who have high risk behavior likely to lead to infection with HIV.

![Fig. 1: The proposal as it was made in 2014]

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The fast track strategy also envisaged certain targets set for 2020, which includes:

- Less than 500,000 people newly infected with HIV (75% reduction from 2010),
- Less than 500,000 people dying from AIDS-related illnesses, and
- Elimination of HIV related discrimination.

There was also a commitment to ensure that 30 million people will access antiretroviral therapy by 2020.

What has Happened?

There has been a marked scale up of antiretroviral therapy with over 28 million people on ART as of 2020, bringing the percentage from 25% in 2010 to 67% in 2019. The incidence: prevalence ratio is a metric that measures both the survival patterns and new infections. The global value for this was 7% in 2010 and has dipped to 4.4% in 2019. There were geographic variations. The ratio fell from 7% to 3.5% in Africa, while it was 3% in North America and Central Europe. Among individual countries, 25 have the value at 3%.

According to UNAIDS Global update 2020, among approximately 38 million infected persons all over the world, 81% knew their HIV serostatus, 67% were on antiretroviral drugs, and around 59% had undetectable viral loads. This is achieved by starting ART in approximately 25.4 million persons. This equates to 81-82-88% in comparison to the 90-90-90 figures.

The UNAIDS data as of 2019 is summarized in Figures 2 and 3.

Indian Scenario

India is one among the 193 countries participating in the 90-90-90 strategic plan. With over 2.1 million infected population, India has the third highest burden of HIV after South Africa and Nigeria. The National Health Policy (2017) and the HIV/AIDS Act (2017) explicitly states the commitment toward this. As stated therein “every person who is in the care or custody of the State shall have the right to HIV prevention, counseling, testing, and treatment services.” This ensures that all including women and children, prisoners, and all irrespective of caste, creed, gender and beliefs, sexual, or otherwise will have equal access to counseling, diagnostic, and treatment services.

NACO has released data, according to which 79.4% of the 21.40 lakh PLHIV in India know their status; 82.3% are on ART; 74% (among those tested) virally suppressed (Fig. 4). The viral load testing is now available in ART centers across the country and the treatment cascade is being implemented effectively.5

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**Fig. 2:** HIV testing and treatment cascade, global, 2019
Beyond Numbers
What the 90-90-90 strategy can achieve with full achievement of all targets is that 81% (90% of 90) of those infected will be put on treatment and 73% (90% of 81) of all infected is likely to be virally suppressed. This does not mean that 27% of infected persons are not going to be benefitted.

- Many studies have demonstrated the benefits of early detection in case of HIV infection. Test All strategy adopted by World Health Organization in 2016 has led to the following changes:
  - Supportive HIV testing policies have been accepted by most countries, an increase from 6 to 77 between 2015 and 2019. Self testing is promoted in 38 countries, as compared to 14 in 2017.
- Early and quick initiation of ART is producing wonders in the field of HIV care:
  - 60% of LMIC have started treating all infected persons regardless of CD4 count.
  - Lifelong ART for pregnant women is now standard practice in almost all countries.
  - 80% of countries have introduced treat all for children.
  - 72% countries have adopted single tablet regimen (TLE) as first line.
  - Dolutegravir (DTG) at lower price as a fixed combination drug is available in approximately 60% of LMIC.
- The cut off for start of therapy with antiretroviral drugs has been going up from the CD4 count of 200 cells/cm³ to 350, 500, and has reached any CD4 count now. Starting ART early prevents the occurrence of opportunistic infections and malignancies and delays death. New data and analysis reveal the reduction in risk of developing non-AIDS events as well. This occurs regardless of age, sex, race, baseline CD4 cell counts, geographic region, or economic status. This benefit has been definitely shown to outweigh any difficulty with ART including toxicities, adverse outcomes, etc...
- Quick initiation immediately after diagnosis is another area that helps the achievement of 90-90-90 targets. Rapid initiation of ART is defined as starting therapy within 7 days of diagnosis. This has to be based on person’s willingness and readiness. As early as 2017, same day initiation of ART was practiced in South Africa. This envisages the initiation of ART on the same day as diagnosis. This is reported to improve the outcomes faster but has been occasionally alleged to be associated with reduced rate of retentions.
- The quest for achieving the 90-90-90 targets has also led to more widespread availability and accessibility to viral load testing facilities. All over the world, this is now accepted as the standard monitoring tool during follow-up visits.
- The impact of the above measures on transmission need not be over emphasized. The equation “Undetectable = Untransmissible” is now widely accepted. This means that if a person takes ART and is virally suppressed (as envisaged in the 90-90-90 strategy), his undetectable Viral load is likely to be associated with a significantly less number of transmissions as well. This becomes a strong weapon for HIV prevention activities as well. Treatment as prevention thus becomes a reality.6
The inclusion of lifelong treatment for women will also lead to less number of women with high viral loads and almost complete elimination of vertical transmission, offering lower incidence of HIV infection among newborns as well.

HIV treatment saves money: Many modeling exercises show the cost effectiveness of ART as a cost-effective tool in the long run. Investments in HIV treatment scale-up lead to economic benefits at least double that of prevented medical expenses, as well as that in care of orphans and productivity in labor. The initial increase in cost attributed to cost of infrastructure, logistics, drugs, testing laboratories, etc. is expected to pay in the long run to reduce total cost of decreased morbidity and survival.

**Conclusion**

It is evident from the discussion above that the 90-90-90 strategy put forth by UNAIDS and embraced by all countries including LMIC is making changes not only in the counts but also in various aspects related to prevention, diagnosis, treatment, monitoring, and survival, thus ensuring better life to the HIV infected and to the upcoming susceptible generation.

**References**

2. UNAIDS. Ending AIDS. Progress towards 90-90-90 targets (2017). Available from https://reliefweb.int/report/world/ending-aids-progress-towards-90-90-90-targets#:~:text=90%2593%00%2580%2593%00%2520progress&text=The%20targets%20were%20launched%20in,antiretroviral%20therapy%20are%20vируally%20suppressed
Keeping Parent-to-Child Transmission Zero for a Decade—Trichur Experience

Ajithkumar Kidangazhiathmana, Lathika Nayar

Abstract

Knowledge about the efficacy of ARV drugs in preventing parent-to-child transmission (PPTCT) helped developed countries to achieve very low mother to child transmission rate. Due to various reasons, this remained unachievable in developing countries like India. PPTCT programme in India started in 2003 with Single dose Nevirapine schedule remained suboptimal till the adoption of Option B+ in 2014.

The Southern state of Kerala with health indicators comparable with the developed countries was always been an HIV low prevalent state. A model ART care facility was initiated in Govt. Medical College, Thrissur with the objective of providing comprehensive HIV health care incorporated to the existing public health system. Comprehensive PPTCT care by a dedicated “Team” was introduced as part of this package addressing various aspects of PPTCT, adjusted to existing the social milieu. This model proved quite successful and lead to near Zero transmission of HIV from mother to child in the last decade. Subsequently this model was adopted to other part of the state.

Introduction

Human immunodeficiency virus (HIV) continues to be a significant public health challenge world over. The fight against this pandemic started soon after the identification of the virus in 1982. With the knowledge that antiretroviral (ARV) drugs are useful in preventing mother-to-child transmission of HIV and that this is probably the only mode of transmission that can be prevented, Prevention of Parent/Mother-to-child transmission (PMTCT/PPTCT) became the major HIV prevention strategy aiming at reducing new infections, morbidity, and mortality. Currently, the transmission of infection from mother to child is eminently preventable.

A series of interventions were tried to achieve PPTCT at various levels. This include reduction of infection in the general community especially women of reproductive age group, avoidance of unplanned pregnancies, prevention of transmission from mother to child, post-exposure prophylaxis to the child and planning infant feeding options. PPTCT became a reality in the West in the mid-1990s with the introduction of zidovudine in pregnant women. However, it took decades for PPTCT to become competent in reducing the transmission in a significant proportion, mainly due to various hurdles in implementing PPTCT programs in the developing world, and because of the lack of adequate health-care delivery and public health infrastructure. Kerala a state known for high health indices and female literacy and equitable health care facilities remained an exception keeping both HIV prevalence and mother-to-child transmission to a minimum.

History of PPTCT

Global Scenario

ACTG 076 trial marked the beginning of a new era in PPTCT with zidovudine being recognized as the first
effective drug in preventing mother-to-child transmission and the USA Public Health Service recommending its use in August 1994.1 According to the ACTG 076 regimen, HIV-infected pregnant women were recommended zidovudine, from the 14 weeks of gestation until delivery, followed by peripartum zidovudine infusion. Newborns were given 6 weeks of zidovudine together with replacement feeding. The treatment regimen reduced the risk of HIV transmission by approximately two-thirds.

Since then, many clinical trials have been undertaken to find out the most effective and affordable antiretroviral therapy (ART) regimen to prevent mother-to-child transmission. This search began with various modifications of ACTG 076 recommendation, like shortening zidovudine use to 8 weeks in the antenatal period.2,3 Various trials with zidovudine for prevention of mother-to-child transmission of HIV are summarized in Table 1. The effectiveness of the “long-short” course (from 28 weeks in pregnancy for the mother and the up to 3 days for the baby) and the “short-long” course (from 35 weeks in pregnancy for the mother and up to 6 weeks for the baby) did not differ from that of the “long-long” course.4

Subsequently, PETRA Trials proved that starting zidovudine plus lamivudine at 36 weeks of gestation, followed by oral intrapartum dosing and 7 days’ postpartum dosing of mothers and infants also can significantly reduce MTCT. Two-drug and three-drug regimens were tried subsequently for antenatal mothers, which too proved to be effective in reducing HIV transmission significantly.4 The HIVNET012 trials conducted in Uganda, which confirmed the efficacy of the single-dose nevirapine regime in preventing vertical transmission of HIV was plagued by controversies soon after the release of its results in 2004.5,7 But gradually this regimen became well accepted primarily because of the simplicity in implementation. Table 2 summarizes the various treatment regimens proposed for PPTCT before the current three-drug regimen.

In June 2011, the Joint United Nations Program on HIV/AIDS (UNAIDS) introduced the Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive, which aimed at a 90% reduction in new childhood HIV infections and a 50% reduction in HIV-related maternal deaths by 2015.8

The WHO recommended two approaches for PMTCT prophylaxis. “Option A” recommended zidovudine monotherapy in the antenatal period, single-dose nevirapine during labor and a week-long tail of zidovudine and lamivudine in the postpartum period. HIV exposed infant was given daily nevirapine until the cessation of breastfeeding. An alternate option, “Option B” differed from option A in that, all pregnant women, even if not eligible for ART were advised three-drug combination ARV in the antenatal period, which was continued till the cessation of breastfeeding. Infants have advised zidovudine/nevirapine prophylaxis for the first 6 weeks of life.9 A third option B+ that recommended triple ART for all HIV infected pregnant women irrespective of the clinical or immunological stage was also included in this update.

With the recommendation for the initiation of ART at any CD4 cell count in the 2014 updated guidelines, the PMTCT Guidelines Committee also adopted the WHO option B+, so that all pregnant women would continue triple-drug therapy after delivery in the same way as all other adults.9

PMTCT guidelines committee of our country adopted the Option B+ in 2014 so that all pregnant and breastfeeding women would be initiated on Triple ART irrespective of the stage, which would be continued lifelong.9

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**TABLE 1** Summary of Zidovudine Trials for prevention of mother-to-child transmission of HIV

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>Antepartum</th>
<th>ARV intrapartum</th>
<th>Neonatal</th>
<th>% Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACTG 076</td>
<td>A</td>
<td>ZDV at &gt;14 weeks</td>
<td>ZDV</td>
<td>ZDV for 6 weeks</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>22.6</td>
</tr>
<tr>
<td>PHPT-1</td>
<td>SS</td>
<td>ZDV at &gt;35 weeks</td>
<td>ZDV</td>
<td>ZDV for 3 days</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>ZDV at 28 weeks</td>
<td>ZDV</td>
<td>ZDV for 6 weeks</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>LS</td>
<td>ZDV at 28 weeks</td>
<td>ZDV</td>
<td>ZDV for 3 days</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>SL</td>
<td>ZDV at 35 weeks</td>
<td>ZDV</td>
<td>ZDV for 6 weeks</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Adapted from: World Health Organization. Anti-retroviral therapy for treating pregnant women and preventing HIV infection in infants; recommendations for a public health approach - 2010 revision. Geneva, Switzerland: WHO Press; 2010.10
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACTG 076 Trial 65% reduction of transmission</td>
<td>1998 Thai Bangkok AP/IP AZT Trial 50% reduction</td>
<td>Cote d'Ivoire AZT Trial 37% reduction</td>
<td>PETRA AZT/3TC 50% red with long arm 38% reduction with short arm</td>
<td>Two dose IP/PP NVP (HIV NET 12) 47% reduction breastfeeding</td>
<td>Thai long vs. short AZT 4% transmission (Non breast feed)</td>
</tr>
</tbody>
</table>
Infant feeding recommendations given by WHO in 2006 and later in 2010 promoted 6 months exclusive breastfeeding followed by complementary feeding with the gradual cessation of breastfeeding by 12 months when nutritionally adequate and safe alternate nutrition is established, along with ARV prophylaxis to mother and infant.\textsuperscript{10} In 2016, infant feeding guidelines were updated, with the recommendation to continue breastfeeding to 24 months like general population along with the continuation of ART.

**Indian Scenario**

NACO launched India’s first PPTCT program in May 2003 with the recommendation to administer single-dose NVP 200 mg regimen to all seropositive mothers not receiving highly active combination anti-retroviral therapy (HAART) at the onset of labor, and this was followed by one dose of 2 mg/kg nevirapine administered to all babies within 72 hours of delivery.\textsuperscript{11} This was continued till 2014 after which there was a significant change in the scene with the adoption of Option B+.

**Challenges in Implementation of PPTCT in India**

PPTCT is not just provision for ART. It is a comprehensive care package involving various steps. These steps include (but are not limited to) women agreeing to HIV testing, receiving their results, undergoing ART eligibility screening, initiating treatment or prophylaxis, and adhering to the prescribed regimen.\textsuperscript{11} Infants must adhere to anti-retroviral prophylaxis regimens and undergo appropriately timed HIV testing.\textsuperscript{12} Attrition at each point should be identified and corrected. But the implementation of PPTCT services in developing countries is not often practical due to various factors, which include:\textsuperscript{15-16}
- Large HIV positive population
- Problems in testing
- Issues related to confidentiality, stigma, and discrimination
- Non-availability of maternal and child health services
- Low education status of mothers
- Non-availability of medicine
- Non-availability of health-care delivery system
- Lack of political commitment
- Difficulty to prioritise PPTCT among other health care services

**Kerala Scenario**

Kerala, a small southern state, has always maintained a coveted position in health and social development, often comparable with the developed world. Kerala has always remained a low-HIV prevalent state, and this low prevalence was no accident.\textsuperscript{17} Kerala’s health indicators are almost comparable to Western Europe, with equitable health-care facilities, very high female literacy and empowerment, and low HIV prevalence. This helped Kerala to adopt a different model of PPTCT practice silently. Various social factors like high-literacy rates, women empowerment, better socioeconomic status, good public health and MCH services, good health-care seeking attitudes, the involvement of public health in HIV prevention services, availability and accessibility to state-run ART clinics across the state, commitment from government and health-care workers in implementing the program helped the state in evolving its model.

**The Trichur Experience**

The Thrissur model HIV Care facility (TMHC) evolved as a comprehensive HIV care facility in 2002. This facility was recognized as one of the models that helped the evolution of the national ART program.\textsuperscript{18,19}

The basic principle of this model was that it is possible to provide comprehensive HIV care by making use of existing infrastructure and human resources in the public health system of India.\textsuperscript{20} This model also suggested that provision of health care to PLHIVs at the existing health care systems would reduce the stigma and discrimination tremendously thereby improving the health care seeking attitude of the patients. These were the guiding principle for the care of pregnant women as part of comprehensive HIV care from the inception of HIV care facility in 2002.

We also believed, it was possible to provide better PPTCT services in Kerala if we make use of the strengths of its health care system and the society comprehensively. One of the authors (K Ajithkumar) was instrumental in providing the zidovudine prophylaxis probably for first time in India immediately after the report of ACTG 076 was published in 1994 while he was part of HIV team at CMC Vellore. The first pregnant lady who approached this facility received ACTG 076 protocol, and this became the standard practice in the institution. The success of this approach led to the referral of many more pregnant HIV infected women from different parts of the state.
As more and more patients were approaching the center for PPTCT, the center evolved a team of health-care workers and devised its protocol for PPTCT services. The protocol thus evolved included:

- Testing and confirmation of HIV status of every pregnant lady and the partner
- Counselling of the PLWA and family addressing the confidentiality of individuals involved
- Helping the patient for disclosure to the immediate caregiver
- Offering lifelong care
- Counselling of the pregnant lady and the family by obstetrician and pediatrician and involving them in the team as early in the pregnancy as possible
- Planning feeding options early in the pregnancy
- Ensuring regular antenatal care and near 100% institutional delivery
- Initiating ART as early as possible in pregnancy
- Lower section cesarean section as the mode of delivery
- Supporting the couple/family in facing social and financial issues, including stigma and discrimination
- Linkage with PLWHA networks and other ART care centers for follow-up
- Linkage with other services like NGOs, CBOs, etc.
- Training of health-care workers in PPTCT
- Supporting private health-care providers in providing PPTCT services

All these components continue even now with appropriate modifications.

In the early days of TMHCF, there was no India specific guideline for PPTCT. So we evolved our own protocol and incorporated modified ACTG 076 protocol as part of this package. As intravenous zidovudine was not readily available, we continued oral zidovudine peripartum also. When the evidence on two drugs PPTCT became available, we shifted to it for a brief period.

Thus over the time with the evolving evidence, drug regimens for prophylaxis changed from zidovudine monotherapy through zidovudine + lamivudine and eventually to zidovudine + lamivudine + efavirenz. The time of initiation of ARV prophylaxis also changed accordingly. By 2010 every pregnant lady was receiving triple regimen as early as feasible.

Each HIV positive pregnant woman was counselled by the HIV team, pediatrician, and the gynecologist. An individualized treatment plan was charted for each patient considering their socioeconomic and health status and followed up by the counsellor. We followed planned elective cesarean section as mode of delivery. If the pregnant lady was not able to deliver in our hospital, her local gynecologist and pediatrician were contacted by our HIV team, and a suitable plan for the management of pregnancy was formulated. As far as possible, they were encouraged to bring the child to our institution for follow up, especially for nutritional evaluation and early infant diagnosis at the sixth week. Each mother-baby pair was followed up till at least the child reached 18 months and tested negative. Those women who were not registered in our center, but were referred late in pregnancy or in active labor and those who moved back to their primary care centers after delivery were also monitored.

**Mode of delivery:** Planned LSCS was the option from the early 2000s in our institution. Vaginal delivery was resorted to only if the pregnant lady reaches the institution in advanced labor.

**Flowchart 1** shows the flow of patients in PPTCT at TMHCF.

**Infant feeding:** We counselled not just the pregnant lady but the whole family regarding feeding options. The practical difficulties in avoiding breastfeeding, including the social stigma and confidentiality issues were acknowledged, and tailor-made plans were implemented for each family. Majority of our mothers opted exclusive replacement feeding initially, and these children were followed up regularly to make sure the children have not affected adversely by avoiding breastfeeds. Recently the infant feeding option has shifted more to breast feeding with more women getting diagnosed and initiated on ART early or prior to pregnancy, allowing well controlled disease states. The parents and families (especially in-laws) were regularly counselled and supported. The PPTCT was never a standalone service. It was synchronized and integrated with general MCH care and HIV care. So regular follow-up of mother and child was integrated with immunization services, pediatric/neonatal care, ART, etc. The strong relationship built between the pediatrician and the ART team continued until the child reaches adulthood irrespective of HIV status.

We made sure the social norms were followed by the pregnant ladies and families so that stigma and discrimination could be avoided.
This model was helpful for both patients and gynecologists, as almost all deliveries were planned. This model addressed the medical and nonmedical problems faced by these women comprehensively and ensured adequate compliance and follow-up.

The success of Trichur team sent messages all around the state, and most ART teams followed this model across the state. This lead to the declaration of zero transmission of HIV from mother-to-child transmission in Kerala by Hon. Health Minister in 2010. Few mothers, who were lost to follow-up were all referred late in pregnancy or in labor. Till now, to best of our knowledge, only one baby, whose mother discontinued ART due to reduced tolerance and psychiatric illness, has become HIV infected.

**Conclusion**

Vertical Transmission of HIV is an eminently preventable infection. Like any other disease, the medical factors are equally or more critical in implementing a successful strategy. Though possible in principle, very few developing countries could reach zero PPTCT of HIV so far. The latest strategy of integrating PPTCT with HIV care and providing lifelong ART to every HIV infected individual will help in preventing mother-to-child transmission as well in the coming years.

The Govt. Medical College, Thissur, could achieve a near-zero mother-to-child transmission rate from early 2000 itself solely due to the comprehensive, individualized HIV care by a dedicated team of health-care workers, integrating HIV care with the routine MCH services addressing the medical and psychosocioeconomic aspects of HIV infection simultaneously and not due to any significant upscaling of infrastructure. Because of this, Trichur model is one that can be adapted in most health-care settings in developing countries.

**References**


Abstract
HIV arrived in India 5 years after the western world. There experience guided our policies. The illiteracy, poverty, population, and inadequate health infrastructure were the imposing problems. The prompt response with awareness programs, cost free testing, management of OIs did help the patients. But the game changer was free access to cARVs. It lessened the morbidity and increased the longevity. However, the newer challenges emerge from time to time.

Introduction
Alma Ata declaration of Health for All by 2000 AD was made in 1980. It was in reference to conquering the known microbes and controlling infectious diseases in the Southern hemisphere.

The Clinicians even at that time were well aware that the newer challenges will be posed by resistant microbes including bacteria, fungi, and newly emerging viruses.

Over last four decades we are experiencing various viral epidemics and as a paradox almost all of them are emerging from the Southern hemisphere.

June 1981, exactly 6 months after Alma Ata declaration, a new disease entity was reported in MMWR which baffled the medical world. Young people were dying of Opportunistic infections without any evidence of known immune suppression. However, the investigations revealed cell-mediated immune-deficiency. Clinical spectrum evolved slowly, modes of transmission became known and the etiological virus was identified.

Indian Scenario
India was in second wave countries as HIV reached India in 1986 when Prof Jacob John could procure an ELISA kit and tested few samples of CSW in Chennai and detected positivity in two of them. This heralded the arrival of HIV in India. People were ignorant about it and few who read about it boasted about our culture and prophesised that it would never come in India. But, Govt. of India promptly responded and ICMR started the serosurveillance. Due to limited resources the universal safety precautions were almost non-existent. Glass syringes were boiled and reused. By 1990, we started getting clinical cases. The HIV phobia was so much that the private sector doctors were turning away the pts. And the Govt. hospitals had to bear the brunt. Even in our tertiary care Govt. hospital, I had to first impart training to our resident doctors and all the paramedics for safety precautions. Second, I started a dedicated HIV OPD in view of keeping patients’ confidentiality, avoiding discrimination and giving enough time for counseling of the patients. Gradually, the attendance in the OPD went on increasing. Many of the cases presented in critical condition and succumbed within 24 hours. Autopsy of these cases was necessary. My pathology colleague accepted the challenge and we could carry out 150 autopsies of AIDS cases. Autopsies were good learning lessons.
We could establish mycobacteriosis—organs teeming with mycobacteria (Fig. 1) in absence of clinical or gross pathological evidence on autopsies.

We noticed multiple pathologies in one single patient endorsing severe immunodeficiency. Sixty-seven percent showed tuberculosis along with other OIs. All these OIs were newly seen by us; hence, we had to develop appropriate tests to diagnose them. It was a time-consuming process as these OIs were not seen earlier because 1994–1995 neither long-term steroid used nor an ambitious organ transplant program was in place. Slowly we evolved.

It was necessary to share our experience of lack of preparedness for infrastructure to manage increasing number of HIV cases and how we could surmount the difficulties. A proper training had to be imparted for medical fraternity in the country. National AIDS Control Organization (NACO) was set up by Govt. of India. Under the aegis of WHO, NACO, CMAI (NGO) with support from Norad, we 21 Professors conducted training workshops in the country. It was a great experience. This was in 1992–1993.

In 1981, this new disease entity was identified as a mysterious dreadful disease. With revelation of deficiency of cell mediated immunity (CMI) presenting with various OIs (Syndrome—cluster of symptoms) the disease got its first name as Acquired Immunodeficiency Syndrome (AIDS). Now we know it as retroviral disease. It spread rapidly all over the world causing a serious pandemic without any treatment. The natural history was unfolding. Medical research finally identified the causative organism—the first human retrovirus which was called as Human Immunodeficiency Virus (HIV). After the discovery of HIV, the laboratory diagnostic tests were developed.

The serodiagnosis was based on detection of anti-HIV antibodies by ELISA technique. A positive test needed confirmation by Western Blot test, which was immunoblotting multiple antibodies. The test was cumbersome, expensive, and time consuming. Further facilitation came by using the same principle of detecting multiple antibodies using three different antigens to detect three different antibodies using technically different three tests S, R, and E—simple, rapid, and elisa.

These tests are indirect tests which detect antiviral antibodies indicating exposure to the virus. It had its window period. Science was evolving as the pandemic was spreading relentlessly. The direct tests detecting virus itself qualitatively by DNA PCR and quantitatively by RT-PCR to measure viral load developed over the time period each having its own indications.

CD4 counts were used to assess the severity of immune deficiency.

This disease no longer remained only a medical problem. It encompassed all the aspects of human life. Just to give a small example—I would recall that NACO held a special meeting of experts regarding issue of a death certificate. The discrimination was to the extent of refusing cremation/burial of a patient whose death certificate mentioned AIDS as the cause of death.

The story of evolution of HIV will remind the readers of prevailing situations with various RNA virus epidemics in last decade or so.

### Clinical Spectrum

Clinical spectrum varied depending on the severity of immune deficiency. Over three decades, I have seen almost all the OIs in our patients. However, predominant was tuberculosis. It occurred minimum 2–3 times in a patient. Depending on the severity of immune deficiency the TB presentation differed. In early immunodeficiency it was like any non-HIV TB, with moderate immunodeficiency it was extrapulmonary or disseminated TB and severe deficiency (CD4 <50) it was mycobacteriosis. Multiple OIs were seen simultaneously in the stage of AIDS.
It was intriguing for me to see patients with cryptococcal meningitis treated with inj Amphotericin responding by negative test for crypto antigen. And within a week patient clinically deteriorated and showed presence of fungus in CSF on India ink preparation. So we carried out fungal culture of CSF in these cases and were surprised to note that the etiology of fungal meningitis was as shown in Table 1. Fungal culture positive in 75.6% of cases.

Four cases of dementia of six months duration were subjected to neuro-imaging (Fig. 2).

The aspiration from these lesions demonstrated AFBs, but the culture grew Nocardia. I had a large series of various lymphomas associated with HIV. Just to cite one of them (Fig. 3), with huge hepatomegaly, ptosis, with infiltration of extraocular muscles and CD4 110 cells only.

In the decade of 1991, despite all efforts of community awareness and expanding centers for HIV care, the patients used to report to the hospital very late. Antiretroviral therapy was not available; hence, the life span was limited, and morbidity and mortality were high.

During these years, some of our concepts had to be re-examined and appropriate measures had to be taken.

One such misconception was that if either of the spouses is positive the other will also be HIV infected.

We used to do couple counseling extensively so as to protect either of them from OIs and STDs. Couples were counseled regarding barrier protection with condom. But our study showed that about 25% were strictly abstinent. About 40–50% were using condom occasionally and the remaining expressed their inability to follow the protection due to hutment, poverty, fear of getting identified in a joint family, etc.

The intriguing fact was that 40% of our couples having 3–4 kids were discordant. Later on I had undertaken a

**TABLE 1** Etiology of fungal meningitis

<table>
<thead>
<tr>
<th>Fungal Species</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans</td>
<td>21</td>
</tr>
<tr>
<td>Rhodotorula mucilaginosa*</td>
<td>28</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>03</td>
</tr>
<tr>
<td>Trichosporon</td>
<td>02</td>
</tr>
<tr>
<td>Ascosporides</td>
<td>01</td>
</tr>
<tr>
<td>Geotrichum</td>
<td>02</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>03</td>
</tr>
<tr>
<td>Normal</td>
<td>17</td>
</tr>
</tbody>
</table>

*Largest series of Rhodotorula from aseptic CSF compartment.

*Fig. 2: Nocardial abscesses in brain*
study of mannose receptors (Fig. 4) in vaginal epithelium of discordant couples.

The seronegative wives had mannose receptors but the seropositive wives were deficient in these receptors.

**Antiretroviral Treatment**

Azidothymidine (AZT): The first antiretroviral drug was discovered in 1987, had expedited approval of US FDA. HIV had just arrived in our country in 1986 so there was...
no question of its use then. But in western world AZT being the only hope; it was used inadvertently and like penicillin within few months serious side effects and AZT resistance became apparent. Over next 3–4 years combination therapy became successful to control the viral load. Combination antiretroviral (cARV) therapy was not affordable to 95% of HIV infected people living in the developing world.

NACO was giving free therapy for OIs but treating OIs without ARVs was like amputating a diabetic gangrene without treating DM. Fortunately in 2000, the Special Session of United Nations General Assembly (UNGASS) upheld health as a basic human right and providing access to free ARVs became the responsibility of the Federal Govt. WHO launched an ambitious program of treating 3 million HIV patients by 2005.

Western world had ARV experience since 1987. With experience the guidelines were modified from time to time. There are American (DHHS), British (BHIVA), IAS (European) guidelines but as they have unlimited access to ARVs the guidelines have individualistic approach. But our National guidelines are based mainly on WHO guidelines.

A community oriented therapy program needs uniform guidelines, based on the efficacy of drugs, availability of resources including finance, apart from other factors like distribution, storage, etc. Indian National Guidelines were developed by Technical Experts of the country under the NACO initiative.

Govt. of India launched the free ART program in March 2004, the launch started from my institute having the largest number of HIV patients in J J Group of Govt. Hospitals, Mumbai.

It was a game changer. The first combination that was used for maximum number of patients was STAV + LAM + NVP being the lowest cost yet effective combination. The rise in CD4 was significant as shown in Figure 5. As the immunity improved the OIs almost disappeared, great improvement was seen in morbidity and mortality.

But as said earlier within a short time, a large number of side effects of cARV were seen. The most obvious was lipodystrophy (Fig. 6) which disfigured patients who
started looking sick although the disease status was improving. They feared being identified and discriminated.

The ARV toxicity profile to the first-line ART in my experience is shown in Table 2.

Patients’ therapy compliance was a challenging issue. Ignorance, working pattern, inherent forgetfulness, and in few cases their alcohol addiction were major obstacles in compliance. In addition, Mumbai being the financial capital of India, a large number of the patients were migrant laborers. It was a major factor for their risk behavior and also a major factor for non-compliance because 3 months in a year they used to go back to their native place for farming. As a result the drug resistance was developing.

From 2004 to 2008, ART centers were being established all over the country. Apart from uniform therapy guidelines, the doctors had to be trained in this new arena.

Although a network of ART centers was being developed large number of the patients refused to attend the nearby centers for the fear of being identified. The social implications of the disease made the management difficult.

In 2008, first-line drug therapy was showing evidence of therapy failure mostly due to development of drug resistance. It was necessary to change the ARVs; therefore, second-line ART was initiated from 2008. The major change was introduction of tenofovir (TDF) and in few cases ritonavir boosted protease inhibitors.

In first 6 months after TDF, I had 17 cases of TDF induced nephropathy. Nephropathy was not anticipated with less than 6 months exposure to TDF. Three years later a study on TDF nephropathy showed long-term exposure to STV use prior to TDF was the culprit.

In this exercise I detected quite a few cases of immunovirological discordance. These patients had low CD4 and undetectable viral load. I thought of a possibility of HIV-2 infection which so far was not identified in the country.

### Table 2: ARV toxicity

<table>
<thead>
<tr>
<th>ARV toxicity</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>AZT marrow suppression</td>
<td>8%</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td>34%</td>
</tr>
<tr>
<td>Toxic neuropathy</td>
<td>10%</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2%</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>5%</td>
</tr>
<tr>
<td>Hyperlactatemia</td>
<td>2%</td>
</tr>
<tr>
<td>Drug rash</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Fig. 6: Lipodystrophy*
It was not possible in a Govt. set up at that time so I tied up with a private set up which had newly introduced HIV-2 Western Blot. I could detect 167 cases of HIV-2 which till then were receiving NNRTI in vain. After these results, diagnostic tests to differentiate between HIV-1 and HIV-2 were introduced and therapy was appropriately amended. Many newer drugs have been added to the armamentarium.

Despite offer of cost-free CD4, free viral load and free therapy, still we keep getting patients with OIs. It clearly indicates therapy failure due to non-compliant patient.

My recent data analysis showed that 31.3% of cases on ART were receiving cARV for past more than 15 years. The ART initiation criteria then was CD4 <200 cells. It can be deduced that these cases acquired the infection 8–10 years prior to initiation of ART. In earlier years, in absence of ARVs, patients were succumbing to AIDS within few days to weeks. But longevity increased so well after ART that people who acquired the infection in the age group of 25–35 years are now in their fourth and fifth decade. Quite a large number of them have crossed 60 years of age. And now apart from retroviral disease 18% of the cases are suffering from non-communicable diseases like hypertension, diabetes mellitus. It adds to the complexity of management.

In our earlier counseling in order to build up the hope and dispel their anxiety, patients were informed that soon there will be a breakthrough to wipe out the virus. We also hoped for anti-HIV vaccine but the virus is far more tricky than expected. We succeeded in controlling the viral load but could not get rid of it. The recent development of long acting injectables offers hope for improved compliance and long-term viral suppression.

HIV vaccine remained elusive over three decades. There is no breakthrough as yet because of multiple portals of entry, multiple groups and subgroups of HIV and constant mutation.

Avoidance of human risk behavior is the mainstay of prevention but it is the most challenging task, almost impossible. Safer sex practices, targeted interventions, PrEP, all have limitations and are related to human behavior. Finally, the only hope is to control human reservoir by Test and Treat!

HIV is a forerunner of all the new viruses, which emerged in last decade. For example, SARS, Chikungunya Nipah, H1N1, H5N1, Zika, Ebola they all, like HIV, are single stranded RNA viruses. No vaccine against any of these RNA viruses has so far been developed. Although HIV warned us about universal precautions, we have miserably failed in developing necessary infrastructure and safe culture! It is evident from the recent pandemic of SARS-CoV-2.

There is a long way to go!!

**Conclusion**

Knowledge about various aspects grew as the epidemic evolved. Though ART is a game changer, presently the main challenges are compliance of the patients and emergence of drug resistance. After all it is not possible to change the human behavior.

**Suggested Readings**

Abstract
Management of HIV/AIDS has undergone a revolution in recent years. Introduction of HAART lead to dramatic decrease in mortality associated with opportunistic infection that complicates advanced HIV infection. Incidence of chronic hepatitis has declined tremendously after introduction of vaccination of infants for Hepatitis B. But there is increased prevalence of HIV-HBV coinfection because both share common modes of transmission. HIV-HBV coinfection shows more rapid progression to end stage liver disease and liver fibrosis. Agents selected for the treatment of HIV-HBV coinfection should be active against both viruses.

Introduction
In recent years the management of HIV/AIDS has undergone a revolution. There was a rapid and dramatic decrease in mortality associated with opportunistic infection that complicate advanced HIV infection after the introduction of HAART. Since the emergence of vaccination of infants for Hepatitis B, the incidence of chronic hepatitis has declined tremendously. But as both Hepatitis B & HIV share common modes of transmission, there is increased prevalence of HIV-HBV coinfection. Hepatitis B infection is more frequent and more severe in HIV patients. The progression to cirrhosis and end stage liver disease is more rapid than in those not HIV infected. Coinfection of HIV may cause reactivation of Hepatitis B in HBsAg antibodies patient, especially in immunocompromised people. One of the most frequent causes of non-AIDS related death in HIV patients is liver disease caused by Hepatitis B.

Epidemiology
Since transmission routes of Hepatitis B and HIV are more or less similar (e.g., sexual contact, mother to child transmission at birth, parental (blood to blood), and through other infected bodily fluids. So there is high frequency of coinfection of HIV with hepatitis B. Worldwide nearly 10% of HIV infected population also infected with Hepatitis B. It is expected to be higher approximately 20% in Southeast Asia, 5% in North America and Western Europe. Higher rate of coinfection of HBV and HIV has been observed in MSM (men having sex with men) than heterosexuals or injecting drug users. Prevalence of HBsAg (2–14%) has been observed in HIV infected Indian population. Another studies indicated approximately 22% and 30% showing quite high frequency. These variations in study most probably due to small sample size data multicentre studies and unavailability of multirisk group data. Thus, in India, overall epidemiological trend remains obscure. According to NACO in 2017 National Adult (15–49 years), HIV prevalence in India is estimated at 0.22%. Total number of PLHIV is estimated at 21.40 lakhs. India is estimated to have 87.58 thousand new HIV infection in 2017. According to Journal of Clinical & Translational Hepatology (2017) it is estimated that about 200 crore of worldwide population have been exposed to the Hepatitis B Virus (HBV) of whom 350 million harbor...
it chronically. India falls in the intermediate endemi city zone (prevalence of 2–7%, with average of 4%) with disease burden of about 50 million. Out of 36.7 million PLHIV globally, 2.7 million people also had HBV infection.

Pathogenesis

Hepatitis B is an immune mediated infection. Interaction of the virus and the host immune system leads to liver injury progressing to cirrhosis and hepatocellular carcinoma. HIV weakens the immune system by infecting and destroying CD4+ T Cells which leads to immunodeficiency. HIV attached to the CD4+ protein on the surface of these and other cells to gain entry. HBV is more or less 100 times more infectious than HIV. The risk of chronic Hepatitis B is greater in cases of HBV/HIV coinfection. It is demonstrated that in coinfection of HIV with HBV mortality due to liver disease is 19 times that of HBV infection alone and eight times more than in person with HIV infection alone. Mortality increase in individuals with CD4+ T-Cell counts. After initiation of highly active antiretroviral therapy (HAART), there is immune reconstitution leading to more liver damage. There are higher HBV DNA levels, lower serum ALT, more liver fibrosis, and more risk of end stage liver disease in the patient with HIV-HBV coinfection. Although healthy adults who are infected with HBV has less than 10% chance to develop into chronic hepatitis B, when an HIV positive adult is infected, the risk is up to 25%. CD4 restoration is less than satisfactory in response to HAART in these patients.

Treatment

For the treatment of HIV-HBV coinfection, agents selected should be active against both viruses. First goal of the clinician is to select the patient whether to treat for HIV alone, for HBV alone or for both the viruses. For patients having HIV or HIV with HBV the treatment endpoints remains the same although loss of HBeAg or HBsAg as well seroconversion to anti-HBeAg and anti-HBs is not common. The treatment must include agents active against both viruses in HIV-HBV coinfection. Not doing so will lead to emergence of HIV strains that are resistant to NRTI (nucleoside reverse transcriptase inhibitor). The recommendations from the recent the USA & Europe guidelines advocate the use of two anti-HBV drugs as part of HAART in HBV-HIV coinfection. The aim of this combination therapy is to decrease the development of resistance even though very little data exists on either mono- or coinfected patients with such therapy. The preferred treatment for dual HBV/HIV coinfection is the combination of tenofovir and lamivudine (emtricitabine). Removal of HBV therapy or change in HIV therapy for virologic failure may lead to rebound hepatitis. Hence, on changing ART always consider HIV therapy with activity against HBV. Latest studies suggest that despite faster decline of antigen level on addition of pegylated interferon for the treatment of HBV active ART in HBsAg positive coinfected person, HBeAg, or HBsAg clearance did not increased. Tenofovir alafenamide (TAF) is now available with comparable efficacy to Tenofovir but with reduced toxicity. Others—New antiviral agents like HBV entry inhibitors are currently in development. Even after HBsAg seroconversion, cessation of HBV active NRTI is safe or not remains unknown.

Vaccination

Vaccination against Hepatitis A and B should be given to all HIV patients who are not immune. In HIV positive patients the immunogenicity to HBV vaccination is decreased that is reflected by lower antibody titers, gradual waning immunity and seroconversion rates of 18–65%. Response to vaccination is poor in HIV patients especially in those with lower CD4 counts. These individuals poorly maintain the antibody titers after vaccination. May consider increase dose (double the dose of HBV vaccine) for adequate response. One month after completion of vaccine schedule anti-HBS titers should be checked. Patients with anti-HBS titer less than 10 IU/mL, a second vaccine cycle is recommended. Improved response may expect with higher CD4 counts and undetectable plasma HIV RNA on doubling the HBV vaccine dose.

Conclusion

The liver is frequently affected in patients with HIV. HIV/ HBV coinfection shows more rapid progression to end stage liver disease and liver fibrosis. Since both HIV and HBV share common modes of transmission so the incidence is high with coinfection. Liver disease considered to be one of the leading causes of death in patients with HIV in post HAART era. Agents selected, for the treatment of HIV-HBV coinfection, should be active against both viruses. For better outcome in HIV-HBV coinfected patients there is increase need of close working relationships between primary care providers, infectious disease specialists, and hepatologists.
Suggested Readings


Abstract

The life expectancy of the PLHIV (People Living with HIV) has increased significantly because of increased availability of ART and “treat all” strategy, leading to increased proportion of patients with HIV are living longer. The challenges faced by aging PLHIV can be either associated with HIV related pathology (increased risk for chronic conditions), complications due to HIV treatment and age related pathology (cardiovascular diseases, diabetes, etc.).

Often older individuals are detected late as clinicians do not think that they are at risk for HIV infection. Early detection of HIV and prompt start of ART in older PLHIV should be done to decrease mortality. Aging PLHIV are at increased risk of malignancies. The risk of anal canal, colon, prostate, lung, hepatic, and oral cavity malignancies are increased in PLHIV as compared with age-matched general population, especially after 50 years of age. Screening for these malignancies should be done for early detection and effective management.

Long-term use of ART there is an increased risk of metabolic syndrome in the form of increase in centripetal fat, raised triglyceride & cholesterol levels, raised blood pressure and insulin resistance which are all risk factors for cardiovascular disease. Focus should be on drugs with excellent efficacy and minimal drug interaction and side effects when considering any ART for aging PLHIV. As this population is at increased risk for cardiovascular disease, counseling for lifestyle modifications like smoking cessation, regular exercise, and healthy diet would also decrease mortality and morbidity.

Introduction

With easy availability of antiretroviral therapy (ART), Treat All strategy by WHO, the life expectancy of the People Living with HIV (PLHIV) has increased significantly leading to increased proportion of patients with HIV a living longer. PLHIV are known to experience age-related comorbidities at relatively younger ages when compared with the general population. Thus many publications on HIV define older as ≥50 years of age. The challenges faced by these aging PLHIV are due to the disease itself, accelerated aging, and therapy-related toxicities and long-term side effects.

Burden of Disease

Approximately, there were 5.7 million individuals ≥50 years were living with HIV infection by the end of 2016 and it is estimated that by 2020, 21% of PLHIV will be in this older age group. Moreover, there were approximately 110,000 new infections occurring in persons of this age group in 2016. This could be an underestimation as older individuals are frequently not perceived by their clinicians as being at risk for HIV infection and, consequently, are less likely to be tested for HIV compared with younger adults.

In a study of 8,255 older adults who accessed HIV care in England, Wales, and Northern Ireland. Almost half of older adults had CD4 cell count less than 200 cells/μL at the time of diagnosis. They were 14 times more likely to die within a year of diagnosis compared with older adults who were diagnosed at young age. Most studies have demonstrated that, despite successful ART and viral suppression, immune recovery is less robust with increasing age, highlighting the importance of early diagnosis and treatment.
System-wise Non-AIDS Morbidity

The manifestations in older PLHIV could be due to HIV-related pathology, treatment-related complications, and age-associated pathology (Table 1). Other manifestations that occur earlier or more commonly in this subset are bone-related pathologies like osteoporosis and fractures, neuropsychiatric manifestations, malignancies, and renal failure. Immune activation: HIV infection is a major source of inflammation in both treated and untreated individuals. ART that suppresses the viral load reduces these inflammatory markers but does not make it normal. This immune activation causes accelerated aging of T cells (immunosenescence) meaning that a PLHIV is physiologically older than his actual age. This causes increased incidence of age-associated conditions including cardiovascular, bone, metabolic, and neurocognitive diseases, which are generally seen at a later age in non HIV patients.

Malignancies: PLHIV are at increased risk of malignancies. The AIDS defining malignancies like Kaposi sarcoma, Non-Hodgkin lymphoma (NHL), and invasive cervical carcinoma are gradually decreasing. With increase survival of PLHIV, the incidences of non-AIDS-defining cancers are increasing. The risk of anal canal, colon, prostate, lung, hepatic, and oral cavity malignancies were excessively raised in PLHIV as compared with age-matched general population, especially after 50 years of age (Fig. 1).

This increased incidence of malignancy among PLHIV may be due to immunosuppression, direct effects of the HIV virus itself, coinfection with other oncogenic viruses, environmental factors, and possibly the use of antiretroviral drugs. Malignancies occur at an earlier age, have higher tumor grade, are more aggressive, and are at an advanced stage at presentation. Thus the focus should be on early screening, smoking cessation, HPV and HBV vaccination, treatment of Hepatitis C, and Hepatitis B.

Cardiovascular system: Long-term use of ART there is an increased risk of metabolic syndrome in the form of increase in centripetal fat, raised triglyceride & cholesterol levels, raised blood pressure, and insulin resistance, which are all risk factors for cardiovascular disease. The cardiovascular risk is also related to the duration of treatment with antiretroviral drugs and increases with uncontrolled disease, particularly in presence of other risk factors.

The risk of acute myocardial infarction (MI) and advanced subclinical cardiovascular disease is increased in PLHIV when compared to age matched general population. With increasing age, focus should be shifted on the treatment adherence and management of hypertension, dyslipidemia, obesity, and diabetes. Lifestyle modifications like smoking cessation, regular exercise, and healthy diet would also help in reducing cardiovascular mortality.

Central Nervous System

Neurocognitive disorders: It is estimated that the approximately 50% of the PLHIV on long-term ART have some amount of neurocognitive dysfunction. HIV-associated dementia is three times higher among patients ≥50 years than among patients aged 20–39 years. The most severe form of HIV-associated neurocognitive disorders is HIV-associated dementia (HAD), classically manifested as a subacute onset of impairments in subcortical function, such as decreased attention/concentration and psychomotor slowing. ART is known to have beneficial effect on the treatment and prevention of HAD. As HAD is associated with local replication of HIV in the CNS, it is

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**Table 1** Causes of morbidity in PLHIV

<table>
<thead>
<tr>
<th>HIV-related pathology</th>
<th>HIV treatment complications</th>
<th>Age-associated pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV-related increased risk for chronic conditions</td>
<td>• Lipodystrophy</td>
<td>• Cardiovascular disease</td>
</tr>
<tr>
<td>• HIV infection-related immunosenescence</td>
<td>• Cardiac disease</td>
<td>• Diabetes</td>
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<tr>
<td></td>
<td>• Dyslipidemia</td>
<td>• Osteoarthritis/osteoporosis</td>
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<td></td>
<td>• Diabetes</td>
<td>• Glaucoma/catarract</td>
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<tr>
<td></td>
<td>• Metabolic syndrome</td>
<td>• Sarcopenia</td>
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<td></td>
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<td>• Neurocognitive diseases</td>
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recommended that ART, which penetrates the CNS should be used. Some of the preferred regimens are Tenofovir-emtricitabine plus dolutegravir; Abacavir-lamivudine plus dolutegravir; or Tenofovir-emtricitabine plus ritonavir-boosted darunavir.

It is also important to distinguish between HIV-associated neurocognitive disorders and other neurodegenerative disorders, especially Alzheimer’s disease. The incidence of neuropsychiatric manifestation especially depression is more in PLHIV as compared to the general population and it increases with age and should be recognized and treated early.14

Peripheral neuropathy: Ageing is a risk factor for peripheral neuropathy. In an observational study of 2,141 antiretroviral-naïve PLHIV who were seen annually between 2000 and 2007, ageing was associated with peripheral neuropathy despite virologic and immunologic control of HIV.14 Almost 50% of the PLHIV are having some amount of HIV-associated sensory neuropathy (HIV-SN). This could be either be HIV-associated or as an adverse effect of ART. However, with the decrease in the use of antiretrovirals like stavudine, didanosine, etc. the incidence of ART induced neuropathy is decreasing.

Skeletal system: PLHIV are prone to a wide range of musculoskeletal problems including opportunistic bone infections, osteonecrosis, osteopenia, and osteoporosis, which could be either due to HIV itself or ART induced. The chronic inflammatory state, antiretroviral drugs like tenofovir, abnormal vitamin D metabolism, cigarette smoking, alcohol use, depression, opiate use, low testosterone levels, and premature menopause are the factors responsible for enhanced bone loss in PLHIV.15 With increasing age, bone fractures (especially hip fracture) are responsible for very poor quality of life and a major physical and psychological impact on the patients and their family.16

Apart from the earlier mentioned problems, PLHIV also have sarcopenia, that is, loss of skeletal muscle mass. Many of the factors responsible for sarcopenia are already present in a PLHIV. Along with these factors, ART is also responsible for differential body fat distribution (already described earlier) and also sarcopenia.

Liver disease: Coinfection with hepatitis B and C viruses (HBV and HCV) is common among PLHIV and HIV coinfection increases the likelihood of chronic infection and a faster rate of liver fibrosis progression. Thus, chronic liver disease is a frequent finding in older adults with HIV. Thus, all efforts should be made to detect these chronic infections early and treat them. Vaccination for Hepatitis B should be done for all PLHIV at the time of diagnosis who are HBsAg negative.

Renal system: In general population, glomerular filtration rate (eGFR) decreases with increasing age normally. problems arising from age-associated diminished renal function may be compounded among older adults living with HIV. Kidneys are the reservoir for the virus, and...
hence the risk of renal dysfunction is higher in PLHIV. Risk of acute renal failure is increased with Low CD-4 cell levels and long-term use of ART. HIV-associated nephropathy (HIVAN) has a high risk of developing end-stage renal disease (more often seen in African-Americans as compared to whites). Many ART drugs (tenofovir) are nephrotoxic, and hence may require dose modification in these patients or even require change in therapy.

**Hypogonadism:** Hypogonadism is common in men with HIV and has been associated with advanced disease and, in the ART era, persistent viremia. In one study of the Multicenter AIDS Cohort Study (MACS) cohort, the rate of decline in testosterone level decline over 10 years appeared similar between men with or without HIV, although HIV may be associated with greater loss of diurnal variation.\(^8\)

**Geriatric syndromes and functional impairment:** In addition to facing multimorbidity and polypharmacy, older adults with HIV may also be dealing with geriatric syndromes, such as falls, frailty, functional impairments, and disability. As with certain comorbidities, these geriatric syndromes may also occur at relatively younger age in adults with HIV compared with the general population.\(^8\)

**TABLE 2** Evaluation and monitoring of PLHIV

<table>
<thead>
<tr>
<th>Cardiovascular risks</th>
<th>Blood pressure check</th>
<th>At baseline and annually</th>
</tr>
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|                      | Fasting sugar and/or HbA1C | • At baseline and every 6–12 months  
• 1–3 months after ART initiation |
|                      | Fasting lipid profile | • At baseline and every 6–12 months  
• 1–3 months after ART initiation |
|                      | Weight assessment | At baseline and follow-up visits |
| Tobacco use assessment | At baseline and annually |

| Neuropsychiatric disorders | • Depression screening  
• Screening for cognitive deficits | At baseline and annually  
At baseline and annually |

| Medication toxicity | • Complete blood count with differential  
• BUN and creatinine  
• ALT, AST, and total bilirubin | At baseline, 2–8 weeks after ART initiation and every 3–6 months thereafter |

| Urinalysis | • At baseline  
• At ART initiation or change  
• Annually |

| Dilated fundoscopic examination | Every 6–12 months in patients with CD4 <50 cells/µL  
Annually |

| Other metabolic complications | Bone densitometry | At baseline in postmenopausal women and men ≥50 years |

| Cancers | Colonoscopy | • At 50 years of age in asymptomatic person with average risk  
• Earlier screening in patients with strong family history  
• Subsequent testing based on baseline results |

| Mammography | Annually in all patients of 50–74 year age |

| Cervical pap smear | • At baseline and subsequent testing based on coinfection with HPV  
• Additional tests if abnormal results |

| Anal pap smear | • Consider at baseline and annually  
• More frequent testing if abnormal results |
Management of HIV Infection in Aging Population

Early diagnosis and prevention: Often older individuals are detected late as clinicians do not think that they are at risk for HIV infection. This mindset needs to be changed as early diagnosis and institution of therapy improves mortality in this group. Early screening of hypertension, diabetes, dyslipidemia, and counseling for weight loss, exercise, and tobacco cessation should be part of routine management. Screening for neurocognitive disorders, depression, bone health, and malignancies should be done routinely at baseline as well as part of follow-up (Table 2). Vaccine against influenza, pneumococci, Hepatitis A and B should be given to older PLHIV.

Antiretroviral Therapy

Institution of early ART is recommended in this group so as to reduce the higher risk of non-AIDS-related complications. There are no preferred first-list ART regimens for older adults. However, while choosing the ART regimen focus should be given on concomitant medications and comorbidities, particularly liver and kidney disease. As this group patients are often on polypharmacy, that is, taking five or more medications it can lead to adverse drug events, drug-drug interactions, and inappropriate medication. This can also lead to poor adherence.

Age-associated physiologic changes like increased adiposity, increased gastric pH, decreased albumin levels, and changes in the cytochrome p450 enzyme system alter pharmacokinetics of drugs. Since both NNRTIs and PIs are metabolized by cytochrome p450, older patients with HIV may have significantly higher drug exposure when treated with antiretroviral agents and are thus prone to adverse effects. Moreover, cytochrome P450 interactions of PI and NNRTIs should be considered to minimize risk for drug-drug interactions.19,20

Conclusion

Health system is constantly working on enhancing the life expectancy of PLHIV. Early detection of HIV and prompt start of ART in older PLHIV should be done to decrease mortality. When considering any ART focus should be on drugs with excellent efficacy and minimal drug interaction and side effects. With the emergence of very effective ART the focus is now shifting on decreasing the functional and cognitive impairment, preventing cardiovascular mortality and morbidity, prevention and early detection of malignancy and decreasing the disability, and enhancing the quality of life in PLHIV. Screening and prompt detection of these comorbidities will go a long way in improving morbidity in these age groups. A public health approach that anticipates the needs of the ageing population with HIV will be best suited to prevent and manage these challenges.

References