

Resistance Case # 1

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Antiretroviral therapy in the “highly treatment experienced patient.”

- LD is a 17 year-old perinatally infected female who is currently on truvada/darunavir/ritonavir with a CD4 cell count of 60 cells/mm³(on PCP and MAC prophylaxis) and an HIV viral load of >500,000 copies/ml. The patient has no history of opportunistic infections and is currently doing well clinically. The patient lives with her grandmother and aunt and according to both of them, the patient takes her

“the highly treatment experienced patient”

medications regularly. This has been confirmed by pharmacy refill records. The patient has been on multiple anti-retroviral regimens but has never achieved an undetectable HIV viral load. She was on T-20 in the past and is unwilling to try it again due to injection site reaction/pain. She is also unable to take abacavir due to a prior possible hypersensitivity reaction.

“the highly treatment experienced patient”

Date	ART regimen	CD4	VL
4-01	combivir, amp, sustiva	586	340,000
9-01	combivir, amp, kaletra, sustiva		
11-01	as above	740	58,000
10-02	combivir, tenofovir, kaletra		
9-04	unknown	159	180,000

["the highly treatment experienced patient"]

Date	ART regimen	CD4	vl
10-04	azt, tenofovir, ataz, rit		
6-05	unknown	173	320,000
1-06	combivir, tipra, rit, T-20	100	100,000
10-06	truvada, darun, rit, T-20 (probably not taking T-20)	50	750,000

["Resistance test results--genotypes"]

NRTI: 41L, 44D, 67N, 69N, 70R, 75M, 118I, 184V, 208Y, 210W, 215F/Y, 219Q, 333E.

NNRTI: 101E, 181C, 190A.

PI: 10I, 20R, 32I, 33F, 36I, 46I, 47V, 54M, 58E, 60E, 63P, 71V, 82A, 84V, 90M.

[Three areas to focus on:]

- 1. The patient: psychosocial issues, adherence, clinical status including CD4 cell count, “can and will do.”
- 2. Goals of therapy.
- 3. Assessing activity of each class of drugs using antiretroviral history and resistance test results(genotype, phenotype, virtual phenotype).

[Antiretroviral agents]

- NRTIs.
- NNRTIs including etravirine.
- PIs.
- Fusion inhibitor : T-20.
- Integrase inhibitor: raltegravir.
- CCR5 inhibitor: maraviroc.

[Regimen options]

- Focusing on these three areas will help you to generate antiretroviral regimen options for the highly treatment experienced patient.

[Questions]

1. The patient:
 - What are some of the challenges in treating perinatally –infected adolescents?
2. Goals
 - What are the goals for this patient in terms of antiretroviral therapy?

[Questions]

3. Assessing activity of antiretroviral agents:
- Would you include any of the NRTIs in your regimen?
 - Would you continue 3TC or FTC in the regimen and why?

[Questions]

3. Assessing activity of antiretrovirals:
- Based on the NNRTI mutations, do you think etravirine will be effective?
 - Based on the PI mutations, would darunavir be an active agent? Would you obtain a phenotype to determine darunavir's sensitivity?
 - Do you think T-20 is still active? Is there any benefit of continuing T-20 in the face of T-20 resistant mutations?

[Question]

- WHAT REGIMEN WOULD YOU SUGGEST FOR THIS PATIENT?

[Challenges in treating perinatally-infected adolescents]

- Just being 16 years old and all the psychosocial issues that come with being 16(affect on adherence).
- On antiretrovirals all their life(“pill-fatigue”).
- Doing well clinically but CD4 60 cells/mm³(i.e. feels well but lab value poor).

What are the goals of antiretroviral therapy?

- DHHS(Dec 2007):
 - “The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virological suppression, HIV RNA <50 copies/mL.
 - “Adding at least 2, preferably 3, fully active agents to an optimized background antiretroviral regimen can provide significant antiretroviral activity.”

Extensive prior treatment and drug resistance

- DHHS(Dec 2007):
 - “In some cases, however, viral suppression may be difficult to achieved. If maximal virological suppression cannot be achieved, the goals are to preserve immunological function and to prevent clinical progression(even with ongoing viremia). Even partial virological suppression of HIV RNA >0.5 log10

[Extensive prior treatment and drug resistance.]

copies/mL from baseline correlates with clinical benefits; however, this must be balanced with the ongoing risk for accumulating additional resistance mutations.”

[NRTIs]

Patient has the following mutations:

NAMs: 41L, 67N, 70R, 210W, 215F/Y, 219Q.

3TC/FTC: 184V.

Based on these mutations, all NRTIs resistant.

Would you include any of the NRTIs in your regimen?

DHHS(Dec 2007): “Some NRTIs may contribute partial activity to a regimen, despite drug resistance.”

- However, which NRTIs to use and how many remains undefined.

Would you continue 3TC or FTC in the regimen and why?

- Even with the M184V mutation, 3TC and FTC will decrease HIV viral load by 0.5 log₁₀(Campbell, 2005). Due to reduce viral fitness/residual activity?
- In addition, the M184V mutation phenotypically enhances the activity of AZT and/or tenofovir(Whitcomb, 2002).

Based on the NNRTI mutations, is etravirine still active?

- DUET 1 and 2 studies identified the following mutations 13 mutations associated with etravirine resistance:
 - V90I, A98G, L100I, K101E/P, V106I.
 - V179D/F, Y181C/I/V, G190S/A.
- PRESENCE OF 3 or MORE mutations significantly decreases effectiveness of etravirine. This patient has 3 of the above mutations.

Based on the genotype, is darunavir still active?

TMC114-C213 and TMC114-C202 Study:

- ≥ 7 mutations at 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, 90.

TMC114-C213, TMC114-C202, TMC 114-C215/C208 Study:

- ≥ 3 mutations: V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V.

[Obtain a phenotype to determine darunavir sensitivity?]

- Presence of multiple mutations on the genotype suggest that darunavir would not provide significant antiviral activity.
- A phenotype might be helpful in identifying darunavir activity but unlikely.

[If all PIs are resistance would you still use a PI in this patient?]

- It is unclear as to whether continuing the PI in this situation is of any benefit from a virological standpoint.

[Is T-20 still active?]

- Has a low genetic barrier to resistance(Menzo, 2004).
- If remove resistant T-20 from the regimen, there is an increase of 0.19 log₁₀ copies/mL in the viral load at 24 weeks(Deeks, 2007).

[Is there any benefit of continuing T-20 even if resistant?]

- V38A/E mutation which confers T-20 resistance was associated with increased CD4 cell count throughout the Toro study; with other T-20 mutations, CD4 cell declined(Melby, 2006).

[Generating a regimen.]

- The patient: 16 year old, clinically doing well but CD4 of 60 cells/mm³, will not take T-20, possible abacavir hypersensitivity.
- Goals: What would be your goal?

[Generating a regimen]

- Drug activity:
 - NRTI-genotypically resistant to class.
 - NNRTI-genotypically resistant to class including etravirine.
 - PI-genotypically resistant to class.
 - T-20—pt will not take.
 - Raltegravir.
 - Maraviroc(need tropism test).

[Potential regimen]

Combivir + tenofovir or truvada
plus
darunavir + ritonavir
plus
raltegravir
plus
maraviroc

[Potential regimen]

Combivir + tenofovir or truvada
plus
darunavir + ritonavir
plus
raltegravir

[Only one active agent]

- DHHS(Dec 2007): “In general, adding a single, active antiretroviral drug is not recommended because of the risk of development of rapid resistance. However, in patients with a high likelihood of clinical progression(e.g. CD4 cell count of <100/mm³) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because

[Only one active agent]

even transient decreases in HIV RNA and or transient increases in CD4 counts have been associated with clinical benefits. Weighing the risks and benefits of using a single active drug in a heavily treatment experienced is complicated...”

[Potential regimen]

truvada
plus
darunavir + ritonavir

[Cannot identify at least 2 fully active agents]

DHHS (Dec 2007): “It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and absence of CD4 increase, decreases the risk of disease progression.”

Approach to the “highly treatment experienced patient”

- Focus on:
 - Patient
 - Goals
 - Assess drug activity by class.
 - Regimen options—best to keep patient on something.