

# Can the further clinical development of bevirimat be justified?

Mark A. Wainberg<sup>a</sup> and Jan Albert<sup>b</sup>

*AIDS* 2010, **24**:000–000

**Keywords:** bevirimat, protease inhibitor resistance

HIV-infected patients who fail standard therapeutic regimens are in need of new drugs that will remain active against drug-resistant viral variants. There is a constant need to develop new compounds that will not be compromised by problems of cross-resistance, as so often occurs among members of the same family of drugs, for example, nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors. Indeed, successful second-line and salvage regimens will commonly include members of drug classes to which a patient has not previously been exposed, for example, a protease inhibitor and an integrase strand transfer inhibitor (INSTI) in the case of an individual who began therapy with two NRTIs and a NNRTI, as well as the use of fusion inhibitors, for example, enfuvirtide, and CCR5 antagonists, for example, maraviroc.

One of the hopes in the field has been the potential success of a novel family of drugs termed maturation inhibitors. These compounds work by blocking the processing of the Gag precursor protein by the viral protease enzyme. The lead compound of this series is termed bevirimat (BVM) that has been demonstrated to have dose-dependent anti-HIV potency in both phase I and phase II clinical studies [1]. BVM apparently prevents cleavage of the CA-SP1 (p24/p2) junction within Gag, resulting in the release of noninfectious virus particles that contain an uncleaved p25 precursor protein [2].

Not surprisingly, however, HIV resistance against BVM has been selected in tissue culture. Mutations responsible for resistance have been identified within flanking sequences of the p24/p2 cleavage site and have been confirmed as possessing biological relevance by site-directed mutagenesis [3]. These mutations can sometimes interfere with the ability of BVM to bind to its target, although, in most cases, increased cleavage efficiency at the p24/p2 junction may also occur [3,4].

Recent results have revealed that naturally occurring polymorphisms located within p2, close to the p24 cleavage site, may be present in some individuals, resulting in lower BVM anti-HIV efficacy. In addition, clinical investigators have long suspected that BVM might potentially be less effective in the treatment of patients who have failed a previous protease inhibitor-containing regimen and whose viruses have developed drug resistance mutations within the protease gene [5]. The reason for this is that such viruses will commonly also have developed compensatory mutations within Gag that may sometimes overcome fitness deficits associated with protease mutations and even, in some instances, restore sensitivity to protease inhibitors [6]. Some of these mutations may be located at positions within Gag that are also associated with resistance to BVM.

Indeed, this is the subject of an excellent article by Verheyen *et al.* [7] that appears in the current issue of *AIDS*. These investigators sequenced positions 357–382

<sup>a</sup>McGill University AIDS Centre, Jewish General Hospital, Montreal, Quebec, Canada, and <sup>b</sup>Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet and Department of Virology, Swedish Institute for Infectious Disease Control, Solna, Sweden.

Correspondence to Dr Mark A. Wainberg, McGill University AIDS Centre, Jewish General Hospital, 3755 Chemin Cote Ste-Catherine, Montréal, Québec, Canada H3T 1E2.

E-mail: mark.wainberg@mcgill.ca

Received: 5 August 2009; accepted: 11 August 2009.

DOI:10.1097/QAD.0b013e328331c83b

of the HIV-1 Gag region of 484 subtype B isolates that were derived from both treatment-naïve ( $n=270$ ) and treatment-experienced ( $n=214$ ) patients; 166 of the latter contained protease resistance-associated mutations. Remarkably, they found that 45% of the protease inhibitor-experienced patients also possessed at least one mutation within Gag known to be associated with BVM resistance, and, in some instances, an accumulation of several such mutations was observed. Indeed, a correlation apparently existed between the numbers of protease resistance mutations within a given isolate and the likelihood of accumulation of multiple BVM resistance mutations within Gag. Even more ominously, these investigators also observed that approximately 30% of isolates from drug-naïve patients possessed at least one mutation associated with BVM resistance.

The authors conclude their study by arguing that patients who might be eligible to receive BVM as part of a future clinical regimen should first undergo genotypic screening for the 357–382 amino acid sequence within Gag, to ensure that no preexisting mutations or polymorphisms, potentially associated with resistance against BVM, are present. Although this consideration is certainly valid, the unfortunate reality is also that these data call into question the durability of any potential virological benefit that is likely to be achieved through use of BVM-containing therapeutic regimens. For one thing, it is likely that resistance against BVM will almost certainly turn out to be sexually transmitted, potentially to an extent that exceeds transmission of resistance against NRTIs, NNRTIs, and protease inhibitors, given that BVM apparently possesses a very low genetic barrier for resistance and that HIV may have a propensity to easily accumulate BVM-related resistance mutations. Second, it is likely that additional BVM-related resistance mutations will be identified in the future that will add to the list of the five or six such mutations that have been identified until now.

Finally, recent clinical observations suggest that subtype C isolates of HIV contain one of the BVM-related resistance polymorphisms, that is, A370 in subtype C in the place of V370 in subtype B, as part of their consensus sequence [8]. This would help to explain the lesser degree of clinical responsiveness to BVM of subtype C-infected patients in clinical studies. In view of the fact that subtype C viruses are currently responsible for over 50% of all new HIV infections worldwide, this is not a trivial consideration [9].

The article by Verheyen *et al.* in this issue of *AIDS* does indeed make a compelling case for the use of resistance genotyping prior to the clinical use of BVM as part of an anti-HIV regimen. In reality, though, the fact that multiple mutations associated with diminished responsiveness to BVM are located at or close to the p24/p2 cleavage junction has long suggested that BVM is likely to be a drug with a very low genetic barrier for resistance, calling into question the durability of its effectiveness, even when combined with two other excellent drugs in a therapeutic regimen. The truth might now be that the future clinical development of BVM should be abandoned. Hopefully, the companies and scientists responsible for work carried out with BVM until now will persist and develop a second-generation maturation inhibitor that will not suffer the myriad of resistance-related problems that have long plagued the development of BVM.

## References

1. Smith PF, Ogundele A, Forrest A, Wilton J, Salzwedel K, Doto J, *et al.* **Phase I and II study of the safety, virologic effect, and pharmacokinetics/pharmacodynamics of single-dose 3-O-(3',3'-dimethylsuccinyl) betulinic acid (bevrimat) against human immunodeficiency virus infection.** *Antimicrob Agents Chemother* 2007; **51**:3574–3581.
2. Zhou J, Huang L, Hachey DL, Chen CH, Aiken C. **Inhibition of HIV-1 maturation via drug association with the viral Gag protein in immature HIV-1 particles.** *J Biol Chem* 2005; **280**:42149–42155.
3. Zhou J, Chen CH, Aiken C. **Human immunodeficiency virus type 1 resistance to the small molecule maturation inhibitor 3-O-(3',3'-dimethylsuccinyl)-betulinic acid is conferred by a variety of single amino acid substitutions at the CA-SP1 cleavage site in Gag.** *J Virol* 2006; **80**:12095–12101.
4. Salzwedel K, Martin DE, Sakalian M. **Maturation inhibitors: a new therapeutic class targets the virus structure.** *AIDS Rev* 2007; **9**:162–172.
5. Malet I, Wiriden M, Derache A, Simon A, Katlama C, Calvez V, Marcelin AG. **Primary genotypic resistance of HIV-1 to the maturation inhibitor PA-457 in protease inhibitor-experienced patients.** *AIDS* 2007; **21**:871–873.
6. Nijhuis M, van Maarseveen NM, Lastere S, Schipper P, Coakley E, Glass B, *et al.* **A novel substrate-based HIV-1 protease inhibitor drug resistance mechanism.** *PLoS Med* 2007; **4**:e36.
7. Verheyen J, Verhofstede C, Knops E, Vandekerckhove L, Fun A, Brunen D, *et al.* **High prevalence of bevirimat resistance mutations in PI resistant HIV isolates.** *AIDS* (this issue).
8. Salzwedel K, Hamy F, Louvel S, Sakalian M, Reddick M, Finnegan C, *et al.* 2009. **Susceptibility of diverse HIV-1 patient isolates to the maturation inhibitor, bevirimat, is determined by clade-specific polymorphisms in Gag CA-SP1.** In: *Proceedings of the 16<sup>th</sup> Conference on Retroviruses and Opportunistic Infections*; 8–11 February 2009; Montreal, Canada.
9. Martínez-Cajas JL, Pant-Pai N, Klein MB, Wainberg MA. **Role of genetic diversity amongst HIV-1 non-B subtypes in drug resistance: a systematic review of virologic and biochemical evidence.** *AIDS Rev* 2008; **10**:212–223.