Where we could never achieve CD4 target: Case reports (CD4 discordance in viral suppression)

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AGENDA

- Case reports
- Prevalence
- Persistently Low CD4 Counts in Patients with Suppressed HIV RNA
- Immunologic Recovery Based on Specific Antiretroviral Regimens
- Causes of Discordant Responses with Poor Immunologic Recovery
- Interleukin–2 for Persistently Low CD4 Cell Counts
- Recommendations for Patients with Persistently Low CD4 Cell Counts
46yrs male
Presented with continued low grade fever and loss of weight and appetite for more than a month in October 2011
Temp. Was initially 99–100 degree F and subsequently went upto 104 deg F
Antibiotics and antimalarials didn’t work
Chest Xray showed an oval rt. Anterior mediastinal SOL and CT scan was advised
CT Scan showed Non–Nerotic Lymphadenopathies at prevascular & right paratracheal region and additional lymphadenopathies at left axillary region.
ESR found to be 52 Serum ADA was 126, Tuberculosis IgG – 136, IgM – 0.15, IGA – 1260.
ATD started and biopsy of lymph node to exclude Lymphoma was planned.
Before Biopsy in Routine screening it was found HIV- Suspicious, HCV Negative, HBsAg- Negative.

Then HIV 1 & 2 Antibodies Screening Test done, result found positive with Index Value 946.16

For Confirmation, HIV1 & 2 Antibodies, Western Blot test was done, Found HIV 1 - Positive, HIV2- Negative.
Absolute CD4 count was 151 and viral load was 7,107,899

- After ATD Cat I was started, two weeks following ART with Tenofovir 300mg + Emtricitabine 200mg and Effavirenz 600mg was started.

- Additionally patient was on Febuxostat 40, Thyroxine 75, Nebivolol 5 and Rosuvastatin 10 and other supportive medications.

- Alongwith cotrimexazole and fluconazole prophylaxis.
Within a month the Viral load was undetectable and CD4 went only upto 175

After 3 months when Viral load was still undetectable, CD4 was only 185

The ART regimen was changed to Atazanavir 300mg + Ritonavir 100 mg along with Tenofovir 300mg + Emtricitabine 200mg

Patient was also on cotrimexazole and Fluconazole prophylaxis
After 3 months when Viral load was still undetectable, CD4 was only 220.
Raltegavir 400 bd was added to the regimen
Patient had no opportunistic infection and completed the course of ATD cat I
Three months later CD4 came down to 159 with undetectable viral load with the present regimen. Patient was compliant and very meticulous in taking the drugs. Still there was no opportunistic infections and other metabolic problems were under control.
On followup CD4 steadily declined to reach present level of 135 with undetectable Viral load
Genetic resistance testing was negative due to low viral load
Patient is active and asymptomatic carrying out his professional activities very aggressively
- On further workup HIV 2 and PCR for Hepatitis B and C was negative.
- Total leucocyte count was persistently within normal range
- There was no history of treatment with any alternative medicines
- Patient was not on steroid or any immunosuppressive drugs
- There was no evidence of any related malignancy
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<thead>
<tr>
<th>Test Description</th>
<th>Biological Reference</th>
<th>Observed Value</th>
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<tbody>
<tr>
<td>HIV - 1 RNA Quantification/ Viral Load</td>
<td>Non Detectable</td>
<td>7,107,899</td>
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<tr>
<td>Log Value - Viral Load</td>
<td></td>
<td>6.85</td>
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<tr>
<td>Total Leucocytes (WBC) Count</td>
<td>4,000 to 10,500/c.mm</td>
<td>6,900</td>
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<tr>
<td>CD45 Absolute (Lymphocyte Gated)</td>
<td>1000 to 3000/c.mm</td>
<td>2,364</td>
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<tr>
<td>CD3 (T Cell) Percentage</td>
<td>56% - 86%</td>
<td>84</td>
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<tr>
<td>CD3 (T Cell) Absolute</td>
<td>723 - 2737 (cells/ul)</td>
<td>1,980</td>
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<td>CD4 (Helper T Cell) Percentage</td>
<td>33% - 58%</td>
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<tr>
<td>CD4 (Helper T Cell) Absolute</td>
<td>404 - 1612 (cells/ul)</td>
<td>151</td>
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<tr>
<td>Haemoglobin (Hb)</td>
<td>13.5 to 18gm/dL</td>
<td>11.5</td>
</tr>
<tr>
<td>Palate Count</td>
<td>150 to 450 * 1000/c.mm</td>
<td>258</td>
</tr>
<tr>
<td>CD8 (Suppressor T-Cells) Percentage</td>
<td>13% - 39%</td>
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</tr>
<tr>
<td>CD8 (Suppressor T-Cells) Absolute</td>
<td>220-1129 (cells/ul)</td>
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</tr>
<tr>
<td>CD4/CD8 Ratio</td>
<td>0.9 - 2.5</td>
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Case Report 2

South Indian farmer on ART, was hospitalized on 24th March 2011 for a non-healing ulcer in the right side of the lower lip.

- Patient was tested HIV positive in November 2006 (HIV 1 positive); and was put on siddha (alternate Indian medicine system) medications and Cotrimoxazole (CTZ) prophylaxis since July 2007.

- CD4 cell count: zero.
- Age: 49 yrs
- ART: AZT + 3TC + NVP

Sputum was negative for Acid Fast Bacilli (AFB) during February 2008 and again on March 2008.

Ulcerated lesion on the right side of the lower lip with smooth margin, ulcerated base and serous exudation was first documented in May 2009.

No improvement with a course of acyclovir
Dec 2009, a biopsy revealed granulomatous tissue with predominant lymphocytes and epithelioid cells.

Smear for AFB was negative.

ATT started— Rifampicin, Isoniazid, Ethambutol and Pyrizinamide 3x week.

Lesion regressed within a week.
- Adherence to ART with greater than 95%.

- A single ulcer of 2 cm × 1 cm size, over right side of lower lip, without tenderness, with irregular margins and the base was indurated with little amount of crusting.

- Non-alcoholic, non-smoker, No history of chewing of tobacco

- Current ART: AZT+ 3TC + EFV
December 2010: Three rapid HIV tests were repeated for HIV 1 and HIV 2 antibodies and the result showed HIV 1 positive and HIV 2 negative.

February 2011: HIV 1 viral load was carried out and it was <50 copies/ml
Treatment failure in this case is considered because:

- (1) clinical failure—the non-healing lower lip ulcer, an extra-pulmonary tuberculosis, a stage IV illness of WHO clinical staging for HIV

- (2) immunological failure—the repeated "nil CD4 counts" in spite of continuous ART with more than 95% adherence and more than 6 months of continuous anti-retro viral therapy
Case review and conclusions

- Immunological failure with "nil CD4 counts" after 6 months of continuous ART and 95% adherence with stage IV clinical illness.
- It indicates poor primary immunological response to first line ART.
- The patient was on AZT + 3TC + NVP since February 2008. NVP was substituted with EFV after starting of anti tuberculous therapy.
Persistent zero CD4 count with well-suppressed viral load is rare.

The zero CD4 count cannot be named as suboptimal treatment response because the viral load is suppressed well and remained less than 50 copies.

Virological and immunological discordance can be considered but CD4 count remaining persistently at zero is very unusual.
Poor immunologic response despite adequate virologic suppression

- (a) bone marrow suppression by the use of AZT,
- (b) history of use of systemic corticosteroids or chemotherapeutic agents,
- (c) co-infections other than tuberculosis, which included hepatitis C co-infection,
- (d) sjogren's syndrome,
- (e) sarcoidosis, cotrimoxazole and
- (f) technical error.

The investigations ruled out the above conditions.
Case Study: Discordant CD4 Cell Count and Viral Load Responses to ART

A 42–year–old HIV–infected woman with a CD4 count of 36 cells/mm$^3$ and an HIV RNA level of 126,000 copies/ml is newly diagnosed with HIV.

She starts on daily Trimethoprim–Sulfamethoxazole and weekly Azithromycin followed 3 weeks later with Tenofovir–Emtricitabine, Atazanavir, and Ritonavir.

Within 16 weeks, she has an HIV RNA level less than 50 copies/ml and she maintains an undetectable HIV RNA during the next 3 years of ART. **Her CD4 cell count, however, does not increase significantly, remaining in the 110–130 cells/mm$^3$ range.** She is tolerating her medications without any difficulty.
Case Study:

What would you recommend in this setting?

A. Give subcutaneous interleukin-2 twice daily for 5 consecutive days every 8 weeks until the CD4 count is greater than 200 cells/mm³.

B. Switch the ATV/r to LPV/r.

C. Discontinue antiretroviral therapy, since it appears the patient has not had a good CD4 cell count recovery.

D. Continue the current antiretroviral regimen and *Pneumocystis* prophylaxis, but discontinue azithromycin.
Correct ANS is option D. Continue the current antiretroviral regimen and *Pneumocystis* prophylaxis, but discontinue Azithromycin.

Although ART has not generated the desired CD4 cell count response in this patient, she has achieved persistently undetectable HIV RNA levels and has tolerated the regimen well.

Maintaining long-term virologic control provides clinical benefit, independent of CD4 cell count responses.

Since her CD4 count has been greater than 100 cells/mm³ for longer than 3 months, the patient no longer needs the Azithromycin for *Mycobacterium avium* complex prophylaxis.

In this patient, it would be reasonable to switch the *Pneumocystis* pneumonia prophylaxis from trimethoprim–sulfamethoxazole to another agent less likely to cause marrow suppression.
Where We Could Never Achieve CD4 Target – A Case Report

Outline ...

- Case study
- **Prevalence**
  - Persistently Low CD4 Counts in Patients with Suppressed HIV RNA
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Prevalence of discordant immune response on ART
Within the cohort, 220 (24%) experienced a discordant immune response within 6 months of ART initiation. At baseline, the mean CD4 cell count in the discordant group was 218 cells/mm³ (SD ±168).

Conclusions: Discordant immune response following ART initiation was common and associated with baseline anemia and CD4 cell count in our cohort. Intensive monitoring of at-risk individuals may improve clinical outcomes.
The prevalence of discordant immunologic and virologic responses in the present study was 9%, a value which, despite the different definitions of this phenomenon, is within the range of values reported by others (between 8% and 16%).

Higher prevalence has been reported by other authors. These vary between 17% and 21% and above 24%. The discrepancies can be explained by the different criteria used to define the discordant response, especially as far as CD4 cell count is concerned. The period used to establish discordant immunologic and virologic responses also varied between studies.
prevalence of therapy responses after 48 weeks of HAART of a closely followed cohort of 51 ARV-naïve patients. This cohort is well balanced in age, PI-based regimen, hepatitis C virus co-infection, and AIDS-defining events at baseline.

In summary, 15.7% patients had a poor CD4 count increment despite having a significant viral load reduction or a complete virus suppression (virologic response).
Methodology: The CD4 counts and viral loads of 142 treatment naïve HIV 1 patients who were put on anti retroviral treatment were carried out by Immunocount assay and Real Time PCR respectively. The counts obtained every three months during January 2009 to December 2011 were analysed and mean CD4 counts and viral load values calculated.

Results: On the basis of the mean values, the patients were categorized into four groups based on different permutations and combinations of the low or high CD4 counts and viral loads. Only 30.95 % of individuals showed an improvement in CD4 counts and reduction in viral load while 35.71% showed a discordant response.
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Persistently Low CD4 Counts in Patients with Suppressed HIV RNA

- Among patients who take antiretroviral therapy and achieve suppression of HIV RNA levels, most have a substantial increase in their CD4 cell count.

- Typically, patients have a brisk increase in CD4 cells in the first 3 to 6 months after starting antiretroviral therapy, predominantly due to a release of memory CD4 cells trapped within lymphoid tissue. 
  \[\text{Lancet Infect Dis. 2006;6:280–7.}\]

- In the second phase of CD4 recovery, there is a gradual increase in CD4 counts that continues for 3 to 6 years; this phase involves both naive CD4 cells (from the thymus) and memory CD4 cells.

- Approximately one-third of patients who maintain continuous suppression of HIV do not recover their CD4 cell count to a level above 500 cells/mm³ after 5 years.
  \[\text{Swiss HIV Cohort Study. BMJ. 1997;315:1194–9.}\]
Persistently Low CD4 Counts in Patients with Suppressed HIV RNA

- A smaller proportion of patients (less than 10%) fail to recover their CD4 count at a level greater than 200 cells/mm$^3$ despite virologic suppression.

- This is often referred to as a "discordant" or "immuno–virological discordant" response (good virologic response and poor immunologic recovery). This discordant response is associated with increased risk for developing an opportunistic infection and increased progression to AIDS or death.

  J Infect Dis. 2011;203:364–71,
  Acquir Immune Defic Syndr. 2008;47:553–8,
  Ann Intern Med. 2000;133:401–10 &

- But the risk of developing new AIDS–defining event declines substantially after the first 6 months of virologic suppression.

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Immunologic Recovery Based on Specific Antiretroviral Regimens

- Most patients who achieve sustained virologic suppression with one of the recommended modern ART regimens have good CD4 count recovery.

- Data suggest that in ARV-naive patients, EFV produces lower CD4 cell count recovery than with boosted PIs, Maraviroc and Raltegravir. 
  

- In ACTG 5142, patients receiving LPV/r plus two NRTIs had greater CD4 cell count increases at 96 weeks than patients taking EFV plus two NRTIs (287 versus 230 cells/mm³).  
  

- In addition, AZT-based regimens may have poorer CD4 count responses, presumably because of the marrow suppressive effect of AZT. 
  
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Causes of Discordant Responses with Poor Immunologic Recovery

- When patients have poor CD4 cell count responses in the setting of sustained virologic suppression, several potential reversible causes should be considered, including receipt of marrow-suppressive medications and infiltrative bone marrow processes.

- Common marrow suppressive drugs used in HIV-infected patients include AZT and AZT containing fixed combination pills Trimethoprim–Sulfamethoxazole, Interferon and Peg–interferon preparations, Pyrimethamine, Sulfadiazine, Ganciclovir, Valganciclovir, and Etoposide.

- Medication–related marrow suppression is more likely to occur when a combination of marrow suppressive agents are used, such as AZT plus Trimethoprim–Sulfamethoxazole.
Causes of Discordant Responses with Poor Immunologic Recovery

- Marrow infiltrative processes, such as lymphoma and disseminated histoplasmosis, should also be considered.

- Only after excluding reversible causes of poor immunologic should the patient be considered to have a true discordant response with poor immunologic recovery.

- Factors identified with poor immunologic recovery include low baseline CD4 cell count, older age, and possibly co-infection with HCV.

Risk factors for not achieving a CD4 count >200 cells/μL

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<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Lower initial CD4 count,</td>
</tr>
<tr>
<td>Male heterosexual</td>
</tr>
<tr>
<td>Injection drug use transmission</td>
</tr>
<tr>
<td>cART initiation after 1998</td>
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<tr>
<td>Longer time from initiation of cART to start of the virally suppressed period</td>
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This risk was greatest in the first 6 to 12 months after initiation of ART
CD4 and progression to death

Sub-optimal CD4 increases were associated with an increased risk of death

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Several studies clearly established that interleukin–2 given with antiretroviral therapy causes substantially greater increases in CD4 cell counts than antiretroviral therapy alone. 

*JAMA. 2000;284:183–9.*

In contrast, interleukin–2 given without antiretroviral therapy generates inferior CD4 count responses when compared with antiretroviral therapy alone.

*AIDS. 2009;23:203–12.*
Interleukin–2 for Persistently Low CD4 Cell Counts

- To determine whether the addition of interleukin–2 to antiretroviral therapy reduced the risk of opportunistic diseases or death, the NIH sponsored two large phase 3, randomized, international trials:

  (1) Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) and

  (2) Subcutaneous Recombinant Human IL–2 in HIV–infected Patients with Low CD4 Counts under Active Antiretroviral Therapy (SILCAAT).

Interleukin–2 for Persistently Low CD4 Cell Counts

- In ESPRIT, 4,111 patients with a CD4 cell count greater than 350 cells/mm³ were randomized to receive interleukin–2 (Proleukin) plus ART or ART alone.

- Interleukin–2 was given at a dose of 7.5 MIU twice daily for 5 consecutive days every 8 weeks for at least 6 months, and patients had an average follow-up of 7 years.


Although patients who received interleukin–2 and antiretroviral therapy had an average CD4 count 159 cells/mm³ greater than those who received ART alone, there was no difference in clinical outcomes.
Investigators in SILCAAT randomized 1,695 patients with a CD4 cell count between 50 and 299 cells/mm$^3$ to receive interleukin–2 plus ART or ART alone, with follow-up of approximately 7 years. Interleukin–2 was given at a dose of 4.5 MIU twice daily for 5 consecutive days every 8 weeks for 49 weeks.


Patients who received interleukin–2 and ART had an average CD4 count 53 cells/mm$^3$ greater than those who received antiretroviral therapy alone, but no differences in clinical outcomes were observed.

The reason for the lack of clinical benefit despite increased CD4 counts remains unclear.
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Recommendations for Patients with Persistently Low CD4 Cell Counts
Recommendations for Patients with Persistently Low CD4 Cell Counts

- For persons who have sustained virologic suppression for at least 2 years but have CD4 counts consistently less than 200 cells/mm³, the following approach is recommended.

- **First**: Make certain the patient is receiving appropriate prophylaxis for opportunistic infections.

- **Second**: Examine the patient's medication list for medications that can suppress bone marrow. In patients taking a potentially marrow suppressive drug, change the medication to a non-marrow suppressive drug, if possible. For example, consider switching from a AZT-containing regimen to a regimen that does not contain AZT.

- **Third**: Evaluate the patient for clinical manifestations, such as systemic symptoms or pancytopenia, which suggest a marrow infiltrative process.

- **Fourth**: Continue ART, even if the patient has not had a good CD4 cell count response. Multiple studies have shown that achieving a durable virologic response translates into clinical benefit independent of CD4 count.

Conclusions:

There are no "switch" data that support a change from one suppressive regimen to another, and there may be potential benefit of switching to a non AZT–containing regimen.

There is evidence, discussed above, that regimens containing RTV –boosted PIs, MVC, and RAL result in greater CD4 cell count responses than EFV–based regimens, although there is currently little evidence supporting modification or intensification of EFV–based regimens in patients with discordant CD4 responses.

The intensification approach is currently being evaluated in clinical trials. Finally, existing data do not support the use of interleukin–2 in this setting.

Although preliminary data with other investigational agents, such as interleukin–7, have demonstrated an increase in CD4 cell counts, there are no clinical data to support the use of such therapies in clinical practice.


Lower thymic volume in patients with virologic response could contribute to the slower increment of CD4 counts

Conclusions:

- Simple mechanism like irregular treatment compliance might play an important role in immune response.
  

- Compared with immune responders, patients with immuno–virological discordance seem to remain at increased risk for AIDS. **Absolute risk is greatly reduced after the first 6 months of complete viral suppression.**
  
  *JID 2010:203 (1 February) d Zoufaly et al.*
There is no consensus in current HIV guidelines on the definition of adequate CD4 response.

It is important to continue serial CD4 count measurements in the first year post–ART initiation, even after achieving viral suppression.

Appropriate prophylaxis for OIs hence should be continued in these patients since high rates for TB as a new AIDS diagnosis among those with poor CD4 recovery.

Thank you