

## Case Report

# Checking the Checkpoint Inhibitors: A Case of Autoimmune Diabetes After PD-1 Inhibition in a Patient with HIV

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**Abbreviations:** CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DM, diabetes mellitus; GAD65, glutamic acid decarboxylase 65; HAART, highly active antiretroviral therapy; HbA1c, glycated hemoglobin A1c; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IA-2, islet autoantigen-2; ICI, immune checkpoint inhibitor; ICI-DM, immune checkpoint inhibitor-associated diabetes mellitus; irAE, immune-related adverse event; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PET-CT, positron emission tomography-computed tomography; T1DM, type 1 diabetes mellitus.

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## Abstract

Immune checkpoint inhibitor-associated diabetes mellitus (ICI-DM) is a known immune-related adverse event (irAE) following treatment with programmed cell death protein 1 (PD-1), with a reported 0.9% incidence. We hereby present the first case, to our knowledge, of ICI-DM following ICI use in a human immunodeficiency virus (HIV) patient. In this case, a 48-year-old man with HIV stable on highly active antiretroviral therapy (HAART) was diagnosed with Hodgkin lymphoma and initiated treatment with the PD-1 inhibitor nivolumab. His lymphoma achieved complete response after 5 months. However, at month 8, he reported sudden polydipsia and polyuria. Labs revealed a glucose level of 764 mg/dL and glycated hemoglobin A1c (HbA1c) of 7.1%. Low C-peptide and elevated glutamic acid decarboxylase 65 (GAD65) antibody levels confirmed autoimmune DM, and he was started on insulin. Major histocompatibility complex class II genetic analysis revealed homozygous HLA DRB1\*03-DQA1\*0501-DQB1\*02 (DR3-DQ2), which is a known primary driver of genetic susceptibility to type 1 DM. Autoimmune DM has been reported as an ICI-associated irAE. However, patients with immunocompromising conditions such as HIV are usually excluded from ICI trials. Therefore, little is known about such irAEs in this population. In this case, risk of ICI-DM as an irAE was likely increased by several factors including family history, a high-risk genetic profile, islet-related immunologic abnormalities, active lymphoma, and HIV infection with a possible immune reconstitution event. Clinicians should maintain a high

index of suspicion for development of irAEs associated with ICI, particularly as use of these therapies broadens. Thorough investigation for presence of higher-risk features should be conducted and may warrant inclusion of pre-therapy genetic and/or autoantibody screening.

**Key Words:** immune check point inhibitors, type 1 diabetes, ICI-DM, HIV, autoimmunity, PD-1

Immune checkpoint inhibitors (ICI) have truly become an important mainstay of anticancer therapy since initial introduction in 2011 [1]. However, concomitant with the rise of immune checkpoint blockade has also emerged a set of side effects known as immune-related adverse events (irAEs) [2, 3]. Checkpoint inhibition can upregulate a number of specific immune signal cascades depending on the site of action, which can result in a wide range of irAEs, from mild individual symptoms to full-blown life-threatening toxicities [3]. ICI-associated diabetes mellitus (ICI-DM) is one such manifestation, particularly noteworthy because of its frequent presentation in diabetic ketoacidosis and near-universal irreversibility [4-6]. While the occurrence of irAEs such as ICI-DM remains somewhat unpredictable, case similarities are increasingly being characterized [2, 4-7]. We herein present to our knowledge the first case of ICI-DM in a patient with human immunodeficiency virus (HIV) and examine retrospectively his risk profile for developing this complication. With these factors in mind, we propose that more thorough assessment of irAE susceptibility through detailed history, genetic screening, and initial antibody titers may be prudent in certain patients with preexisting immune conditions such as HIV.

## Case

A 48-year-old man with stable HIV on efavirenz, emtricitabine, and tenofovir for 5 years and postablative hypothyroidism for Graves' disease in the remote past presented with a palpable right axillary mass. Work up of the mass revealed stage 2B Hodgkin lymphoma, nodular sclerosis type. After his lymphoma proved refractory to 6 cycles of COPP (cyclophosphamide, oncovin, procarbazine, prednisone), 6 cycles of brentuximab (with gemcitabine in cycles 4-6), and 2 cycles of ICE (ifosfamide, carboplatin, etoposide), he was started on therapy with a programmed cell death protein 1 (PD-1) inhibitor, nivolumab, 250mg (3mg/kg) every 2 weeks. Positron emission tomography-computed tomography (PET-CT) showed complete response after 5 months of nivolumab, and treatment was continued to achieve sustained clinical remission.

Eight months into nivolumab therapy, he experienced new and sudden polydipsia and polyuria. Laboratory workup showed severe hyperglycemia (plasma glucose

764 mg/dL) with normal anion gap, glycated hemoglobin (HbA1c) of 7.1%, and random C-peptide of 1.0 ng/mL (1.1-4.4 ng/mL, simultaneous glucose not collected). Glutamic acid decarboxylase (GAD65) autoantibodies were elevated to 73.3 U/mL (0-5 U/mL), whereas islet autoantigen-2 (IA-2) and insulin antibodies were both negative. He was diagnosed with ICI-DM related to nivolumab use. He did not have any personal history of overt diabetes, although impaired fasting glucose was noted, with past HbA1c as high as 6%. Multiple family members had diabetes, including his mother (likely type 1 diabetes mellitus [T1DM]: insulin-dependent, diagnosed in her early teens), his maternal aunt (unknown type, but also on insulin), and his father (type 2 DM). He was started on insulin therapy immediately after diagnosis. Nivolumab was held briefly during initial workup and insulin titration, then subsequently resumed with an infusion frequency decrease to every 3 weeks. After 10 additional months, a repeat PET-CT demonstrated sustained clinical remission, and nivolumab infusions were discontinued. A discussion related to the treatment of this patient's lymphoma and attainment of remission was published previously [8].

Nine months after discontinuation of nivolumab, his lymphoma recurred, and treatment was resumed. However, as the lymphoma did not respond to an additional 9 months of treatment, nivolumab was discontinued, and the patient was enrolled in an outside clinical trial.

Relevant labs and additional studies throughout his 48-month treatment course are displayed in [Table 1](#) and [Fig. 1](#). C-peptide levels were 0.2 ng/mL (simultaneous glucose 59 mg/dL) 1 month after diagnosis and remained low while GAD65 autoantibody titer decreased by about half but remained elevated. Genetic analysis revealed homozygous class II human leukocyte antigen (HLA)-DRB1\*03-DQA1\*0501-DQB1\*02 and heterozygous class I HLA-A23,30-B58,58-C07,07. He has continued to require insulin since diagnosis with ICI-DM.

## Discussion

In this case, development of ICI-DM manifested after the use of the PD-1 inhibitor, nivolumab. Yet importantly, it also occurred in a background environment, including a personal history of preexisting autoimmune disease (Graves' disease) and a family history of possible T1DM, at high risk

**Table 1.** Pancreatic Beta-Cell Function and Endocrine Autoantibody Titers

Months since		Plasma	C-peptide	Proinsulin	GAD65	IA-2	Insulin Ab	TPO (0-34	TSI	21-Hydroxylase
		glucose	(1.1-4.4 ng/	(0-10	(0-5 U/		(<5 uU/	IU/mL)	(0-0.55	Ab (<1.0 U/mL)
HL	Starting	(mg/dL)	mL)	pmol/L)	mL)		mL)		IU/L)	
diagnosis	nivolumab									
22	8	-	1	-	73.3	Negative	<5	-	-	-
23	9	59	0.2	-	80.9	Negative	-	-	-	-
42	28	83	<0.1	0.4	43.5	Negative	-	-	-	-
44	30	22	<0.1	<0.3	49.8	Negative	<5	20	<0.1	-
48	34	304	<0.1	0.4	42.3	Negative	<5	22	-	<1.0

Note, all labs listed are random (not fasting) values

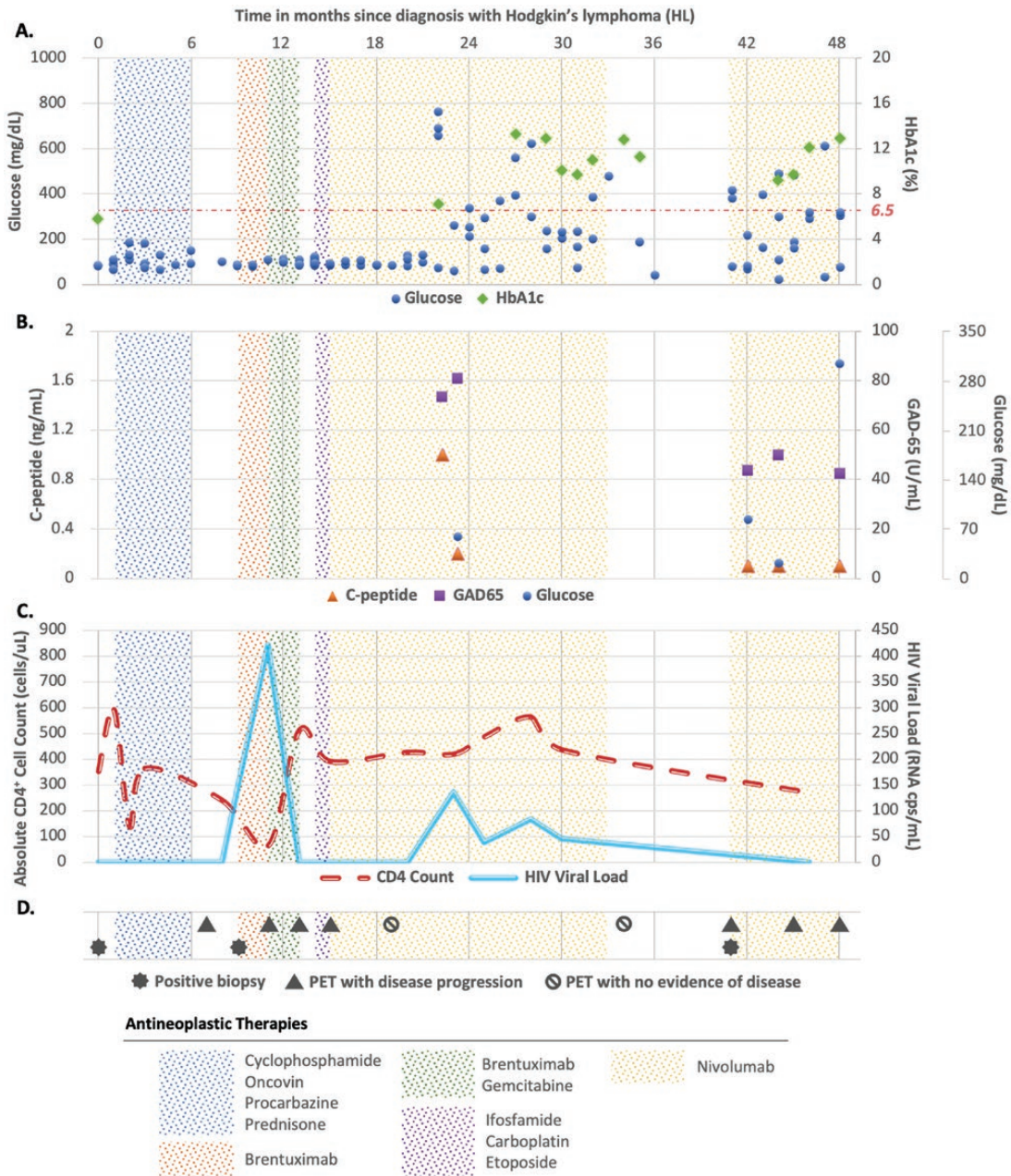
Abbreviations: Ab, antibody; GAD65, glutamic acid decarboxylase antibody; HL, Hodgkin lymphoma; IA-2, islet antigen-2 antibody; TPO, thyroid peroxidase antibody; TSI, thyroid stimulating immunoglobulin.

for progression to overt autoimmune diabetes. As use of these immunotherapies broadens, identification of patients with higher probabilities of irAEs will become increasingly important. Two cases were recently published of immune-related endocrinopathies after ICI use in patients at high risk for autoimmune disease [9]. No case of ICI-DM in an HIV-positive patient has been described. We present this case and propose that this patient, who developed ICI-DM after the use of nivolumab, was distinctly susceptible from a complex combination of factors, including family history, a high-risk genetic profile, islet-related immunologic abnormalities, active lymphoma, and HIV infection with a possible immune reconstitution event.

IrAEs are well-known complications of ICIs and can involve a number of endocrinopathies, including ICI-DM. An increasing number of diabetes cases resulting from the use of ICIs have been reported, and the estimated incidence among ICI users is higher than 0.9%, as originally described [5, 6]. The complication has been further characterized recently [2, 4-6]. A majority of cases are associated with PD-1/PD-ligand 1 (PD-L1) inhibitors and rarely from inhibition of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [4, 7]. ICI-DM usually develops within about 3 months of drug initiation, although timing varies widely, from a few days to more than a year [4-7]. Onset is abrupt, and more than half of cases present with diabetic ketoacidosis [2, 4, 6]. Genetic susceptibility associated with ICI-DM is common, with up to 85% of genotyped patients found to have known predisposing alleles [4, 5]. Interestingly, unlike conventional T1DM, wherein islet-related autoantibodies are present in the majority of patients, autoantibodies only develop in approximately half of ICI-DM cases (although notably, screening for antibodies other than GAD65 has not been universally reported) [4, 5]. One possible explanation of the latter finding is that in ICI-DM, T-cell and autoantibody responses may recognize as-yet-unidentified islet autoantigens.

Our patient's account of his mother's history is compatible with T1DM, although not confirmed. She is described as a "skinny" and "brittle" insulin-dependent diabetic, diagnosed in her early teens. Reporting of family history has been relatively limited in relevant case reports; however, it is notable that approximately 5% to 6% of first-degree relatives of patients with T1DM develop overt T1DM during their lifetimes [10, 11]. Given the frequency of known high-risk haplotypes to T1DM identified in ICI-DM [4, 5, 9], analysis with HLA molecular genotyping was performed in this case. The primary drivers of genetic susceptibility to T1DM are class II major histocompatibility complex (MHC) haplotypes DR/DQ on chromosome 6p21, especially DR4-DQ8 and DR3-DQ2 [11, 12]. Correspondingly, genetic analysis in this patient revealed homozygous HLA DRB1\*03-DQA1\*0501-DQB1\*02 (i.e., DR3-DQ2). Among patients in the Type 1 Diabetes Genetics Consortium (T1DGC), this haplotype conferred a predisposition to disease development with an odds ratio of 3.64 (confidence interval, 2.89-4.58) [12]. Furthermore, polymorphisms within the HLA class I locus have also been associated with the development of T1DM; for instance, HLA A30 may confer increased risk specifically to those with DR3 haplotype [13]. This haplotype was also identified in our patient (heterozygous HLA-A23,30-B58,58-C07,07). As such, this patient already possessed significant antecedent genetic risk toward the development of autoimmune DM.

Unfortunately, GAD65 autoantibody titers prior to nivolumab treatment were not available in this case. There is a wealth of data demonstrating that islet autoantibodies can circulate for years or even decades before disease onset in first-degree relatives of those with T1DM [14, 15]. We cannot speculate on whether they may have been present in this case, particularly as autoimmune DM development was not spontaneous; however, in this subject at risk of developing autoimmune



**Figure 1.** Chart depicts the 4-year time course of this patient’s cancer treatment, from diagnosis (month 0) through enrollment in an outside clinical trial (month 48). The various antineoplastic regimens are shaded according to the legend. **1A.** Details glycemia measurements, including plasma glucose (65-110 mg/dL) and glycated hemoglobin (HbA1c, 4.2%-5.8%). His initial HbA1c corroborates his history of impaired fasting glucose and several early elevations in plasma glucose (months 2-6) are attributable to prednisone therapy; however, an abrupt spike and dispersion of glucose measurements in month 22 indicates the onset of T1DM. HbA1c and glucose variability are increased thereafter. **1B.** Portrays markers of  $\beta$ -islet autoimmunity, i.e., glutamic acid decarboxylase (GAD65) antibody titer (0-5 U/mL), and function, i.e., C-peptide (1.1-4.4 ng/mL). Peak in GAD65 level and drop in C-peptide occur 1 month after diagnosis with T1DM, after which GAD65 slowly trends down while C-peptide remains low. Fasting C-peptides were not able to be obtained; all were random values collected in the early afternoon. Simultaneous plasma glucoses are included where available in each case for reference. **1C.** Outlines absolute CD4<sup>+</sup> cell count (500-1400 cells/uL) and HIV viral load (0 RNA copies/mL) over this time. Of note, month 11 shows a CD4 nadir and simultaneous peak in viral load followed by a sudden and swift restoration of CD4 count and drop in viral load to undetectable level, perhaps suggestive of an immune-reconstitution event. **1D.** Indicates diagnostic and surveillance imaging (PET-CT) and pathology (lymph node biopsies) over the 4-year time period. Complete remission was demonstrated with negative PET-CT scans in months 19 and 34, followed by relapse with disease progression on PET-CT and positive biopsy in month 41.

DM, ICIs may have hastened a durable immune response leading to pancreatic beta-cell damage, and in turn, full-blown diabetes.

Even still, in light of a later demonstration of GAD65 autoantibodies in this patient, it is interesting to note his history of Graves’ disease. Patients with autoimmune



thyroid disease, especially Graves' disease, show higher titers of GAD65 antibodies than the general population, and the presence of both autoimmune thyroid disease and GAD65 antibodies may synergistically potentiate the development of T1DM [16-18]. Thus, in addition to his genetic predisposition to autoimmune DM, the personal history of Graves' disease may have contributed further risk toward ICI-DM.

It is also likely that general autoimmune potential was augmented in this case due to the presence of refractory lymphoma. A small study of patients with temporally coinciding diagnoses of cancer and scleroderma demonstrated the formation of antibodies to a mutated tumor-specific neoantigen (RPC1), which were universally cross-reactive and likely induced the autoimmune development of scleroderma via a resulting immune response to the original nonmutated wild-type antigens [19]. Likewise, a similar mechanism has been proposed to explain the association of class II MHC alleles with the development of T1DM [20]. Moreover, lymphomas have been separately associated with higher frequencies of circulating autoantibodies and increased risk of autoimmune disease development [21]. Taken together, it is therefore reasonable to consider this patient's active lymphoma as a factor increasing his overall autoimmune risk.

A final but critical autoimmune consideration in this patient is HIV. Autoimmune disease in HIV has become a well-known phenomenon since HIV first surfaced in the early 1980s. Persons with HIV demonstrate higher overall prevalence of circulating autoantibodies [22], possibly related to dysregulated B-cell proliferation as well as molecular mimicry with self-antigens, HIV proteins, and tumor neoantigens [2, 23, 24]. Autoimmunity can also be provoked through immune reconstitution, typically developing in the later of 2 phases. The first, more commonly identified phase entails rapid redistribution and recovery of active CD4<sup>+</sup> T-cells, the classic consequences of which relate to direct macrophage action on relatively predictable antigens (e.g., from tuberculosis). The second phase is characteristically delayed 3 to 6 months from the initial rapid CD4 count reclamation, but even up to 2 years in some cases. In this subsequent period, the distinctive feature is the recovery of CD4<sup>+</sup>CD25<sup>+</sup> T-regulatory cells [25]. Several autoimmune manifestations of reconstitution have been described, including hematologic, rheumatic, hepatobiliary, neurologic, and endocrine [25, 26]. However, little has been reported about the occurrence of autoimmune diabetes in HIV. One case series [27] describes 3 HIV-positive patients who developed GAD antibody-positive autoimmune diabetes months after

an immune reconstitution event. All 3 had heterozygous class II MHC antigens with at least one high-risk haplotype. None of the patients were known to be on immune checkpoint inhibitors.

Hence, mere concurrent HIV infection may have further increased the autoimmune milieu in this patient; however, HIV could also have facilitated autoimmunity by way of immune reconstitution. His HIV was historically well-controlled. He continually maintained stable CD4 counts (468-634 cells/dL) and undetectable viral loads since HIV diagnosis and initiation of HAART therapy about 5 years prior to the discovery of his lymphoma. Yet, a couple months after beginning chemotherapy, CD4 counts began to decline. Viral load rose, and then it abruptly fell along with a sudden restoration of CD4 count several months before starting nivolumab (Fig. 1C). This may represent a reconstitution event which conceivably could have precipitated autoimmune disease on its own or could have affected even more favorable conditions for the development of an irAE.

An important factor in immune reconstitution and autoimmune disease development in HIV, particularly as it relates to this case, is the potential complicity of PD-1 in this processes [28, 29]. As a critical site of HIV-related immune dysfunction, or "T-cell exhaustion," interest in PD-1 in the HIV population has grown. Therapeutic inhibition of PD-1 has been forecast as a possible method to reactivate exhausted T-cells and thus reawaken the immune system's response to HIV infection [28]. Moreover, it may also be an effective strategy to target and eliminate those nonproliferating CD4<sup>+</sup> T-cells harboring latent HIV [30]. However, although exciting, these potential antiviral effects have yet to be demonstrated in humans, and there are currently few data toward that end. With the prospect of immunologic complications, patients with HIV were largely excluded from trials of ICIs in cancer treatment. Accordingly, use of immune checkpoint inhibitors against cancer has been limited in these individuals. A 2019 systematic review by Cook et al consisting of 73 patients with HIV who were treated with ICIs (PD-1 inhibitor, CTLA-4 inhibitor, or a combination of both) for advanced-stage cancer did not find a higher incidence of irAEs compared to those without HIV [31]. None of the cases included in this series reported on the occurrence of immune reconstitution associated with ICI treatment. No concerning findings were detected with regard to ICI efficacy or changes in viral load and CD4 count while these patients were on ICI therapy. Yet larger-scale data on the safety and the immunologic repercussions in this population are still primarily lacking. Meanwhile, with increasing popularity, their use has begun to expand,

including among some HIV-infected individuals such as ours [32, 33].

## Conclusion

Currently, in clinical practice, testing for predisposition toward ICI-DM and other irAEs is not commonly performed; however, when using an ICI in a patient such as this, baseline levels of islet autoantibodies and HLA genotyping before initiation could be considered. These data could help assessment of ICI-DM risk and guide monitoring during treatment. Our patient had a preexisting autoimmune disease (Graves' disease) as well as a family history of probable T1DM, likely increasing his risk of developing irAE. Islet cell autoantibodies and HLA genotyping made his predisposition for ICI-DM retrospectively more evident on later analysis. Yet if performed prior to ICI initiation, these tests may have provided a more pronounced anticipation of this risk. In this case, hyperglycemia arose abruptly, but fortunately was detected early. This likely avoided an otherwise probable development of ketoacidosis. Additionally, in HIV-positive patients such as ours, more frequent routine monitoring of CD4 counts and viral load should be considered before and during treatment to avoid potentiating an immune reconstitution-like picture.

As ICIs are more widely used, the incidence of irAEs could be expected to increase dramatically [6]. Likewise, use in broader ranges of patients, including those with a predisposition to autoimmunity, warrants close observation. Herein, we present a case of sudden-onset ICI-DM as a result of PD-1 inhibition in a patient with HLA class II and class I alleles conferring high risk for the development of autoimmune DM. We suggest that certain genetic and immunologic biomarkers may help in identifying risk for and/or early stages of autoimmune diseases, such as ICI-DM. Further research is needed to understand if early serologic analysis for irAEs is warranted in these patients.

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## Additional Information

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**Data Availability:** Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confi-

dentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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