
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

A 30yo GWM tested HIV positive in 10/01 with symptoms of fever, chills, myalgias, and fatigue. His last HIV test was negative in 7/01. During his visit in 2/02 to the Options program (a cohort study of acute and early HIV infection), his detuned antibody was found to be 0.236, indicating infection of <6 months duration. In August 2004 he was started on Trizivir (abacavir, lamivudine, zidovudine) + tenofovir + lopinavir/r (Kaletra) + T-20 (Fuzeon). The patient has experienced only mild adverse reactions to his regimen over the duration of treatment (mild nausea and minimal injection site reactions) and has exhibited excellent adherence. His laboratory testing and antiretroviral (ARV) history are summarized below:

Date	CD4	CD4 %	CD8	CD4/CD8	HIV RNA (bDNA, Chiron)	HIV RNA (PCR, Roche)
02/11/2002	522	29	1,080	0.48	124,070	203,000
03/04/2002	486	27	1,134	0.43	96,202	
Genotype #1						
04/05/2002	540	27	1,280	0.42	131,756	247,000
05/13/2002	616	28	1,364	0.45	160,844	160,000
06/03/2002	520	26	1,260	0.41	166,035	393,000
07/08/2002	448	28	976	0.46	143,512	298,000
08/20/2002	420	21	1,360	0.31	165,451	
Genotype #2						
10/14/2002	504	21	1,656	0.30	171,652	329,000
Phenotype						
12/09/2002	528	22	1,656	0.32	143,001	
02/07/2003	448	16	2,044	0.22		254,000
04/28/2003	336	16	1,533	0.22		210,000
08/04/2003	442	17	1,898	0.23	95,635	
10/13/2003	399	19	1,449	0.28	106,776	
01/12/2004	298	19	1,068	0.28	116,604	
03/29/2004	226	16	987	0.23	168,351	
Genotype #3						
06/29/2004	235	14	1,193	0.20	165,597	
08/17/2004	132	10	950	0.14	50,940	
Started Trizivir (abacavir, lamivudine, zidovudine) + Tenofovir + Kaletra + T-20						
08/30/2004					2,147	
09/13/2004	174	12	986	0.18	578	
10/11/2004					191	

11/09/2004	312	16	1,248	0.25	75
12/06/2004	316	17	1,135	0.28	75
02/08/2005	356	20	1,068	0.33	75
04/04/2005	420	24	1,015	0.41	75
06/06/2005					75

Resistance Test Findings

Genotype #1 (Gladstone, 03/04/02)

RT	K101E, V118I, Y181C, G190S, T215F
PRO	L10I, V32I, M36I, M46I, I47V, I54V, L63P, A71V, V82A, L90M

Genotype #2 (Gladstone, 08/20/02)

RT	K101E, V118I, Y181C, G190S, T215L/F
PRO	L10I, V32I, M36I, M46I, I47V, I54V, L63P, A71V, V82A, L90M

Genotype #3 (Gladstone, 3/29/04)

RT	K101E, V118I, Y181C, G190S/Q
PRO	L10I, V32I, M36I, M46I, I47I/V, I54I/V, L63P, A71V, V82A, L90M

Phenotype (Virologic, 11/25/02)

Drug	Fold Change
ABC	0.8
ddl	0.8
3TC	2.0
d4T	0.8
TNF	0.6
ddC	0.9
AZT	0.6
DLV	52
EFV	>>>
NVP	>>>
APV	17
IDV	23
LPV/r	45
NFV	45
RTV	>>>
SQV	5.9

Replication Capacity = 64%
Clade B

Interpretation/Implications for Treatment

Specific questions:

- (1) Identify if any changes should be made to his current ARV regimen now?
- (2) Based on the above resistance history, if this patient had presented for initial treatment today, what ARV regimen would be most appropriate?

Members of the Resistance Panel discussed a number of observations about HIV transmission.

- Transmission of drug resistant HIV has been described for many years. The first case of multi-drug resistant HIV was reported in 1998 at SFGH.ⁱ
- Recent high-profile reports of transmission of multi-drug resistant (MDR) HIV with rapid HIV disease progression have brought attention to this phenomenon.ⁱⁱ
 - Differences in virulence (defined as the clinical effects of a specific virus in a specific host) and/or fitness (defined as the ability of the virus to replicate under specified conditions) may be influenced by host factors (e.g. HLA type, immune status, activation of immune system, others) or viral factors (such as tropism). It is generally believed that the unusual event of transmission of an X4 tropic virus (or mixed R5/X4 tropic virus) would be more likely to result in rapid clinical progression.
 - Transmission of drug-resistant HIV was increasing during the 1990s, but may be stabilizing at a rate of ~10-15%.^{iii,iv}
- Antiretroviral drug resistance selected in an individual as a result of antiretroviral therapy is not usually detected on routine resistance testing 6-12 weeks (average) following discontinuation of therapy.^v In contrast, drug resistant virus transmitted during initial HIV infection may persist for many months-to-years in the absence of drug pressure.^{vi}
- Regardless of whether resistance is acquired from transmission or generated by selective drug pressure, it is equally important when choosing antiretroviral regimens. The implications in this case are that his initial ARV regimen will be more similar to a "salvage" regimen than a naive regimen.
- In the setting of a high prevalence of transmitted drug resistance, the term "drug-naïve" can be misleading and should not be interpreted to mean the presence of "drug-sensitive" or "wild type" virus.

*****RECOMMENDATION:** If infection may have occurred in areas of high transmitted drug resistant (such as the United States and Europe), all patients should have resistance testing done at the time of diagnosis, whether acute or chronic infection and whether or not antiretroviral treatment is started immediately.

Members of the Resistance Panel discussed a number of observations about this specific case:

- Documented persistence of MDR resistance in this ARV-naive patient for more than 2 years is interesting, but is consistent with prior reports in the literature.^{vi}
- Identifying this patient's co-receptor tropism would be informative, as the X4 tropic virus is associated with more rapid disease progression than the R5 tropic virus. However, this information would be unlikely to alter his treatment unless/until a co-receptor blocker is being considered for treatment. Currently, CCR5 co-receptor blockers are in advanced phases of clinical development and are expected to be available in the near future.

Panel members noted the absence of Thymidine Analog Mutations (TAMs) in this patient, which would be expected in a virus with this degree of nonnucleoside reverse transcriptase (NNRTI) and protease inhibitor (PI) mutations. Mutations at position 215 do indicate prior thymidine exposure in this virus, and the sequential loss of T215F to T215L/F to T215T is notable. Mutation V118I is another indication of nucleoside reverse transcriptase inhibitor (NRTI) resistance, as this mutation is commonly seen in conjunction with TAMs; however it may also be seen in 2% of untreated patients. Panel members were concerned about the possibility of additional NRTI resistance that is not evident on these resistance tests, but would still consider NRTI a useful class of drugs to treat this virus. Panel members indicated that performing resistance testing on cellular HIV DNA (which can be done in research settings only) might identify whether additional NRTI mutations were initially present; however, this information is unlikely to affect future treatment decisions. It was also interesting to see how clinically susceptible the virus has been to lopinavir/ritonavir in this patient, especially with a 45-fold change to lopinavir/ritonavir on the phenotype prior to treatment. Generally, susceptibility to lopinavir/ritonavir is associated with <40-fold change.

Some panel members postulated the role of less heterogeneous viral populations in the setting of transmitted drug resistance when compared to drug resistant variants generated while on therapy, citing anecdotal experience that transmitted drug resistance was easier to suppress than acquired drug resistance.

Recommendations

Regimen Options

Option 1: There was general consensus that the current regimen should be continued based on his excellent virologic suppression for more than one year and excellent tolerability. This is particularly important as there are limited options for effective treatment of this multi-resistant virus, and mistakes in management could have highly significant consequences.

However, if the panel was choosing a regimen for initial treatment of this patient's virus today (August 2005), many panelists would have chosen Trizivir, Tenofovir, T-20, plus ritonavir boosted saquinavir or possibly boosted tipranavir instead of the lopinavir/ritonavir based on the phenotype, noting however, that there may be more toxicities and drug interactions with a tipranavir-containing regimen.

Option 2: One panelist suggested the possibility of simplifying the regimen by removing the T-20, suggesting that the NRTIs plus Kaletra may be sufficient to maintain virologic control. However, this panelist also noted that if this were done, it would be prudent to also remove one other active drug (such as 3TC), so that if the patient developed virologic failure there would be 2 new drugs available for optimal viral suppression.

Option 3: Entry inhibitors are an interesting option for oral therapy in this patient; however, it would be important to know his co-receptor tropism prior to starting this class of drugs. Also, drug interactions with co-receptor blockers are possible and are not well known, so caution should be used.

Option 4: "Would stopping antiretroviral therapy be considered in this patient? If so, under what circumstances?" Most members felt that if the patient were tolerating the regimen, they would continue treatment even at a high CD4 count. Since the patient's CD4 count was <200 cells/mm³ at the time of treatment initiation, it would likely to decline to that level relatively quickly after treatment discontinuation. A minority of panelists felt that a treatment interruption, guided by careful monitoring of his CD4 count and resumption of therapy when the CD4 approached 200, might be an effective strategy for the patient.

Dosing, Monitoring, and Follow-up Recommendations

Lopinavir/ritonavir (Kaletra®) 3 capsules PO bid or Kaletra tablets 2 tablets PO BID + tenofovir (Viread®) 300mg daily + Trizivir® (lamivudine 300 mg plus abacavir 300 mg plus zidovudine 300 mg) one tablet twice daily plus T-20 (enfuvirtide, Fuzeon®) 90 mg subcutaneous injection twice daily. Take with food to minimize GI distress.

Selective Side effects:

Lopinavir/ritonavir: nausea/vomiting, diarrhea, liver toxicity, hyperlipidemia

Tenofovir: nausea, vomiting, GI upset, renal insufficiency, Fanconi's syndrome (very rare), flatulence

Abacavir: hypersensitivity reaction, nausea/vomiting

Zidovudine: GI upset, insomnia, anemia, neutropenia, rarely hepatitis

Enfuvirtide (T-20): injection site reactions, bacteria pneumonia

The patient should have regular, routine follow-up, as he has apparently been getting. At the first evidence of virologic rebound, resistance testing should be repeated and used as the basis – along with treatment history – for the design of subsequent regimens.

References

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