Major improvement in DNA vaccine technology over the past decade has reinvigorated this platform which has conceptual advantages over traditional vaccine platforms. In humans prior generations of DNA vaccines were poorly immunogenic. Through multiple improvements including synthetic optimization, genetic adjuvant technology with enhanced EP delivery this technology exhibits improved performance. These synthetic DNA vaccines drive immune responses similar or superior to live viral vectors. We present data in animal models and in human studies that illuminate their immune potency and clinical efficacy targeting both established infection and in prevention approaches to EID.