Virologic effectiveness of ibalizumab clinical trial experience compared to real-world clinical care without ibalizumab in the OPERA® Cohort

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Background

Ibalizumab (IBA) is a monoclonal antibody approved for heavily treatment experienced (HTE) people with HIV with ongoing viremia. Because ethical considerations prevented the inclusion of comparison arms in IBA clinical trials, its benefit relative to other regimens is unknown. Our objective was to compare the effectiveness of IBA-containing regimens to non-IBA-containing regimens among HTE individuals using external controls derived from routine clinical care.

Methods

Individuals who received 800 mg IBA every two weeks from the TMB-202 (24-week) and TMB-301/311(24-week, optional extension >96-weeks) clinical trials (treated) were compared to HTE individuals on non-IBA-containing regimens in routine care in the OPERA® cohort (control). Standardized mortality rate (SMR)-weighting ensured balance between the treated and control groups in baseline age, CD4 cell count, viral load (VL), and susceptibility to specific antiretrovirals (ARV). Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using SMR-weighted Cox proportional hazard models. Viral undetectability and suppression (first VL <50 or <200 copies/mL, respectively) were assessed within the first 24 weeks of follow-up. Loss of undetectability or suppression (first VL ≥50 or ≥200 copies/mL, respectively) were assessed after their respective achievement at any point during follow-up.

Results

The analysis included 76 treated and 65 control individuals; covariate balance was achieved with SMR-weighting [Figure 1]. At 24 weeks, a statistically significant doubling of the likelihood of viral undetectability was observed in the treated compared to the control group (SMR-weighted HR: 1.98, 95% CI: 1.02, 3.69) [Figure 2]. Achievement of viral suppression was also improved but did not reach statistical significance. Once achieved, 95% of treated individuals maintained undetectability through the end of follow-up, compared to 27% of control individuals. The likelihood of losing undetectability or suppression was 16 to 18 times higher for controls without IBA; confidence intervals were wide but statistically significant [Figure 3].

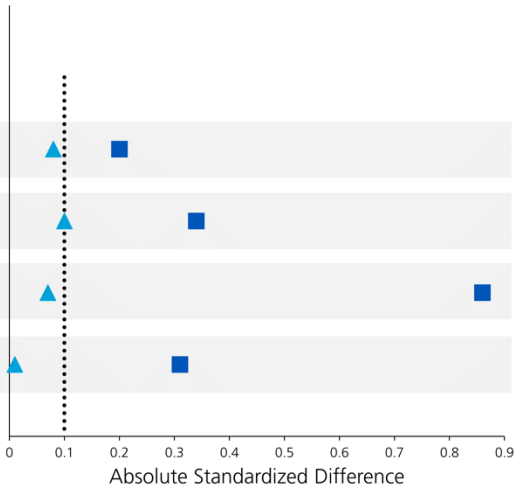
Conclusions

In this first study comparing IBA in clinical trials to non-IBA regimens in routine care, use of IBA was associated with shorter time to virologic undetectability and a longer durability of undetectability and suppression. With more individuals achieving and maintaining undetectability, IBA could have important clinical and public health implications for HTE individuals.

Word count: 350/350

Figure 1. Distribution of baseline characteristics and balance between IBA-containing and non-containing regimens before and after SMR-weighting[a]

	IBA Regimen (N=76)	Unweighted Non-IBA Regimen (N=65)	SMR-weighted[a] Non-IBA Regimen (N=76)
Age ≥55	26%	35%	30%
OSS[b] ≥2	42%	59%	48%
CD4 ≥150	31%	71%	35%
Log VL ≥4	71%	57%	72%

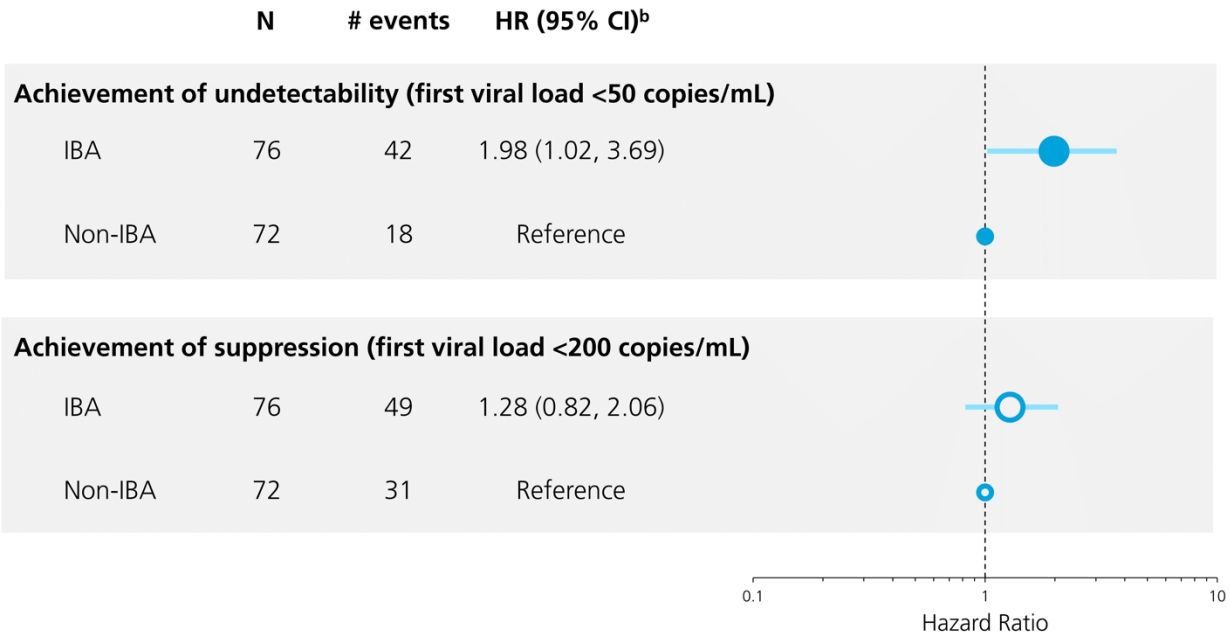


IBA, ibalizumab; SMR, standardized mortality ratio; N, number; OSS, overall susceptibility score; VL, viral load

[a] SMR-weighting is a form of propensity score weighting in which the external control group is weighted to look like the treated group. Individuals in the treated group receive a weight of 1 and those in the control group receive a weight derived from their probability of receiving IBA based on their baseline characteristics (i.e., baseline age, CD4 cell count, viral load, and a measure of susceptibility to specific antiretrovirals in their regimen)

[b] The overall susceptibility score provides a measure of the number of potent antiretrovirals in the regimen, where the influence of each is scaled by relative resistance to that drug class. Antiretrovirals included in the derivation of the score are darunavir, dolutegravir, emtricitabine, etravirine, lamivudine, tenofovir disoproxil fumarate and tenofovir alafenamide

Figure 2. Achievement of viral undetectability or suppression over the first 24 weeks of follow-up in the SMR-weighted population[a]



CI, confidence interval; HR, hazard ratio; IBA, ibalizumab; SMR, Standardized mortality ratio; N, number

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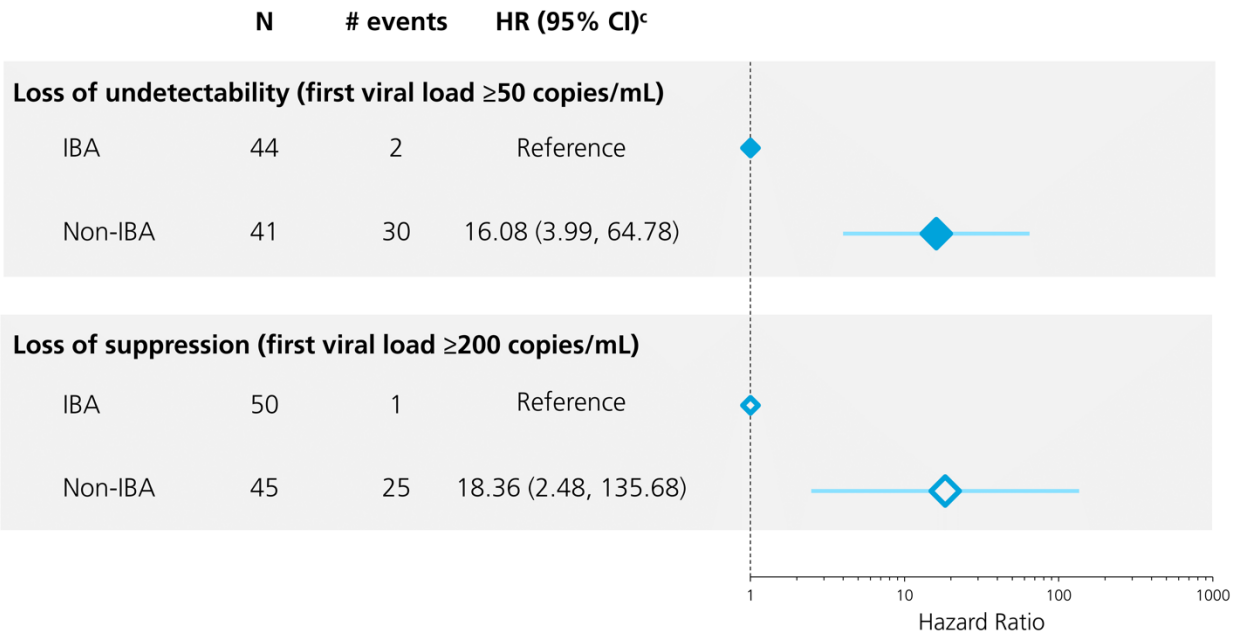
[b] SMR-weighted Cox proportional hazards models; bootstrapped confidence intervals; missing viral loads imputed with multiple imputation with chained equations

Figure 3. Loss of virologic control in the SMR-weighted population[a] of individuals who had previously achieved control over up to 96 weeks of follow-up[b]



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[b] New propensity score models were fitted to obtain SMR weights for each analysis because the study population changed

[C] SMR-weighted Cox proportional hazards models