

Sir,

Please, allow us to sincerely acknowledge the comments and suggestions of all reviewers.

According to his/her comments we made modifications in the manuscript that believe helped improving it. These modifications are highlighted in grey in the main text.

Yours sincerely,

Celso Cunha

### **Answers to reviewers**

#### **Reviewer 1:**

We acknowledge the comments of the reviewer. This reviewer raises a question concerning the expression system used in this study. We are aware of this possible limitation but nevertheless chose *E. coli* because of the advantages in producing large amounts of labeled protein necessary for the NMR experiments. The role of different PTMs in S-HDAg function and subcellular localization is now also more detailed discussed (see highlighted text in the end of Discussion section).

We now explain the meaning of the arrow in figure 2.

In figure 6, we corrected the legend and apologize for the mistakes.

#### **Reviewer 2:**

We acknowledge the comments of this reviewer.

#### **Reviewer 3:**

We corrected the text and included a significant part of the suggestions. Please, see highlighted text throughout the manuscript.

**Reviewer 4:**

We acknowledge the comments of this reviewer. The hypothesis as to why S-HDAg lacks specificity for its interaction with any nucleic acid was already mentioned in the text (lines 494-496). However, we tried to improve the discussion (lines 479-489) addressing the possible implications of S-HDAg structural plasticity and PTMs in the virus replication cycle and clinical presentation of the disease.