Phylogenetic trees were generated for reverse transcriptase and V3 sequences from matched donors and recipients. In one instance, the donor and recipient V3 viral sequences were clustered together, a finding that supports the presence of superinfection in a single sample (Fig. S6 in Supplementary Appendix 1).

A direct comparison of graft survival and overall survival between HIV-positive patients who received an organ from an HIV-positive donor and other patients who underwent transplantation in South Africa is difficult to perform because the other patients are not followed in a systematic manner, and HIV-positive patients rarely receive organs from HIV-negative donors. However, the 5-year overall survival and graft survival of 83.3% and 78.7%, respectively, are similar to the 3-year overall survival and graft survival observed among HIV-positive patients who received an organ from an HIV-negative donor in the United States (88.2% and 73.7%, respectively).³

The ability to detect superinfection was limited because of the inherent low proviral loads found in patients who have viral suppression with ART and because of ATG-induced T-cell depletion, which occurs after transplantation. However, we could detect superinfection down to a median of 1% of the viral population. Although the low levels of donor virus detected in patient KID139 might suggest a transient, subclinical superinfection, they are more likely to represent lingering viral inoculum and shedding of infected donor cells from the kidney into the recipient's blood. Either way, whether this finding has any clinical relevance is questionable, because no increases in viral load or new viral resistance have been observed in any patients.

The favorable clinical outcomes and the absence of transmitted drug resistance, as well as the absence of evidence for sustained donor-derived superinfection, support the use of HIV-positive–to–HIV-positive renal transplantation as a treatment option.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


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**Comparison of Dual Therapies for Lowering Blood Pressure in Black Africans**

**TO THE EDITOR:** Ojji et al. (June 20 issue)¹ report that amlodipine plus hydrochlorothiazide effectively lowered blood pressure at 6 months in black patients in sub-Saharan Africa. Many primary care providers are unaware of the association between hydrochlorothiazide use and skin cancer.²

The Medicines and Healthcare Products Regulatory Agency has reported a dose-dependent

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The Medicines and Healthcare Products Regulatory Agency has reported a dose-dependent
risk of lip and skin cancers among patients taking hydrochlorothiazide.² Regarding melanoma,³ 413 cases were identified among high users of hydrochlorothiazide (patients who had taken a cumulative dose of ≥50,000 mg of hydrochlorothiazide), yielding an adjusted odds ratio of 1.22 (95% confidence interval [CI], 1.09 to 1.36), as compared with controls, with no cumulative dose–response pattern. Regarding nonmelanoma skin cancers,⁴ high use of hydrochlorothiazide was associated with odds ratios of 1.29 (95% CI, 1.23 to 1.35) for basal skin cancer and 3.98 (95% CI, 3.68 to 4.31) for squamous-cell carcinoma, as compared with controls.

Hydrochlorothiazide has been classified as a possible carcinogenic drug by the International Agency for Research on Cancer (in Group 2B [possibly carcinogenic to humans]).⁵ Therefore, the treatment with hydrochlorothiazide that was suggested by Ojji et al. cannot be considered to be safe.

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TO THE EDITOR: The trial conducted by Ojji et al. included risk factors that may be unique to sub-Saharan Africa.¹ Although the region has a high burden of untreated hypertension and worse outcomes than elsewhere, there are no clear treatment guidelines for blacks Africans.²

The current 2017 American Heart Association (AHA)–American College of Cardiology (ACC) guidelines on hypertension recommend thiazide-type diuretics or calcium-channel blockers (or both), alone or in multidrug regimens, for blacks in North America.³ These guidelines are somewhat in agreement with the trial conducted by Ojji et al., in contrast to what the authors suggest.

The authors’ selection of hydrochlorothiazide and amlodipine was reportedly based on affordability and availability. However, those factors were not reflected in the choice of perindopril as the angiotensin-converting–enzyme (ACE) inhibitor for the trial. Cheaper generic drugs, such as enalapril and lisinopril,² would be more cost-feasible for patients who would benefit from ACE inhibitor therapy. In a region with the lowest per capita income in the world,¹² the burden of treatment costs falls on the patient and should be a major criterion in medication selection, both in trials and in practice.

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5. TO THE EDITOR: Ojji et al. report the results of the CREOLE (Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans) trial, which was a six-country, randomized, controlled trial that compared three antihypertensive regimens in black Africans who had uncontrolled hypertension. The trial provides substantive data to guide hypertension management in black populations and may help to estab-
lish locally relevant and globally applicable standards of care. However, we must not ignore the substantial barriers to accessing these medicines that patients face in the very countries where the trial was conducted.

In Uganda, we identified multiple within-country disparities regarding medicines for treating noncommunicable diseases and found that nearly 60% of the doses prescribed for these medicines in public-sector hospitals were not dispensed owing to stock-outs or rationing. This included hydrochlorothiazide, which was specifically selected by the CREOLE trial investigators because of its perceived high availability. Viable solutions to improve access include simplifying drug procurement and selection by means of fixed-dose combinations and standardizing treatment algorithms and minimizing out-of-pocket expenses by means of biopharmaceutical access programs and universal health coverage. Without a simultaneous focus on improving access, trials such as CREOLE will ultimately fail to improve health among the populations studied.

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TO THE EDITOR: Although there is diversity regarding hypertension risks and prevalence among African-descent populations,1,2 Oji et al. provide timely evidence of therapies that effectively lower blood pressure in black Africans. Although the authors note that these findings may not apply to black populations outside sub-Saharan Africa, the results are relevant to treatment issues in patients of African ancestry in the Caribbean region, who also face a high prevalence of hypertension and potentially ineffective treatment.3 For instance, a study showed that 41% of Barbadians 25 years of age or older had hypertension according to blood-pressure measurement, but adequate blood-pressure control was achieved in only 38%.4

International initiatives to improve hypertension prevention and control, such as the Global Hearts Initiative, advocate for increasing access to affordable and effective antihypertensive drugs for treatment.5 However, they do not address the potential need for different therapeutic interventions in populations of African origin. Governments in settings with limited resources may face difficult decisions about improving prevention efforts that target populations with a high risk of hypertension and about determining appropriate drug therapies to manage hypertension in persons in whom treatment is indicated. We need both.

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**The Authors Reply:** In response to Domínguez-Rodríguez et al.: neither the authors of the recent article linking hydrochlorothiazide to skin cancers nor any health authorities currently recommend stopping hydrochlorothiazide therapy for this reason, because the risk–benefit ratio associated with hydrochlorothiazide use strongly favors the associated cardiovascular benefits. The possible photosensitizing effect of hydrochlorothiazide probably reinforces the need to advise patients using hydrochlorothiazide to avoid overexposure to ultraviolet light and may add to other data that support the preferential use of thiazide-like diuretics over thiazides. However, the observational data that were based on fair-skinned white Danes and published after our trial was completed may not apply to dark-skinned black Africans.

In response to KagboKue et al.: combinations of antihypertensive therapies that are recommended for black patients in the 2017 ACC–AHA guidelines and the 2018 guidelines from the European Society of Cardiology and the European Society of Hypertension include a thiazide-type diuretic with a renin–angiotensin system blocker. However, the results of our trial suggest that other calcium-channel blocker–based combinations are more effective. Perindopril (supported by extensive trial evidence regarding morbidity and mortality) was chosen over lisinopril and enalapril because we wanted to use once-daily agents that provide good 24-hour control (hence enalapril was excluded) and because perindopril was available from the company that also donated amlodipine and hydrochlorothiazide for the trial.

We agree with Schwartz and Ssinabulya that implementing the results of a trial such as CREOLE depends on improved access to relevant medicines. However, only once the most effective agents have been identified can the various solutions to improving access to medications be put to best use. Meanwhile, across the six countries that participated in the trial, thiazides were more commonly used than thiazide-like diuretics, and hydrochlorothiazide was the thiazide most commonly in use.

Similarly, we agree with Quashie et al. that although important international initiatives to improve hypertension control advocate increasing access to affordable and effective antihypertensive drugs for treatment, they do not address the potential need for different interventions for African-origin populations. Our trial attempted to fill that gap.

We acknowledge that the results of our trial may not apply to black populations outside sub-Saharan Africa, and we agree that they may relate to patients of African ancestry in the Caribbean and elsewhere. Pending further region-specific trials, ideally with morbidity and mortality outcomes, the results of our trial provide data to inform two-drug combination therapy for black patients with hypertension. Although it is true that governments in settings with limited resources may need to balance costs of improving the prevention of hypertension against providing certain drug therapies, the results of our trial, we hope, provide helpful ethnically specific data on such therapies.

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Since publication of their article, the authors report no further potential conflict of interest.


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