Ketosis-Prone Type 2 Diabetes Mellitus and Human Herpesvirus 8 Infection in Sub-Saharan Africans

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Since 1987, an atypical presentation of diabetes has emerged as one of the most frequent forms of diabetes in populations of African origin. It is a diabetic syndrome characterized by an acute onset with severe hyperglycemia and ketosis or ketoacidosis requiring insulin therapy, followed by long-term insulin-free near-normoglycemic remission periods, frequently interrupted by ketotic relapses. Thus, it resembles type 1 diabetes mellitus (DM-1) at onset and prediabetes or type 2 diabetes mellitus (DM-2) over the long term. Because of the unknown etiology of this form of diabetes, especially in the absence of classic markers of autoimmune diabetes, it has conservatively been classified under idiopathic DM-1 or DM-1B by the World Health Organization (WHO).

Context An atypical form of type 2 diabetes mellitus (DM-2) is revealed by ketosis (ketosis-prone type 2 diabetes mellitus), frequently occurring in individuals who are black and of African origin, and characterized by an acute onset requiring transient insulin therapy. Its sudden onset suggests precipitating factors.

Objective To investigate the putative role of human herpesvirus 8 (HHV-8) in the pathogenesis of ketosis-prone DM-2.

Design, Setting, and Participants A cross-sectional study in which antibodies were searched against latent and lytic HHV-8 antigens using immunofluorescence. The presence of HHV-8 in genomic DNA was investigated in 22 of the participants at clinical onset of diabetes. We also tested whether HHV-8 was able to infect human pancreatic β cells in culture in vitro. The study was conducted at Saint-Louis University Hospital, Paris, France, from January 2004 to July 2005. All participants were black and of African origin: 187 were consecutive diabetic patients of whom 81 had ketosis-prone DM-2 and 106 had nonketotic DM-2, and 90 individuals were nondiabetic control participants who were matched for age and sex.

Main Outcome Measures Seroprevalence of HHV-8 and percentage of patients with HHV-8 viremia at onset in ketosis-prone DM-2.

Results HHV-8 antibodies were found in 71 patients (87.7%) with ketosis-prone DM-2 vs 16 patients (15.1%) with nonketotic DM-2 (odds ratio, 39.9; 95% confidence interval, 17.1-93.4; P < .001) and 36 of the control participants (40.0%) (odds ratio, 10.7; 95% confidence interval, 4.9-23.4; P < .001). HHV-8 in genomic DNA was present in 6 of 13 patients with ketosis-prone DM-2 tested at acute onset and in 0 of 9 patients with nonketotic DM-2. HHV-8 proteins were present in human islet cells that were cultured for 4 days in the presence of HHV-8.

Conclusions In this preliminary cross-sectional study, the presence of HHV-8 antibodies was associated with ketosis-prone DM-2 in patients of sub-Saharan African origin. Longitudinal studies are required to understand the clinical significance of these findings.
Organization and the American Diabetes Association as opposed to classic autoimmune DM-1 or DM-1A. However, there is growing evidence to consider this syndrome as ketosis-prone DM-2, including older age at onset and genetic predisposition. At the initial stages of the disease, insulin secretion in response to glucose is drastically reduced, but the subsequent remission is associated with a restoration of insulin secretion in most patients, which indicates that an acute and reversible phenomenon precipitates the disease in patients otherwise predisposed to DM-2. Patients with classic factors that precipitate or deteriorate diabetes such as bacterial infection, heavy alcohol intake, corticosteroids, and other endocrinopathies, have been formally excluded in most cohorts of ketosis-prone DM-2.

In this study, we hypothesized that ketosis-prone DM-2 may be associated with a viral infection, which may also be the acute and reversible precipitating phenomenon. Indeed, viruses may induce both insulin resistance and insulin secretory defect. Also, there are case reports of diabetic ketoacidosis that are precipitated by genital herpes infection in patients with preexisting DM-1, and a patient with fulminant DM-1 has been reported to be infected by human herpesvirus 6. Because of the acute onset of ketosis-prone DM-2 and the high prevalence of ketosis-prone DM-2 in populations of African origin, we searched for a virus that is commonly found in this population. Among the possible candidates, human immunodeficiency virus (HIV) was not considered because the first cases of ketosis-prone DM-2 were described in sub-Saharan Africa in the 1960s-1970s long before the discovery of HIV. Hepatitis C virus, which has been reported to be associated with DM-2, was also not considered because insulin resistance rather than insulin secretion deficiency has been proposed as the potential mechanism. Thus, we focused only on the human herpesvirus 8 (HHV-8), which is endemic in sub-Saharan Africa where 30% to 60% of adults have markers of HHV-8 infection with no clinical manifestations in most cases. HHV-8 has been associated with Kaposi sarcoma, hence the common name of Kaposi sarcoma–associated herpesvirus. Interestingly, a high prevalence of diabetes has been reported in some cohorts of patients displaying Kaposi sarcoma, whatever their ethnic origin.

The objective of this study was to test the a priori hypothesis that HHV-8 infection is associated with ketosis-prone DM-2.

METHODS

Patients

This cross-sectional study was conducted by the Department of Endocrinology and Diabetes at Saint-Louis University Hospital, Paris, France, over 18 months from January 2004 to July 2005. All consecutive patients of sub-Saharan African origin who were admitted for routine follow-up (yearly screening for diabetes complications and education), treatment modifications, or for treatment of acute metabolic features (onset or relapse) were considered for inclusion if they were born in Africa and had migrated to France at adult age. Exclusion criteria were as follows: (1) positive determination of antiglutamic acid decarboxylase 65, antityrosine phosphatase, and anti-islet cell antibodies; and (2) positive hepatitis B or C or HIV serological testing. Thus, a consecutive sampling with 85% participation yielding a 187-patient sample was constituted. Thirty-seven (20%) patients from this sample participated in our previous studies describing the phenotype.

Patients living in Paris were compared with a group of 90 nondiabetic control participants, which included 49 regular blood donors from Dakar, Senegal, and 41 adults from sub-Saharan Africa who were recruited by public advertisement during the same period and living in Paris. Control participants were matched to the patients for age, sex, and region of origin. All of the control participants who were recruited in Paris were born in Africa and had migrated to France during adulthood.

Patients with known maturity-onset diabetes of the young, endocrinopathies, pancreatic disease, and autoimmune DM-1 were not included in the study.

This study was approved by the ethical committee of Saint-Louis University Hospital, and each participant gave written informed consent to participate.

Diabetes Classification

Our sample of 187 patients included 81 patients with ketosis-prone DM-2 and 106 patients with nonketotic DM-2. The diagnosis of ketosis-prone DM-2 was applied to all patients who had hyperglycemia with significant ketosis at diabetes onset (≥2 urine ketones or >2.5 mmol/L ketonemia) requiring insulin treatment at onset followed by a minimum 3-month duration of near-normoglycemic remission defined by a glycated hemoglobin (HbA1c) level of less than 6.5% without insulin treatment, and who had negative determination of antiglutamic acid decarboxylase 65, antityrosine phosphatase, and anti-islet cell antibodies. A DM-2 diagnosis was applied to all patients who had nonketotic hyperglycemia at diagnosis of diabetes that was initially controlled without insulin and who had no evidence of autoimmunity. Patients were included irrespective of diabetes duration. For all patients, we recorded their place of birth, age at migration to France, and characteristics at inclusion and at onset of diabetes including age, body mass index (calculated as weight in kilograms divided by height in meters squared), HbA1c level, blood pressure, serum lipid levels, and microvascular complications.

Procedures

We investigated the seroprevalence of HHV-8 in all of the patients and control participants. We also performed the detection of HHV-8 DNA in peripheral blood mononuclear cells in 13 patients with ketosis-prone DM-2 who presented at onset or during a ketogenic relapse, and in 9 patients with nonketotic DM-2 at diagnosis.
Serological Study. Serological determination of HHV-8 infection is still hindered by the lack of a criterion standard technique. Detection of HHV-8 antibodies was therefore blindly performed using 3 different techniques: (1) an indirect immunofluorescence assay for antibodies against lytic antigens using an IS1-1 cell line \(^{22}\) (1/50 diluted patient sera) \(^{23}\); (2) an indirect immunofluorescence assay for antibodies against latent nuclear antigens using BCP-1 cell line (1/50 diluted patient sera) \(^{23}\); and (3) an enzyme-linked immunosorbent assay method with recombinant fragment (amino acids 86-170) of the HHV-8 capsid protein encoded by open reading frame 65. \(^{24}\) Seropositivity was scored when the results of the 3 techniques gave concordant results.

HHV-8 DNA Detection. Polymerase chain reaction amplification assay for HHV-8 DNA detection was performed using peripheral blood mononuclear cells obtained from blood specimens after Ficoll gradient separation. Peripheral blood mononuclear cells were frozen at −80°C until extraction. DNA extracted using a QIAamp blood extraction kit (Qiagen, Courtabeuf, France) was amplified by real-time quantitative polymerase chain reaction (ABI PRISM 7700; Perkin Elmer, Courtabeuf, France) was amplified by real-time quantitative polymerase chain reaction (ABI PRISM 7700; Perkin Elmer Applied Biosystems, Foster City, California). \(^{25}\) Briefly, dilutions of known amounts (10-10\(^7\) copies) of a fragment of viral DNA (KS 330-233 primer sequences) cloned in a plasmid were used to establish the standard curve. By plotting the cycle’s threshold values against given copy numbers, a linear amplification of 10\(^2\) to 10\(^7\) copies with a coefficient of variation of less than 3% was obtained. Then, the cut-off value of 100 copies/µg of DNA defined the lower limit of linearity from standard curve.

In Vitro Infection of Pancreatic \(\beta\) Cells by HHV-8. In order to determine whether HHV-8 could infect human pancreatic insulin-secreting \(\beta\) cells, isolated islets obtained from a donor with brain death \(^{26}\) were seeded in a volume of 200 µL of serum-free CRML-1066 medium (Invitrogen, Cergy Pontoise, France), supplemented with 0.25% human serum albumin (Baxter, Deerfield, Illinois), and 20 mM L-glutamine, 64 µg/mL gentamycin, and 25 mM Hepes (Sigma, Saint-Quentin Fallavier, France). HHV-8 infection was facilitated by adding 5 µL of filtered BCP-1 supernatant \(^{23}\) in the presence of heparan sulfate at 75 µg/L final concentration. After 4 days of incubation into 5% CO\(_2\) incubator at 37°C and also after staining with rat monoclonal anti-LANA1 (ABI, Columbia, Maryland) and mouse monoclonal anti-insulin antibodies (Sigma-Aldrich, St Louis, Missouri), cultured cells were collected, washed with phosphate-buffered saline, fixed and permeabilized, and visualized on a confocal microscope (Axiovert 10, Carl Zeiss, Oberkochen, Germany). Anti-rat secondary antibodies were coupled with fluorescein isothiocyanate-5 and antimouse antibodies were coupled with Texas Red.

Statistical Analyses

The primary end point of the study was HHV-8 seroprevalence, which was compared between groups using Fisher exact tests. The sample size was estimated assuming an HHV-8 seroprevalence of 30% in the control group, the lowest estimate in the general adult population in sub-Saharan Africa. \(^{10}\) Therefore, 90 participants per group would be sufficient to detect a difference of 25% between ketosis-prone DM-2 patients and control participants with a power of 90%, a type I error of .05, and a 2-sided test. The odds ratio (OR) was given as a measure of association together with its 95% confidence interval (CI). Comparison of the control participants from Dakar vs the control participants from Paris yielded an OR of 1.01 (95% CI, 0.38-2.70; \(P > .99\)). We therefore merged the 2 control samples in the analyses. Fisher exact test was also used for other categorical variables. Quantitative variables were expressed as mean and standard deviation and comparisons between groups were performed using unpaired \(t\) tests. Data were analyzed using SPSS for Windows version 12.0 (SPSS Inc, Chicago, Illinois) and SAS for Windows version 8.2 (SAS Institute Inc, Cary, North Carolina) and the significance level was set at \(P < .05\).

RESULTS

Patient Characteristics

The characteristics of the study sample are presented in TABLE 1. Patient age was similar between groups ranging from 28 to 77 years in patients with nonketotic DM-2 and 21 to 66 years in patients with ketosis-prone DM-2 (\(P = .20\)). Predominance of patients who were men was more marked in the ketosis-prone DM-2 group when compared with nonketotic DM-2 patients (\(P = .01\)). The proportion of patients originating from West Africa and Central Africa was similar in both groups (\(P = .34\)). Patients and control participants living in Paris had been living in Europe for similar duration.

Prevalence of HHV-8 Seropositivity

There was a prevalence of HHV-8 seropositivity (TABLE 2) with or without viral DNA of 87.7% in ketosis-prone DM-2 (95% CI, 78.6-93.3) (71 of 81 patients), and of 15.1% in nonketotic DM-2 (95% CI, 9.4-23.2) (16 of 106 patients). Both groups were significantly different from the control group with an overall prevalence of 40.0% (95% CI, 30.5-50.3) (36 of 90 participants); a prevalence of 39.0% in France (16 of 41 participants), and of 40.8% in Senegal (20 of 49 participants). In comparison with the nondiabetic control group, the OR for ketosis-prone DM-2 was 10.65 (95% CI, 4.86-23.35; \(P < .001\)) and for patients with nonketotic DM-2 the OR was 0.27 (95% CI, 0.14-0.53; \(P < .001\)). When the ketosis-prone DM-2 group was compared with the nonketotic DM-2 group, the OR of HHV-8 seropositivity was 39.94 (95% CI, 17.08-93.36; \(P < .001\)).

HHV-8 in Genomic DNA

When tested for viremia at initial presentation, 6 of 13 patients with ketosis-prone DM-2 but none of the 9 patients with nonketotic DM-2 showed titers of HHV-8 DNA incorporation in their genomic DNA, which ranged from 74 to 501 copies/µg of DNA. Among these 6 patients, 2 were HHV-8–antibody-
negative. Viremia became negative within 1 week in all of these patients.

**Phenotype Associated With Positive HHV-8**

There was no difference in anthropometric and metabolic parameters between the HHV-8–antibody-positive and HHV-8–antibody-negative patients with ketosis-prone DM-2 (data not shown). By contrast, patients with nonketotic DM-2 and positive HHV-8 antibodies (n = 16) were different from patients with nonketotic DM-2 and negative HHV-8 antibodies (n = 90) (TABLE 3). Eleven of the 16 (68.8%) patients with nonketotic DM-2 and positive HHV-8 antibodies were requiring insulin at the time of the study vs 12 of the 90 (13.3%) patients with nonketotic DM-2 and negative HHV-8 antibodies (P < .001). In 5 of 8 patients with nonketotic DM-2 and positive HHV-8 antibodies, gestational diabetes had occurred previously. The prevalence of complications was similar in patients with nonketotic DM-2 and positive HHV-8 antibodies and patients with nonketotic DM-2 and negative HHV-8 antibodies.

**Infection of Pancreatic β Cells by HHV-8**

The FIGURE shows HHV-8 infection in isolated human β cells that were cultured in vitro for 4 days in the presence of HHV-8 and costained for insulin and LANA1. Pancreatic β cells cultured without HHV-8 (control culture medium) are also shown in the Figure and display insulin staining with no viral protein.

**COMMENT**

**Ketosis-Prone DM-2 Associated With HHV-8 Infection**

Our preliminary study shows a strong link between ketosis-prone DM-2 phenotype and markers of HHV-8 infection. Patients with ketosis-prone DM-2 have a very high prevalence of HHV-8 infection, whereas patients with nonketotic DM-2 have a much lower prevalence of HHV-8 infection when compared with the background population. Thus, the prevalence of HHV-8 seropositivity is almost 6-fold higher in patients with ketosis-prone DM-2 compared with nonketotic DM-2 patients. The association between ketosis-prone DM-2 and HHV-8 infection is strengthened by the presence of viremia at the acute ketotic onset of the disease. Our viral load values are close to those described in participants coinfected with HIV and HHV-8 without Kaposi sarcoma.27 Lower values have been reported in patients with posttransplantation Kaposi sarcoma during clinical remission.23 Of note, in the Amsterdam Cohort Studies in which HIV-infected homosexual men were prospectively followed up, viremia was detected in only 10.3% of the 215 participants undergoing HHV-8 seroconversion.26

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketosis-Prone DM-2 (n = 81)</th>
<th>Nonketotic DM-2 (n = 106)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, women</td>
<td>14 (17.3) [10.5-27.1]</td>
<td>38 (34.0) [25.6-43.4]</td>
<td>.01</td>
</tr>
<tr>
<td>West African origin</td>
<td>59 (72.8) [62.2-81.4]</td>
<td>70 (66.0) [56.6-74.4]</td>
<td>.34</td>
</tr>
<tr>
<td>Central African origin</td>
<td>22 (27.2) [18.6-37.8]</td>
<td>36 (34.0) [25.6-43.4]</td>
<td>.34</td>
</tr>
</tbody>
</table>

**Table 2. Positivity of Serological Tests and Viral DNA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ketosis-Prone DM-2 (n = 81)</th>
<th>Nonketotic DM-2 (n = 106)</th>
<th>Control Participants (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive to immunofluorescence BCP-1</td>
<td>74 (91.3) [83.0-96.0]</td>
<td>16 (15.1) [9.4-23.2]</td>
<td>36 (40.0) [30.5-50.3]</td>
</tr>
<tr>
<td>Positive to immunofluorescence ISI-1</td>
<td>72 (88.9) [80.0-94.3]</td>
<td>16 (15.1) [9.4-23.2]</td>
<td>39 (43.3) [33.6-53.6]</td>
</tr>
<tr>
<td>Positive to ELISA</td>
<td>76 (93.8) [86.0-97.7]</td>
<td>18 (17.0) [10.9-25.3]</td>
<td>40 (44.4) [34.6-54.7]</td>
</tr>
<tr>
<td>Positive to all 3 assays</td>
<td>71 (87.7) [78.6-93.3]</td>
<td>16 (15.1) [9.4-23.2]</td>
<td>36 (40.0) [30.5-50.3]</td>
</tr>
<tr>
<td>DNA testing, No.</td>
<td>13</td>
<td>9</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Positive results</td>
<td>6 (46.2) [23.2-70.9]</td>
<td>0</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

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(Reprinted) JAMA, June 18, 2008—Vol 299, No. 23 2773
The design of our study does not allow determination of whether HHV-8 infection precedes the onset of diabetes or is reactivated during the acute presentation, but we have clear indication that the acute metabolic disturbances coincide with significant viremia. The fact that we were able to evidence a viral detection at onset of ketosis-prone DM-2 without HHV-8 antibodies in 2 participants, plausible with early stage of primary infection with rapid viremia disappearance, strongly suggests a temporal relationship. Of note, these 2 participants reported having traveled to West Africa a few weeks prior to acute episode. The likelihood that HHV-8 infection may trigger ketosis in a nonspecific manner (as any acute illness occurring in patients with diabetes) is low because none of our participants displayed clinical signs of infection.
Moreover, the capacity of HHV-8 to infect pancreatic β cells in vitro supports the possibility of a direct effect.

Other Viruses Associated With Diabetes

Viruses have been considered as major potential candidates for the etiology of diabetes for several decades, especially for DM-1. The viral hypothesis was initially based on the temporal relationship between defined viral infections and the onset of overt diabetes, especially with the coxsackievirus B4. The current hypotheses are that viruses may be involved in the pathogenesis of diabetes by triggering β cell-specific autoimmunity or by direct infection and destruction of β cells. In autoimmune DM-1, the etiological infection may take place long before clinical onset, which explains the difficulty in identifying the diabetogenic viruses. In the case of DM-2, only limited investigations have attempted to relate its pathogenesis to viral infections. There is growing evidence of increased prevalence of diabetes in patients infected with hepatitis C virus, and in human herpesvirus 1–infected patients. In hepatitis B virus infection, diabetes has been attributed to interferon therapy. A high prevalence of diabetes (16%-30%) has been reported in cohorts of individuals with Kaposi sarcoma, but the phenotype of diabetes was not described. In the case of ketosis-prone DM-2 that is characterized by an acute onset with a possible evolution toward DM-2, the question is whether a viral infection would explain the specificity of the phenotype, ie, the ketotic acute onset in individuals otherwise predisposed to DM-2. This appears plausible when considering that fulminating diabetes in Japanese patients, a disease that resembles ketosis-prone diabetes, may be precipitated by viruses.

HHV-8 Seropositivity in Nonketotic DM-2 Patients

We found a lower seroprevalence in patients with nonketotic DM-2 compared with control participants. Due to the small number of participants, one cannot exclude a chance effect. However, since our study was to test an a priori hypothesis involving only HHV-8, a high type I error is unlikely. We hypothesize that ketosis-prone DM-2 is an acute-onset DM-2, initially precipitated by an environmental factor such as HHV-8 primary infection or viral activation. Individuals predisposed to DM-2, if infected before the onset of diabetes, develop ketosis-prone DM-2, and if not, develop classic DM-2, which explains the abnormally low prevalence of HHV-8 antibodies in DM-2 compared with the background population. Patients with nonketotic DM-2 and HHV-8 seropositivity compared with patients with nonketotic DM-2 and no HHV-8 seropositivity had specific features such as a high frequency of insulin requirement. Thus, it is possible that we missed the ketotic onset in these patients. In addition, we found a high frequency of gestational diabetes that preceded DM-2, and HHV-8 reactivation during pregnancy has been previously reported in HIV type 1–infected women. Therefore, gestational diabetes may possibly reveal ketosis-prone DM-2 at an early stage.

Possible Mechanisms Involved in the Link Between Ketosis-Prone DM-2 and HHV-8 Infection

Ketosis-prone DM-2 is characterized by an acute and reversible insulin secretion deficiency. Otherwise, it has characteristics of DM-2. Genetic factors implicated in insulin secretion, β-cell differentiation, and protection against oxidative stress may contribute to the pattern of ketosis-prone DM-2 phenotype, but none of these factors on its own explains it.

HHV-8 is a lytrophic herpesvirus known to infect B or T lymphocytes, but also macrophages, oral epithelial cells, and vascular endothelial cells. It may influence the pathogenesis of diabetes either by cytokine secretion or by direct infection of the pancreatic β cell, or both. In our study, we have provided experimental evidence that HHV-8 can directly infect human pancreatic insulin-secreting β cells in vitro, which does not prove a causal relationship between HHV-8 and ketosis-prone DM-2. The ideal demonstration that HHV-8 infection causes ketosis-prone DM-2 would have been to find HHV-8 in patient islet-β cells at ketogenic onset. However, pancreatic biopsies raise ethical considerations and no pancreatic autopsy specimen was available since none of the patients died during the study period. Clearly, its effect on short-term and long-term functional capacity of the infected cells needs further investigation. HHV-8 might affect insulin secretion by inducing an endoplasmic reticulum stress in β cells. Indeed, endoplasmic reticulum stress has been involved in β cell failure and human herpesvirus 1 has been recently reported to activate endoplasmic reticulum stress by stimulating the phosphorylation of protein kinase R-like endoplasmic reticulum kinase (PERK) in mouse 10T1/2, and NIH 3T3 cells.

Potential Limitations of Our Study

Although our results provide a strong preliminary observation of the association between HHV-8 and ketosis-prone DM-2, they are limited by the small sample size, especially regarding the number of participants tested for viral DNA. Also, we have not been able to establish a temporal relationship between the virus and ketosis-prone DM-2 phenotype.

In conclusion, in this cross-sectional study the presence of HHV-8 antibodies was associated with ketosis-prone DM-2. These results need to be replicated in other populations and longitudinal studies are required to understand the clinical significance of these findings.

Author Contributions: Dr Gautier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors had access to all the data and shared final responsibility for the decision to submit for publication.

Study concept and design: Sobngwi, Choukem, Agbalika, Gautier.

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Analysis and interpretation of data: Sobngwi, Choukem, Agbalika, Calvo, Gautier.

Drafting of the manuscript: Sobngwi, Choukem, Cattan, Calvo, Gautier.

Critical revision of the manuscript for important intellectual content: Sobngwi, Choukem, Agbalika,

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ATYPICAL DIABETES AND HHV-8 INFECTION

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Study supervision: Gautier.

Financial Disclosures: None reported.

Funding/Support: This work has been supported by the Assistance Publique-Hôpitaux de Paris (grants AOR 02088 and AOR 0305), INSERM, Association Française des Diabétiques (AFD), and Association de Langue Française pour l’Étude du Diabète et des Maladies Métaboliques (ALFEDIAM).

Role of the Sponsor: The sponsors of the study had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We are grateful to the patients who participated in the study. The excellent work and dedication of the technical and nursing staffs of the Department of Diabetes and Endocrinology and the Clinical Research Centre are warmly acknowledged. We thank M. A. Charles, MD, MPH, Director of Research, INSERM Unit 780, Research in Epidemiology and Biostatistics for her comments on the manuscript. These individuals did not receive compensation for their contributions to this article.

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