Glioma stem cells (GSC) are increasingly recognized as the culprits behind the resistance of glioblastoma to standard therapy, including surgery, temozolomide and radiation therapy. Intensive research is currently underway to uncover novel and effective GSC targeting strategies. Fenofibrate is an FDA-approved hypolipidemic agent in widespread clinical use. Recent evidence has supported a possible role for fenofibrate as an anti-cancer agent in various cancer pathologies, including glioblastoma. Our own previous work has demonstrated that fenofibrate reduces proliferation and induces apoptosis in human high-grade glioma cells. Here, we present our results on the effects of fenofibrate on GSC in the in vitro setting. We chose to examine invasion because this property is known as a hallmark obstacle in the successful treatment of glioblastoma and recent data has implicated GSC. We found that fenofibrate treatment at a dose of 25 microM significantly decreased GSC invasion in a standard Matrigel invasion assay. We then examined the effect of fenofibrate on stem-cell marker expression and chose CD133 and Ooct4. CD133 remains one of the most commonly used GSC markers to date, while Ooct4 is an embryonic stem cell marker linked to glioma grade. Results demonstrated that fenofibrate treatment at 25 microM significantly diminished expression of both CD133 and Ooct4 as measured by flow cytometry and/or immunofluorescence staining. Finally, we investigated possible mechanisms and identified NF-kappaB and CyclinD1 as candidates. Inhibition of NF-kappaB reportedly decreases invasion in GSC and is a well-established property of fenofibrate in the inflammatory setting. Downregulation of Cyclin D1 has been found to correlate with attenuated invasion in human glioblastoma cells and may be observed with fenofibrate treatment of lymphoma cells. Using a panel of established human glioma cell lines, we found that fenofibrate treatment robustly diminished the expression of both NF-kappaB and Cyclin D1 in a dose-dependent and p53-independent manner. In conclusion, our data show that fenofibrate significantly attenuates both GSC invasion and expression of the CD133 and Ooct4 stem-cell markers, in association with diminished NF-kappaB and Cyclin D1 signaling in glioma cells. Based on these results, we propose that fenofibrate should be considered a novel and direct GSC targeting agent. Its relatively low cost, minimal toxicity and availability make it an attractive agent for rapid translation to the clinical setting as an adjuvant treatment for glioblastoma.