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Five case reports on treatment of diabetes by *Artemisia annua* and *Artemisia afra* herbal tea

Abstract

Results registered for five cases in the province of Maniema, RDCongo document for the first time on a scientific and medical basis the antidiabetic effect of Artemisia herbal tea. This happened in the context of large scale clinical trials with *Artemisia annua* and *Artemisia afra* herbal tea, trials which successfully documented the efficacy of these plants against malaria and schistosomiasis, as well as other beneficial health effects.

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Introduction

Diabetes burden is rising sharply in Africa. WHO forecasts in the African region an increase from a total of 7.020.000 cases in the year 2000 to 18.234.000 in 2030 (See annex I for details per country). Similar data are quoted by other studies.[1] Children and adolescents account for almost half of all newly diagnosed cases of type 2 diabetes. And the death toll due to this disease is raising dramatically. Diabetes is a leading cause of blindness, amputation, kidney failure and heart disease. An effect which is less known and studied is the impact on malaria.[2] Africa not only has to fight transmittable diseases but the burden of non-transmittable diseases will also sharply increase.

People suffering from mild diabetes can keep their disease under control by an appropriate diet. If it becomes more severe insulin and/or drugs against blood sugar must be administred. Most of these drugs however are the cause of severe side effects. Traditional and herbal medicines against diabetes have been widely used in the past and are still to-day. Research on these alternative medicines becomes urgent and unavaidable for Africa.We reported previously on clinical trials we successfully completed in the province of Maniema, RDCongo, with Artemisia herbal tea against malaria and schistosomiasis.[3,4] During these trials we noticed that several patients suffered from diabetes. They had fasting blood sugar levels of 180 to 280 mg/ml. In five of these cases we noticed a remarkable alleviation of their disease and we made a close medical follow-up, including blood analysis, anthropometric measurements, records on renal and hepatic functions before, during and after treatment with *Artemisia annua* and *Artemisia afra* aqueous infusions.

The first case which aroused our interest in the potential impact of Artemisia herbal tea was a lady of 40 years of age. During the preliminary interviews and checks for the Artemisia trials we noticed that she had problems with polyurea, polydipsia and weight loss. Her fasting blood sugar (FBS) was at 250 mg/ml and the postprandial one at 275 mg/ml. After the therapeutic treatment of 7 days with 5g/l of dried leaves and twigs per day, we noticed that her bloog sugar had decreased to 180mg/ml. We decided to continue the treatment. 14 days later all symptoms of her diabetes had vanished, despite she lived on a normal diet. Fasting blood sugar was at 110 mg/ml and the postprandial one at 130mg/ml. We continued the herbal treatment for two months at a dose of 5g/L 3x per week. Six months later glycemia values stayed normal and stable, despite a normal diet and without drugs. This success story motivated to run a prospective *Artemisia annua* and *Artemisia afra* pilot study with five patients suffering simultaneously from diabetes and malaria, and keeping an eye on side effects.

Materials and methods

Materials

We used the same *Artemisia annua* and *Artemisia afra* from Senegal, Burundi and Luxembourg as those in the clinical trials for malaria and schistosomiasis (op.cit). The samples were analyzed at the Worcester Polytechnic Institute.

Preparation of the Artemisia herbal tea

5g of dried twigs and leaves of *Artemisia annua* or *Artemisia afra* are added to a liter of tap water boiling at 100°C. The recipient is removed from the fire and the herb is left to infuse during 15 minutes. The objective was to treat malaria infected patients at the daily dose of 1L of this type of infusion during 7 days. For the patients selected for the diabetes-malaria study this same treatment was prolongated during two weeks and after the treatment was reduced to the daily dose of 5g/L 3x per week during 2 months. Each one of these patients was followed by a thorough medical examination by a medical doctor including the required laboraory analyses. This included the following parameters: body weight, blood pressure, blood analysis, renal and hepatic functions. These parameters were measured on day one of the herbal treatment and then repateated every week.

Each patient was asked to describe the effects he ressented during the treatment,like headache, menstrual problems, dizziness, fatigue, palpitations, vomiting, diarrhea, skin eruptions. At the start of the trial patients with serious renal, hepatic, gastro-intestinal or cardiovascular problems were excluded.Each patient was explained in detail the purpose of this herbal treatment.

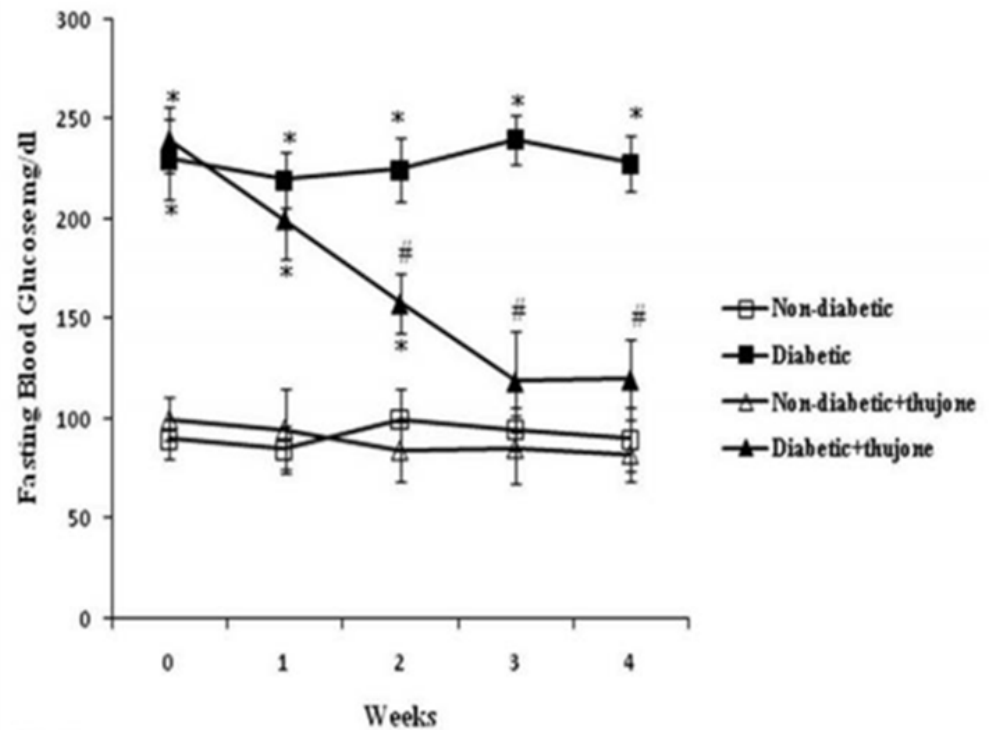

Figure 1 Effect of thujone treatment (4 weeks) on plasma glucose levels. Values are means ±SE (n=6).

*Significantly different from non-diabetic ($p<0.05$).

#Significantly different from diabetic ($p<0.05$).

"This figure is an excerpt of ref 53"

Results

Case 1: Male, 50 years old, married, two children, suffering from diabetes since 5 years. As treatment for his diabetes to lower blood sugar he used oral Daonil at the dose of 4 daily tablets of 5mg each and adapted his diet. One year before our clinical trial his diabetes aggravated and he was admitted to hospital for a treatment by insulin injections at the dose of 40 I.U twice a day. At the start of his participation in our clinical trial his body temperature was at 38.8°C, his heart rate at 100 beats/min, his blood pressure 120/70 mm/Hg, his respiration rate 18/min. The paraclinic tests gave the following results: the rapid malaria diagnostic test (RDT) was positive,fasting glycemia at 250mg/dL, parasitemia at 8 000 trophozoites/mm³ in blood smear, the transaminases ASAT at 60 I.U./L and 50 I.U./L, creatinin at 80µmol/L.

The patient was treated by *Artemisia annua* infusions at the dose of 5g/L, 3 times per day during 7 days, simultaneously with his sugar lowering drug. After 7 days of treatment fever had disappeared, glycemia was at 190mg/dL. 14 days later glycemia had lowered to 140mg/L, Symptoms of polyurea, polydipsia and fatigue had vanished. We continued the *Artemisia annua* treatment for 2 months and this decreased the glycemia to 110mg/dL, with no signs of relapse. His diet had become the standard of his community and he had reduced the dose of Daonil tablets from 4 to 2 per day. 6 months later his blood sugar stayed normal without the need of pharmaceutical drugs. The transaminases ASAT and ALAT were now 30 I.U./L and 35 I.U./L. At the start of the clinical trial the patient suffered from nausea and dizziness.

Case 2: Male, 45, suffering from diabetes since 10 months, treated with oral hypoglycemic Daonil at the dose of 4 daily tablets of 5 mg. At the admission to our clinical trial his fasting glycemia was 270 mg/dL and postprandial glycemia 300 mg/dL. But the patient confessed that he has stopped his Daonil treatment for 4 weeks because he could not afford paying for it. His body temperature was at 38.5°C. The immunochromatographic rapid diagnostic test (RDT) was positive. The blood smear gave a parasitemia of 10 000 trophozoites/mm³. ASAT was 45 I.U./L, ALAT 55 I.U./L, urea, 11 mmol/L creatinine 80µmol/L. Malaria was treated at a daily dose of 5g/L of *Artemisia afra* herbal tea per day simultaneously with Daonil. After one week his parasitemia had decreased to 130 mg/dL and all diabetic symptoms improved. The herbal tea consequently was lowered to 5g/L 3x par week. After 14 days blood glucose was at 120mg/dl. 2 months later his blood glucose stabilized at 110/mg/dl, with a normal diet and without Daonil. Transaminase levels were 30 IU/L for ASAT and 28 IU/L for ALAT.The health effects which had been reported were headache, nausea and vomiting.

Case 3: Female, 35 years of age, weighing 75 kg and 150cm tall. Body mass index (BMI) 33.3, slightly obese (grade 1). Her fasting sugar glucose was 275 mg/ml and the postprandial one of 300mg/ml. She was not aware of her diabetes.Her fever was at 38.8°C, her heart rate at 105 beats/min, the blood pressure at 140/60mm Hg, her respiration rate18/min. The immunochromatographic rapid diagnostic test (RDT) was positive, for parasitemia 7000 trophozoites were found in the blood smear. ASAT 30 I.U./L, ALAT 28 I.U./L, urea 11 mmol/L, creatinine 110µmol/L.She was treated with *Artemisia afra* herbal tea 5g/L during 14 days, without any hypoglycemic drug in parallel, but with the recommandation of an improved diet against diabetes. Her blood sugar decreased to 170mg/dL. The treatment was continued for 2 months at the dose of 5g 3x per week. Diabetic symptoms improved and fasting blood sugar stabilized at 120mg/dL. The patient reported secondary effects like palpitations, dizziness, nausea.

Table 1 Partial phytochemical composition of Artemisia cultivates used in this study (mg/g DW)

Phytochemical	*A. afra* PAR	SEN	1:4 Blend	*A. annua* LUX	BUR
Voucher Id	LG0019528 Universite de Liege	LG0019529 Universite de Liege	Not applicable	MNHNL17732 Herbarium Luxembourg	LG0019527 Universite de Liege
Total terpenoids[a] and flavonoids[b]					
Total terpenoids	47.92a	31.94a	35.14	63.89x	45.14x
Total flavonoids	3.74a	3.03b	3.18	5.55x	3.84y
Artemisinic compounds					
Artemisinin	nd	0.045	0.036	1.34x	1.70y
Arteannuin B	nd	nd	nd	0.93	nd
Deoxyartemisinin	nd	nd	nd	0.32x	0.39y
Artemisinic acid	nd	nd	nd	0.86	nd
Flavonoids					
Luteolin	0.07a	0.11a	0.11	0.07	nd
Phenolic acids					
Cholorogenic acid	0.45a	2.36b	1.98	1.32x	0.09y
Rosmarinic acid	nd	nd	nd	nd	nd
Coumarins					
Scopoletin	0.10a	0.10a	0.1	0.06x	0.05x
Essential oils					
Camphor	3.26a	0.72b	1.24	0.44x	0.33y
Caryophyllene[c]	nd	nd	nd	nd	nd
Caryophyllene oxide[c]	nd	nd	nd	1.27	nd
β-pinene[c]	nd	nd	nd	nd	nd
1,8 cineole (eucalyptol)	0.47a	0.27b	0.31	0.03	nd
Borneol[c]	0.67a	0.07b	0.19	nd	nd
Spathulenol[c]	0.12	nd	0.02	nd	nd
β-neoclovene[c]	0.51a	0.13b	0.21	nd	nd
Phytol[c]	nd	nd	nd	0.40x	0.68y
Thujone[c]	nd	0.86	0.69	nd	nd

Plant cultivator origins (BUR, Burundi; LUX, Luxembourg; PAR, Paris; SEN, Senegal) had an n>4. Significance at P<0.05; a,b letters compare A. afra PAR and SEN; x, y compares A. annua LUX and BUR; nd, not detectable. Statistical analysis impossible when 1 of the 2 samples was nd

[a]Expressed as santonin equivalents

[b]Expressed as quercetin equivalents

[c]Expressed as camphor equivalents

Case 4: Female, 36 years of age. Was aware of her diabetes since 2 years. Despite the use of an antiglycemic drug and diet restrictions, her fasting sugar glucose was at 265mg/mL. Body temperature 37.5°C, heart rate at 70 beats/minute, blood pressure 120/70 mmHg, respiratory rate 17/min, RDT negative, parasitemia of 1000/mm³ trophozoites in blood smear, ASAT 30 I.U./L, ALAT 28 I.U./L, urea 11 mmmol/L, creatinine 100 µmol/L.We applied a treatment of *Artemisia annua* herbal tea 5g/L during 14 days simultaneously with her antidiabetic drug. Blood sugar decreased to 160 mg/dL. Afterwards only the herbal tea was administred for 2 months. Her blood glucose stabilized at 130 mg/mL, her polyuria and polydipsia disappeared and she had gained some weight. Since that date she completely stopped the antidiabetic drug and lives on a normal diet. The patient had reported dizziness and nausea.

Case 5: Male, 31 years of age. He was found to be diabetic in a clinical analysis 2 years before. He was living on a diet low in calories and he used Daonil for his treatment. At the start of our clinical trials his fasting glucose was at 180 mg7dL and the postprandial one at 225 mg/dL. His body temperature was normal, his heart rate at 70 beats/

minure, blood pressure 130/70 mmHg, the respiratory rate at 16/min, RDT negative, no parasites in blood smear, ASAT 40 I.U./L, ALAT 30 I.U./L, urea 12 mmol/L, creatinin 90µmol/L.We adminstred *Artemisia annua* herbal tea for fourteen days at a dose of 5g/L 3x/day and he continued his diet low in calories. His fasting blood glucose decreased to 110 mg/dL and the postprandial one to 130 mg/dL. We continued the *Artemisia annua* treatment for 2 months at a dose of 5g/L3x per weeek.His blood sugar stabilized at 110 mg/dL and he had returned to a standard diet. No secondary effect was observed.

Addtional remark: For patients of case1.and 2.we found high levels of ALAT and ASAT. It is known that diabetes raises these levels. The administration of Artemisia herbal tea signifactly lowered these values and confirms the hepatoprotective efficiency of Artemisias. This hepatoprotective properties had also been observed at the Université des Montagnes in Cameroon for Artemisia annua.[5] But pure artemisinin significantly raises ALAT and ASAT.[6]

Artemisia plants and diabetes

In the large family of Artemisia plants, *Artemisia annua* (L.) is the best known, it is part the the Chinese Pharmacopeia and has widely been used against fever, malaria and other diseases. *Artemisia afra* (Jacq) is known in the African Pharmacopeia, for the treatment of diseases like coughing, rhinitis, headache, dyspepsia, intestinal problems, malaria, diabetes, renal problems.It was surprising to find in our trial similar antidiabetic results for both *Artemisia annua* and *Artemisia afra*. All Artemisia species seem to have a hypoglycemic effect, despite the absence of artemisinin in the latter.Trials and results on animals have been reported earlier.Treatment of rats with *Artemisia annua* aqueous extract reduced the serum glucose after 4 weeks from 110 to 70 mg/mL.[7-17] An excellent review paper has been published in Ethiopia. Some 14 studies clearly showed that both the aqueous and alcoholic extracts of several species of Artemisia produced significant hypoglycemic effects.[18]

Artemisia plants are used in many countries as traditional remedy against diabetes,but *in vivo* trials on humans are scarce. In 1986, in Morocco, fifteen patients with diabetes mellitus were treated with *Artemisia herba-alba* extract. Results showed that the extract caused considerable lowering of elevated blood sugar and 14 out of 15 patients had good remission of diabetic symptoms. But meanwhile it has been recognized that lyophilized extracts of Artemisia are not stable and rapidly lose their properties through evaporation and oxidation.[19] Trials made in Senegal in 2016 by a partner of IFBV-BELHERB and MfL(unpublished results, P.Lutgen) indicated that a 14 day consumption of *Artemisia annua* infusion (100g/person) gives a 15-20 % reduction in glycemia.In fact, the results reported in the present paper and gathered in RDCongo in five cases document for the first time on a scientific and medical basis the antidiabetic effect of Artemisia herbal tea.

Potentiel constituents responsible for the antidiabetic properties of Artemisia plants

Flavonoids and essential oils only have a minor impact and their role is controversial. It is difficult to find scientific papers on this subject.

The question concerning artemisinin and derivatives is crucial. They inhibit and even cause the apoptosis of β-cells, like other peroxides do. These pancreatic cells are essential for the generation and efficiency of insulin. The consumption of ACTs comcommittant with Artemisia herbal tea could thus enhance the diabetes of the patients. The results of research in China showed that artemisinin and dihydroartemisin in significantly increased the apoptosis of β-cells induced by palmitic acid.[20] Worse even, a flurry of publicity appeared recently on internet, proposing the sales of artemisinin and derivatives as drugs against diabetes.They refered to a paper published in 2017 in the journal Cell, where a European consortium reported that artemether could convert α-cells into β-cells. A recent indepth study refuted using anti-malarial drug to treat diabetes. They even found or confirmed that artemether abrogates β-cell insulin secretion in response to glucose.[21] Artemisinin drugs also augment cytochrome CYP3A4, which will accelerate the metabolism of any drug, be it pharmaceutical or natural.[22,23]

Arachidonic acid however increases insulin secretion and the sensitivity to insulin. This had been extensively described in assays with animals. The effect has been confirmed in humans. It acts as an inhibitor of enzymes which induce human β-cell destruction. Arachidonic acidis an extremely important fatty acid involved in cell regulation. It is a polyunsaturated fatty acid (20:4n6).[24-27] Arachidonic acid is present in red meat, eggs; 0.1 in fatty meat, 0.7 in fish oil, 0.3 % in eggs, 0.4 % of the total fat of breast milk, traces in cow milk. Higher plants and vegetables do not produce or contain arachidonic acid. It is only found and extracted from mosses and algae. A phytochemical analysis of five Artemisia species in Turkey shows that saturated fatty acids in these plants represent on the average 40% of the total and the unsaturated fatty acids 60%, including those with antimalarial activities like linoleic acid, arachidonic acid and linolenic acid. The real surprise is that based on the total fatty acid content Artemisia armeniaca contains 6.47% arachidonic acid, *A incana* 7.79%, *A tournefortiana* 2.61%, *A hausknechtii* 7.44% *A scoparia* 3.17%. This is ten times higher than in meat, eggs or fish oil. And it is possibly related to the prophylactic and therapeutic properties of all Artemisia plants.[28,29]

Anthocyanins and proanthocyanidins (condensed tannins) also are able to protect and regenerate β-cells.[30,31]

The fact that mostly aqueous or ethanolic extracts have an antidiabetic impact points to polar rather than to lipohilic constituents of the Artemisia plants. Recent publications confirm this hypothesis and the major apolar contribution stems from proanthocyanidins (condensed tannins).[32] Plants rich in proanthocyanidins like neem, cinnamon, grape seed or peel, sorghum, pomegranate peel, apple, blueberry all have a strong antidiabetic effect.

The consumption of whole fruits, particularly blueberries, grapes, and apples, is significantly associated with a lower risk of type 2 diabetes, whereas consumption of fruit juice barely has an effect. This confirms the proanthocyanidin hypothesis. Grape skins are rich in proanthocyanidins and the latter are absent in grape juice.[33]

Artemisia plants are rich in proanthocyanidins. A very recent paper deals with *Artemisia herba alba* and finds a concentration of 2 100 mg/100g.[34] Another paper detected the presence of anthocyanidins and tannins in several Artemisia species in Iran without quantifying them: *A. absinthium, A. annua, A. biennis, A. diffusa, A santolina, A turanica, A. vulgaris, A. sieberi.*[35,36]

Another molecule which has been studied extensively for its antidiabetic properties is arginine. Experiments conducted by researchers from the University of Copenhagen show that the amino acid arginine–found in a wide variety of foods such as salmon, eggs and nuts–greatly improves the body's ability to metabolize glucose. Arginine stimulates a hormone linked to the treatment of type 2 diabetes, and works just as well as several established drugs on the market.[37] In fact, already in 1966 the University of Michigan had found that the intravenous administration of amino-acids to healthy subjects, either as mixtures or individually, stimulated the release of insulin. The most effective stimulus was by arginine given alone.[38] In 1998 a study from India showed that the action of arginine is related to the production of nitric oxide.[39] Medicinal herbs like *Artemisia annua* or *Artemisia maritima* are very rich in nitrates and arginine.

A recent study from Ukraine has analyzed the amino acid content in some 8 Artemisia plants of this subgenus and found that they are all 5 to 10 times richer in arginine than other herbs or vegetables, with *A annua* top-ranking (2g/100g).[40] Recent evidence suggests that the

supposedly inert anions nitrate and nitrite are metabolized in blood and tissues to form nitric oxide NO and other bioactive nitrogen oxides. These stimulate pancreatic Langerhans islet function and subsequent insulin formation *in vivo*.[41] There is a growing body of evidence that glucose ingestion causes a number of pro-inflammatory changes in normal as well as diabetic humans. Glucose stimulates the endothelial production of the pro-inflammatory Interleukin-8.[42] This has also been described by a research team in Palestine.[43,44]

Chlorogenic acid and other caffeoylquinic acids also have antidiabetic properties. A study on Artemisia argyi led to the successful identification of caffeoylquinic acids as active constituents.[45,46]

Polysaccharides seem to have an effect. They inhibit the intestinal absorption of glucose. They also alleviate β-cell dysfunction.[47,48]

Pentacyclic triterpenes also have an antidiabetic effect.[49,50]

Saponins deserve more research.[51,52]

In the case of Artemisia plants rich in thujone like Artemisia afra, herba alba, absinthium, arborescens, thujone probably plays a major role.[53]

Sulfur present in Artemisias may also play an important role. H_2S has the reputation to be a toxic gas. But at low concentrations it has beneficial health effects and cures several diseases. Most of the balneary tradition is based on the presence of hydrogen sulfide in some mineral waters.The effect may be related to the precipitation of excess iron in the form of insoluble FeS. In their major analytical work Brisibe and Ferreira find that *Artemisia annua* contains 0.3% of sulfur. But only 0.1% in the majority of other plant leaves.[54] Among medicinal plants *Artemisia annua* is the richest in potassium (Brisibe et al., op.cit). Some studies have found low-normal potassium to be associated with increased diabetes risk. In a recent multi-ethnic cohort study, a significant inverse association between serum K and fasting glucose was found, but no significant association with longer-term diabetes risk. The authors conclude that this needs further studies.[55]

Conclusion

Our findings show that *Artemisia annua* and *Artemisia afra* herbal infusions have an high therapeutic efficacy in the treatment of diabetes. In fact these results gathered in RD Congo in five cases document for the first time on a scientific and medical basis the antidiabetic effect of Artemisia herbal tea in humans. Blood sugar could be lowered to standard levels. This confirms previous trials on animals. This antidiabetic property of Artemisia aqueous infusions is a polytherapy where various constituents of the plant work in synergy. No side effects or toxicities were observed in our trials. We recognize that further assays are needed to confirm our observations and better define the rôle of the constituents. Ideally a large scale double blind clinical trial is recommended. This would help to better understand the mechanisms involved and the precautions to be taken to avoid treatment failures.

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Conflicts of interest

We declare that there are no conflicts of interest.

ANNEX I

WHO African Region

Diabetes in the WHO African Region

Country	2000	2030
Algeria	4,26,000	12,03,000
Angola	51,000	1,40,000
Benin	87,000	2,66,000
Botswana	25,000	45,000
Burkina Faso	1,24,000	3,88,000
Burundi	26,000	72,000
Cameroon	70,000	1,71,000
Cape Verde	7,000	24,000
Central African Republic	18,000	38,000
Chad	97,000	2,69,000
Comoros	4,000	15,000
Congo	14,000	39,000
Côte d'Ivoire	2,64,000	6,36,000
Democratic Republic of the Congo	2,91,000	9,10,000
Equatorial Guinea	8,000	21,000
Eritrea	47,000	1,42,000
Ethiopia	7,96,000	18,20,000
Gabon	8,000	14,000
Gambia	22,000	61,000
Ghana	3,02,000	8,51,000
Guinea	34,000	89,000
Guinea-Bissau	17,000	44,000
Kenya	1,83,000	4,98,000
Lesotho	31,000	42,000
Liberia	40,000	1,54,000
Madagascar	1,00,000	3,01,000
Malawi	55,000	1,18,000
Mali	1,40,000	4,05,000
Mauritania	34,000	1,03,000
Mauritius	1,11,000	2,33,000
Mozambique	1,33,000	2,73,000

Table Continued...

Country	2000	2030
Namibia	25,000	60,000
Niger	1,08,000	3,82,000
Nigeria	17,07,000	48,35,000
Rwanda	30,000	77,000
Sao Tome-Principe	1,000	2,000
Senegal	1,43,000	4,21,000
Seychelles	8,000	19,000
Sierra Leone	65,000	1,78,000
South Africa	8,14,000	12,86,000
Swaziland	13,000	21,000
Togo	64,000	1,84,000
Uganda	98,000	3,28,000
United Republic of Tanzania	2,01,000	6,05,000
Zambia	70,000	1,86,000
Zimbabwe	1,08,000	2,65,000
Total	70,20,000	18,234,000

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