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# HIV Resistance Testing Consultation Service Consultation Report

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Consultation is available to California AIDS Drug Assistance Program providers through the California State Office of AIDS Voucher Program by calling the HRSA/ AIDS ETC National HIV Telephone Consultation Service (Warmline) at 1/800/933-3413. The HIV Resistance Testing Consultation Service is supported by a grant from the California State Office of AIDS through the Pacific AIDS Education and Training Center.

**History/Clinical Course**

**History:** The patient is a 46-year-old Native American woman who was diagnosed with HIV in 1994. Her CD4 at that time was 410 cells/mm<sup>3</sup>. A few months later she was found to be pregnant and for unknown reason(s) was incarcerated. Records from this incarceration are not available but the patient states that she had received antiretroviral drugs, including zidovudine (AZT), lamivudine (3TC) and stavudine (d4T), and that she gave birth to an HIV-negative baby. After being released from prison in 1997, the patient had a CD4 count <200 cells/mm<sup>3</sup>. She did not receive therapy at that time due to heavy alcohol, heroin, and crack use. In 2/2005, when her CD4 cell count fell to 95 cells/mm<sup>3</sup> (HIV viral load was 26,275 copies /mL) she briefly attempted a regimen of AZT/3TC and efavirenz, but stopped after one week. In 2006, she was again incarcerated and her initial labs showed a viral load of 126,826 copies RNA/mL. Her HIV genotype (off antiretrovirals) showed only some common protease polymorphisms not clearly associated with resistance (L10I, L63S, and V77I) . No CD4 cell count was done. Based on the genotype, Atripla (efavirenz, tenofovir, emtricitabine) was started in 9-06 with complete viral suppression; however, her CD4 cell count remains at <150 cells/ mm<sup>3</sup> despite over two years of effective viral suppression.

**Question:** What are therapeutic options that might increase the CD4 cell count in this patient who is on an antiretroviral regimen with full virological suppression but with persistently low CD4 cell count?

DATES	REGIMEN	CD4 (cells/mm <sup>3</sup> )	VL (copies/mL)	RESISTANCE TEST FINDINGS	CLINICAL COURSE
8/1994	NONE	410			DATE OF DX
12/1994	PT REPORTED AZT/3TC/D4T?	?	?		PREGNANCY AND INCARCERATION. NO RECORDS FROM JAIL
1997-2/2005	NONE	<200			
2/2005	AZT/3TC/EFV "FOR A FEW DAYS"	95	26,275		
3/2005	NONE	NADIR 60			
9/2006	ATRIPLA	SPECIMEN LOST	126,826	RT - none PI - L10I, L63S, V77I	INCARCERATED
12/2006	ATRIPLA	121	<75		
11/2008	ATRIPLA	137	<40		RELEASED

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## Resistance Test Findings

9/8/2006 Genotype( on no antiretrovirals, HIV viral load: 126,826 copies/mL)

NRT	None
NNRT	None
PI	L10I, L63S, V77I

## Interpretation/Implications for Treatment

Regimen Options:

There are four potential responses to an antiretroviral regimen:

	<u>HIV viral load</u>	<u>CD4 cell count</u>
(1)	Complete suppression	Increase
(2)	Complete suppression	No increase
(3)	Incomplete suppression	Increase
(4)	Incomplete suppression	No increase

Patients who fall into group two are referred to as “immunological nonresponders.” It is estimated that 15%-30% of patients on antiretroviral therapy fall into this group[1]. There is no specific definition for an “immunological nonresponder” however, a general definition is “failure to achieve and maintain an adequate CD4 response despite complete virological suppression”[2]. The latest(November 3, 2008) Department of Health and Human Services’ “*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*” points out that some studies have defined these patients as those “who fail to increase CD4 T-cell counts above a specific threshold (e.g. >350 or 500 cells/mm<sup>3</sup>) over a specific period of time(e.g. 4 -7 years)” or those “who fail to increase CD4 T-cell counts above pre-therapy levels by a certain threshold (e.g. >50 or 100 cells/mm<sup>3</sup>) over a given period of time.”

Several factors associated with an increase risk for immunological nonresponse are (1) CD4 cell count <200 cells/mm<sup>3</sup> when initiating antiretroviral therapy, (2) older age, (3) occult infection or malignancy, (4) coinfection (an important infection that has been associated with blunting of the CD4 cell response is hepatitis C)[3], (5) medications (the combination of tenofovir and didanosine has been associated with blunting of the CD4 cell response)[4,5], (6) persistent immune activation, and (7) loss of regenerative potential of the immune system[2].

The pathogenesis of immunological nonresponse can be broadly divided into two broad categories[1]:

- (1) Failure in CD4 T cell production.

(2) Increase in CD4 T cell destruction.

Failure in CD4 T cell production is thought to be due to persistent bone marrow[6] and thymic impairment[7,8] despite antiretroviral therapy. Increase in CD4 T cell destruction is thought to be due to persistent CD4 T cell activation[9], which may be secondary to ongoing chronic inflammation[7,10,and 11].

The mechanism for persistent inflammation is unknown but may be due to ongoing low-level HIV replication[12] and/or persistent translocation of microbial bioproducts from the gut into the blood[10, 11]. There have been several studies that have demonstrated high levels of plasma lipopolysaccharides(LPS), which is an indicator of microbial translocation in HIV patients [11, 13]. Furthermore, one study showed that high levels of plasma LPS was associated with reduced increases in CD4 counts irrespective of HIV viral load[13].

## Recommendations

“Immunological nonresponders” are at a small, but appreciable risk for AIDS- and non-AIDS-related morbidity and mortality count[14,15,16]. Therefore, increasing the CD4 cell count in these patients might decrease their risk for disease progression. However, there is no consensus on when and how to treat these patients. It is important to rule-out occult infections or malignancies and hepatitis C. Strategies that have been used to increase CD4 cell count include:

### 1. Antiretroviral agents

- (a) Switch to a protease inhibitor(PI)-based regimen if the immunological nonresponder is on a non-PI based regimen. Whether a PI based regimen results in a better CD4 cell response compared to a non-PI based regimen [e.g. a non-nucleotide(NNRTI) regimen] is controversial. However, two studies that compared a PI-based regimen to a NNRTI-based regimen showed that the PI-based regimen resulted in a better CD4 cell response[17,18].
- (b) Intensify with another agent such as maraviroc(CCR5 inhibitor) or an integrase inhibitor(Raltegravir). The Merit Study which is an ongoing randomized, double-blind study comparing maraviroc vs. efavirenz in combination with Combivir in treatment-naïve patients showed that regardless of tropism of R5, X4 or dual/mixed, patients on maraviroc had had an increase in CD4 cell count[19]. In a study of nine “immunological non-responders” the addition of Maraviroc to their antiretroviral regimen did not enhance CD4 recovery to the expected normal rate of 10-15 cells/month, although two patients did have a recovery rate of 121 and 130 cells/month[20].

### 2. Immunomodulators

- (c) Interleukin-2(IL-2): Two studies(ESPRIT[21] and SILCAAT[22]) showed no reduction in opportunistic infections and death despite an increase in CD4 cell count with the addition of IL-2. Thus, IL-2 should not be used to increase CD4 cell count.

- (d) Interleukin-7(IL-7): IL-7 is an essential cytokine for T cell development. One study showed that IL-7 increased both naïve and memory CD4 and CD8 cells in HIV-infected patients[23]. However, at this time, IL-7 should only be used in the context of clinical trials.
- (e) Growth hormone(GH)—One study showed that GH enhanced thymic output resulting in an increase in circulating naïve and total CD4 cells[24]. However, GH should not be routinely used for this purpose.

Despite clear evidence that suboptimal CD4+ T cell gains during otherwise effective antiretroviral therapy has clinical consequences, and despite widespread interest in this issue, there are no proven interventions that can increase peripheral CD4+ T cell counts in a clinically meaningful manner. The panel was therefore not able to provide any direct advice on the next step. It was noted, however,, that delayed increased in CD4+ t cells counts is often observed in clinical practice. It is possible (and perhaps likely) that CD4+ T cells will slowly increase with longer duration of therapy. Given the emerging evidence that lower CD4+ T cell counts may be associated with a higher risk of heart disease, the panel recommended that aggressive cardiovascular risk reduction be considered.

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