Enteroviruses are common human pathogens involved in a wide spectrum of clinical outcomes ranging from mild or non-symptomatic illness to severe diseases with neurological and/or cardiac manifestation. Despite being responsible for significant morbidity and mortality especially in immunocompromised patients and infants, to date no effective vaccines or specific antiviral treatment modalities are available to prevent or treat non-polio enteroviral infections. The discovery of the endogenous RNA interference pathway as an innate defence mechanism conferring intracellular immunity against foreign genetic elements has provided exciting possibilities in the fight against so far intractable, enteroviral diseases. We and others have shown the encouraging potential of RNA interference to limit enteroviral infections, leading to significant suppression of viral replication and cytopathogenicity, in vitro as well as in vivo. Yet, considerable limitations concerning efficacy, stability, specificity as well as viral escape need to be addressed to translate the anti-enteroviral potential into a novel treatment modality.