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# HIV Resistance Testing Consultation Service

## Consultation Report

Co-Chairs: Steven G. Deeks, MD  
Betty J. Dong, Pharm.D.

Panel Members: Richard Aranow, MD  
Brad Hare, MD  
Amy Kindrick, MD, MPH  
Teri Liegler, PhD  
Parya Saberi, Pharm.D.  
Jason Tokumoto, MD

Project Director: Ronald H. Goldschmidt, MD

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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

This is an exposure case in which a non-HIV-infected dermatologist was exposed to potentially infectious body fluids of a known HIV-infected source patient. The physician was suturing an after biopsy of a penile ulcer and had a superficial needle-stick from the suture needle. The suture needle was visibly bloody. The needle-stick did not cause a deep puncture wound.

A detailed prior treatment history on the HIV-infected patient was rapidly made available to help best determine which regimen to recommend for the exposed physician. The patient had been on numerous antiretroviral (ARV) medications in the past. These include sequential nucleoside analogues in the early and mid-1990s as well as multiple partially suppressive combination regimens. The patient is known to harbor high level resistance to most of the available nucleoside analogues (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), including lopinavir/ritonavir (LPV/RTV, Kaletra®), and darunavir/ritonavir (DRV/RTV, Prezista®). Due to past history of T-20 (enfuvirtide, Fuzeon®) failure, it can be assumed that he harbors a T20-resistant virus.

Approximately six months ago, the patient began a “salvage” regimen containing raltegravir (RAL, Isentress®), maraviroc (MVC, Selzentry®), tipranavir (TPV, Aptivus®), ritonavir (RTV, Norvir®), zidovudine (ZDV, Retrovir®), lamivudine (3TC, Epivir®), and tenofovir (TDF, Viread®). During this time his viral load decreased from 100,000 copies/mL to 200 copies/mL. His viral load has been stable around the 200 range for the past two months and he has not had an undetectable HIV RNA level. The patient is not co-infected with HBV or HCV.

| DATE      | REGIMEN                     | CD4  | VL range       | COMMENTS      |
|-----------|-----------------------------|------|----------------|---------------|
|           | Extensive ARV history       |      |                |               |
| 9/2003    | TDF/3TC/LPV/RTV             | 120  | 74,000         | Phenosense GT |
| 2003-2005 | DRV/RTV/T20/3TC/TDF         | >100 | 50,000-145,000 | Phenosense GT |
| 2007      | RAL/MVC/TPV/RTV/ZDV/3TC/TDF |      | 200-300        | Phenosense GT |

### Resistance Test Findings

9/25/03 Phenotype (RC=25%)

|       |   |
|-------|---|
| NRTI  | FC: ABC=8.3, ddI=2.1, 3TC>max, d4T=3.2, TDF=0.9, AZT=14 |
| NNRTI | FC: all>max   |

|    |  |
|----|--|
| PI | FC: APV=50, ATV=51, IDV=61, rLPV=102, NFV=38, SQV=95 |
|----|--|

9/2003 Genotype

|       |  |
|-------|--|
| NRTI  | 41L, 44D, 74V, 118I, 184V, 210W, 215Y, 219R                  |
| NNRTI | 98G, 103N, 108I, 181C, 227L                                  |
| PI    | 10I, 20R, 24I, 33F, 46L, 53F/L, 63P, 70T, 73V, 74P, 77I, 82A |

9/2005 Phenotype (RC=7.4%)

|       |   |
|-------|---|
| NRTI  | FC: ABC=7.6, ddl=2.1, 3TC/FTC>max, d4T=2.5, AZT=3.9, TDF=0.7        |
| NNRTI | FC: all>max   |
| PI    | FC: ATV=192, fos-APV>max, IDV=67, rLPV=174, NFV=60, SQV=56, TPV=0.6 |

9/2005 Genotype

|       |  |
|-------|--|
| NRTI  | 41L, 44E/D, 74V, 118I, 184V, 210W, 215Y, 219R                |
| NNRTI | 98G, 103K/N, 108I, 181C, 227L                                |
| PI    | 10F, 13V, 24I, 32I, 33F, 46L, 53F/L, 54L, 63P, 74P, 77I, 82A |

1/2007 Phenotype (RC=18%)

|       |  |
|-------|--|
| NRTI  | FC: ABC=4.6, ddl=1.6, FTC/3TC>max, d4T=0.7, AZT=0.2, TDF=0.3                 |
| NNRTI | FC: all>max  |
| PI    | FC: ATV=101, DRV>max, fos-APV>max, IDV=76, rLPV>max, NFV=47, SQV=19, TPV=1.3 |

1/2007 Genotype

|       |  |
|-------|--|
| NRTI  | 41L, 74V, 118I, 184V, 210W, 215D/H, 219R   |
| NNRTI | 98G, 108I, 181C, 227L  |
| PI    | 10F, 11V/I, 13V, 24I, 32I, 33F, 46L, 47I/V, 53L, 54L, 58Q/E, 63P, 74P, 77I, 82A, 89M/T |

## Questions Addressed by the Panel:

- 1- What mutations may theoretically be present in the currently detectable low-level viremia?
- 2- Is it likely that the remaining virus is X4-tropic? What is the chance of transmission of X4 or D/M-tropic virus?
- 3- What is a reasonable post-exposure prophylaxis (PEP) regimen?

## Background, Panel Discussion, and Options:

In a prospective study of healthcare providers who had sustained a percutaneous exposure to blood from an HIV-infected individual, the average risk of HIV transmission was approximately 0.3% (95% confidence interval (CI)= 0.2-0.5%).<sup>1</sup> In a retrospective case-control study of healthcare workers with occupational exposures to HIV-infected blood, the risk of HIV transmission from percutaneous exposure to HIV-infected blood was higher when exposure was to a visibly bloody device (odds ratio (OR)= 6.2, 95% CI= 2.2-21), involved a needle that had been utilized in a vein or artery (OR= 4.3, 95% CI= 1.7-12), or a deep injury (OR= 15; 95% CI= 6.0-41).<sup>2</sup> Additionally, the risk was increased when the exposure was to a source patient who died of acquired immunodeficiency syndrome (AIDS) within two months of the exposure (OR= 5.6, 95% CI= 2.0-16), which may have been due to higher HIV RNA levels. In this study, the use of zidovudine (ZDV) as PEP was associated with a risk reduction of HIV infection by approximately 81% (95% CI = 43-94%).

Worldwide, there have been 94 documented and 170 possible cases of HIV transmission following occupational exposures.<sup>3</sup> Of these cases, seven infections were due to a cut or an injury from a sharp object (two cases of scalpel, one case of broken vacuum glass, one case of broken vial, one case of elutriator needle, one case of orthopedic pin, and one case not specified) and one case due to a lancet used to obtain a capillary blood sample.

A review of cases of HIV transmission to healthcare workers in the United States through 2001 found that among the sharp devices and objects causing 51 percutaneous injuries, only six were caused by a solid instrument (two cases of broken glass from blood collection tubes, two cases of scalpels, and two cases of unknown sharp devices).<sup>4</sup>

From these reports, it is apparent that the risk of HIV transmission from solid instruments is lower than hollow-bore needles and superficial injuries carry a lower risk of HIV transmission. It is interesting to note that there has never been a reported case of HIV transmission due to a suture needle.

The duration of PEP therapy is four weeks as this duration of time was found to be protective in occupational and animal studies.<sup>5,6</sup> Factors to consider for all percutaneous exposures to body fluids from an HIV-infected individual are the type of needle (e.g. hollow-bore needle versus solid needle or instrument), the depth of the injury (i.e. superficial versus deep), the presence of blood, and the source patient's HIV viral load, if

the patient is known to be HIV-infected. The Center for Disease Control and Prevention Guideline for the Management of Occupational Exposures states that for less severe exposures (e.g. solid needle and superficial injury) and HIV-positive class 1 source patient (defined as asymptomatic HIV infection or known low viral load of <1,500 RNA copies/mL) a basic two-drug PEP regimen is recommended.<sup>7</sup> However, these guidelines advise clinicians managing an exposure to seek expert consultation in situations where the source patient is known or suspected to be resistant to  $\geq 1$  of the drugs being considered for the PEP regimen.

In deciding on a PEP regimen, the most challenging dilemma is the balance between the toxicity of the antiretroviral (ARV) medications and the benefit of preventing a potential transmission. Therefore, a thorough discussion of the advantages and disadvantages of PEP is essential. In order to determine a PEP regimen that balances the toxicities and benefits of the ARV medications, the panel discussed the advantages and disadvantages of various options.

Raltegravir (RAL) is the first FDA-approved integrase inhibitor and is a well-tolerated ARV with adverse effects similar to placebo. BENCHMRK 1 and 2 are the major efficacy trials leading to the FDA approval of RAL.<sup>8,9</sup> At 16 weeks, RAL demonstrated an HIV RNA reduction to <50 copies/mL in 61-62% of patients as compared to 33-36% in the placebo arm. In the RAL arm, 16% of subjects experienced treatment failure versus 51% in the placebo arm. One of the biggest concerns with integrase inhibitors is that they display a low genetic barrier to resistance and high-level resistance can develop quickly and as early as two weeks.<sup>10</sup> The unsettling point of note in this case is that, even after six months of RAL therapy, the source patient's viral load is still detectable at low levels. In non-RAL-containing regimens, this viral load drop may have been considered a reasonable reduction in HIV RNA levels, but with an RAL-containing regimen, a quick drop in viral load to undetectable levels is expected. Due to the pattern of rapid viral load reduction and rapid increase to baseline level with the development of RAL resistance (sometimes referred to as a "check mark"), some panel members argued that if the viral load was detectable during the last measurement, it may indicate that the source patient has developed RAL resistance, and that the viral load may be at a higher level at the time of exposure. Overall, there may be two possibilities explaining the source patient's presentation: he is either failing RAL, in which case he is likely to have a relatively high viral load at this point; or his viral load has become undetectable and the low-level viremia may have been a small amount of virus "seeping out" from the viral reservoir.<sup>11</sup> Another concern with RAL is that its newness as an ARV agent means very little knowledge and experience exist regarding its adverse effect profile, particularly in HIV-negative subjects.

One interesting and important concern raised by a panel member was about the type of assay that may have been utilized in determining the HIV RNA level of the source patient. The Abbott RealTime HIV-1 assay functions by interrogating the pol integrase as the target region which is the reason for its enhanced utilization in determining viral load in HIV Group M (A-G) as well as Groups N and O.<sup>12</sup> However, a concern in using the Abbott assay in patients failing an integrase inhibitor-based regimen is the possibility

that the integrase inhibitor may block the target region and result in a falsely lower HIV RNA level. Therefore, one theoretical concern in this case may be that if the SP's HIV RNA was measured using the Abbott RealTime HIV-1 assay, his viral load may actually be higher than 200 copies/mL. At this point, this is a theoretical concern and more studies are required to investigate the possibility of a problem.

Maraviroc (MVC) is the first FDA approved CCR5-receptor antagonist. MOTIVATE 1 and 2 are pivotal trials that led to the FDA approval of MVC.<sup>13,14</sup> In these trials, approximately 8% of subjects had a change in tropism between screening and baseline testing (within a four-six week timeframe), and this shift was associated with subsequent failure of a MVC-based regimen. These switches appear to reflect the presence of low-level X4-utilizing viruses (either pure X4 or dual/mixed (D/M)-tropic). The benefit of MVC is that D/M or X4-tropic virus was identified in about 65% of patients who failed MVC<sup>15,16</sup> and the cause of failure was seldom due to the existence of phenotypic resistance to MVC.<sup>17</sup> If the source patient has low level X4-utilizing virus and the low level viremia is either X4- or D/M-tropic, the question of transmissibility of these viruses arises. Most cases of primary HIV-1 infection occur with the R5-tropic virus, even in many cases when the source patient has evidence of X4-utilizing virus.<sup>18,19</sup> Based on a retrospective study by Mendoza and colleagues, from a cohort of 296 HIV-1 seroconverters, X4-utilizing viruses were identified in 17.2%.<sup>20</sup> Intravenous drug users had a higher prevalence of X4-utilizing virus than individuals infected by sexual relationships (35.7% versus 16.5%, respectively; p-value= 0.073). This may be due to the fact that mucosal surfaces have a much higher concentrations of CCR5-expressing cells and therefore the virus transmitted from sexual exposures is typically an R5-utilizing virus. However, parental transmission of HIV does not require CCR5-expressing cells and may be more conducive to the transmission of an X4-utilizing virus.

The biggest concern of most panel members is the adverse effect profile of MVC in immunocompetent individuals. In an HIV-negative female volunteer who had received 600mg once-daily MVC, flu-like symptoms were reported on day 14; orthostatic hypotension, mild thrombocytopenia, fever, rash, and elevated ALT/AST/bilirubin were noted on day 17; and on day 18, eosinophilia was documented.<sup>21</sup> In addition, elevations in IgE and activated PTT and INR were noted. Therefore, MVC has a black-box warning for the possibility of hepatotoxicity with an allergic component.<sup>22</sup> There have been other cases of ARVs causing severe toxicity in immunocompetent individuals. The Center for Disease Control and Prevention reported 22 cases of adverse effects in HIV-negative individuals using nevirapine (NVP, Viramune®) for PEP from March 1997 through September 2000.<sup>23</sup> Of these cases, there were 14 skin reactions, 12 hepatotoxicity, and four cases of both skin reactions as well as hepatotoxicity, of which two were life-threatening. The higher CD4+ cell count of HIV-negative subjects may predispose them to a higher risk of developing NVP toxicity.

Enfuvirtide (ENF) is the first FDA approved fusion inhibitor. The source patient had been on an ENF-containing ARV regimen in the past and resistance was suspected due to ongoing viremia. Charpentier and colleagues<sup>24</sup> associated ENF resistance with the duration of ENF therapy; disappearance of ENF resistance was observed as early as one month after stopping therapy. Therefore, even though the source patient failed ENF, the

ENF-specific mutations have most likely reverted to wild-type and the majority of the virus population is now sensitive to ENF. Another advantage of ENF is its tolerability; apart from injection-site reactions, there are few adverse effects.<sup>25</sup> The main drawback of ENF is the need for twice daily subcutaneous injections, which some individuals may refuse to do. Also, we have no genotypic proof to state with certainty that the patient's virus has actually reverted to wild-type.

As clearly shown in the serial genotypes/phenotypes, the HIV+ source patient harbors a highly resistant virus. There are at least 4 thymidine analog mutations (TAMS) present: 41L, 210W, 215Y, 219R.<sup>26-29</sup> In 2003, the patient had the 215Y mutation that, in 2007, changed to 215D. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations<sup>30</sup> and can be seen in cases of "back mutation" (when ZDV is removed from the ARV regimen of an individual who has developed a mutation) or "reversion" (when a patient is infected with a resistant virus and the virus "reverts" to a more "fit" form due to the absence of selective pressure from drug therapy). The results of this change can be seen in the reduction in fold change (FC) resistance to ZDV and tenofovir (TDF) between the 2003 and 2007 phenotypes. He has also lost the NNRTI mutation, 103N, which may occur when efavirenz (EFV) is removed from the ARV regimen but he is still resistant to all NNRTIs. The fold change for DRV is "greater than maximum" due to the presence of 11I, 32I, 33F, 47V, and 54L.

Panel members believed that a repeat genotype and phenotype may be helpful in determining the patient's current ARV resistance. However, the results of the resistance test, if obtained at the time of the exposure, will not be available in time to influence the choice of the PEP regimen. It is also unclear what the efficacy might be of changing a PEP regimen one-two weeks after initiation.<sup>7,31</sup>

Many panel members were in favor of starting a regimen consisting of Combivir® (combination of ZDV and 3TC (lamivudine)) + TDF + ENF in the dermatologist and repeating the patient's viral load. If the patient's viral load is undetectable, one option is to change the regimen to just Truvada® (combination of TDF and FTC (emtricitabine)) or Combivir® or Combivir® + TDF. However, if the viral load was detectable, at any level, most members favored the continuation of Combivir® + TDF + ENF.

If the exposed dermatologist refuses ENF, other options such as Combivir® + TDF + RAL or Combivir® + TDF can be considered. Even though Combivir® + TDF + MVC is another option, most panel members believed that the toxicity associated with MVC outweighed its potential benefits and would not use the drug.

## **Regimen Options**

### **Option 1:**

Combivir® (zidovudine and lamivudine): 1 tablet orally twice daily +  
Viread® (tenofovir): 1 tablet (300 mg) orally once daily +  
Fuzeon® (enfuvirtide): Inject 90 mg (1 mL) subcutaneously twice daily

**Pros:** If patient's viral load is detectable, then the majority of the viral population is susceptible to ENF. The 2007 phenotype showed some sensitivity to ZDV and TDF.

**Cons:** ENF is a twice daily subcutaneous injection.

**Option 2:**

Combivir ® (zidovudine and lamivudine): 1 tablet orally twice daily +  
Viread ® (tenofovir): 1 tablet (300 mg) orally once daily +  
Isentress ® (raltegravir): 1 tablet (400 mg) orally twice daily

**Pros:** Will not require twice daily injections.

**Cons:** If the source patient has a detectable viral load at the time of exposure, the majority of the virus population is likely to be resistant to RAL. There is limited knowledge regarding the adverse effect profile of RAL in HIV-negative individuals.

**Option 3:**

Combivir ® (zidovudine and lamivudine): 1 tablet orally twice daily +  
Viread ® (tenofovir): 1 tablet (300 mg) orally once daily +  
Selzentry ® (maraviroc): 2 tablets (2 x 300 mg) orally twice daily

**Pros:** Will not require twice daily injections. MVC will be a fully active PEP component if the source patient is failing this regimen but still has an R5-tropic virus that is sensitive to MVC.

**Cons:** If the majority of the virus population is X4-utilizing viruses or if the virus is resistant to MVC, this regimen may not be the most potent. There have been cases of hepatotoxicity with the use of MVC in an HIV-negative individual.

## **Monitoring and Follow-up Recommendation**

**Source patient**

Repeat HIV RNA (using any assay except the Abbott RealTime assay) and repeat genotype and phenotype.

**Exposed individual**

- HIV antibody: at baseline, and then at 6, 12, and 24 weeks.
- Monitor: complete blood count (CBC), serum creatinine, blood urea nitrogen (BUN), and liver function tests (LFTs) at baseline and at 2 weeks.
- Consider re-evaluation in 72 hours to monitor for any adverse effects.

- Ask the exposed individual if taking any other medications (prescription, over-the-counter, or herbal) as MVC has many drug interactions.

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