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Cases Presentation

Analysis of the Factors of Therapeutic Failure after Transition to Acriptega: About Two Cases

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Abstract

Acriptega, a combination of Dolutegravir, Lamivudine, and Tenofovir, is a cornerstone of modern antiretroviral therapy due to its efficacy and tolerability. However, treatment failures persist despite this optimization, raising questions about barriers to successful treatment. Through the analysis of two clinical cases, this study explores the biological and behavioral factors contributing to these failures following a switch to this molecule.

The first case is a 69-year-old female patient, diagnosed with HIV in 2002 following pulmonary tuberculosis, who was regularly monitored with an undetectable viral load and a CD4 count > 500 cells/mm³ until the Acriptega transition and the onset of tumor symptoms in 2024. The second case is a 62-year-old female patient, diagnosed with HIV in 2009 following cerebral toxoplasmosis. She was regularly monitored with good treatment adherence and an undetectable viral load. After switching her triple therapy, she developed gastroenteritis, which led to the discovery of her treatment failure.

This case study highlights that failure after switching to Acriptega is linked to the absence of prior resistance testing (genotyping). A safe switchover requires a rigorous assessment of the patient's virological history to prevent the emergence of cross-resistance. Close monitoring via genotyping is essential.

Introduction

In 2026, Dolutegravir (DTG has become a cornerstone of global antiretroviral (ARV) strategies, constituting a treatment of choice in first- and second-line settings due to its efficacy and tolerability. Its high genetic barrier, making it less susceptible to the emergence of resistance, makes it a pillar for the control of HIV infection [1].

In Congo, the transition to Dolutegravir (DTG) was gradual, with significant movement towards its adoption, particularly for new treatment initiations, following global recommendations. Discussions and implementations were observed as early as 2019-2020 and intensified towards 2021-2022 for full integration into the national HIV program, which began adopting DTG for adults and children, marking a key milestone in HIV treatment in the country [2].

However, despite its advantages, recent reports document an increase in DTG resistance, even in treatment-naïve patients or those exposed in utero, raising major concerns for the future of the epidemic. The emergence of these cases, although a minority, calls into question the sustainability of DTG's efficacy and necessitates increased surveillance [3].

This study aims to contribute to the understanding of this

phenomenon by describing the specific mutational profile and the contributing factors associated with virological failure in two patients under DTG-based treatment, in order to guide treatment and monitoring strategies.

Cases presentation

Case 1

This is a 69-year-old widowed homemaker whose husband reportedly died of a stroke. She lives in Brazzaville. She is HIV-positive and receives regular follow-up care with good adherence to her treatment. She doesn't smoke. She is menopausal and reports having abstained from sexual intercourse since her HIV diagnosis. She has no history of HPV infection and has not been vaccinated against HPV.

The early history dates back to 2002 with the onset of a productive cough, a long-term fever, and weight loss.

The cough was productive, with whitish sputum, sometimes streaked with blood. It was accompanied by chest pain, predominantly on the left, without radiation or a feeling of tightness in the chest triggered by coughing. There was no dyspnea or palpitations.

The fever was constant day and night, with a worsening in the evening, accompanied by profuse sweating and chills.

The clinical picture had been the subject of several self-medication attempts and consultations without success. The appearance of progressive weight loss of approximately 15 kg associated with non-selective anorexia and physical asthenia justified a consultation at the internal medicine department of Army Central Hospital "Pierre MOBENGO" to Brazzaville, where, after clinical and paraclinical examination, the diagnosis of pulmonary tuberculosis against a background of HIV-1 infection was made.

The CD4 count is 340 cells/mm^3; viral load measurement is not yet available in Brazzaville. The patient is started on quadruple antituberculosis therapy (Isoniazid INH, Rifampicin RMP, Pyrazinamide PZA, and Ethambutol EMB) and triple antiviral therapy (600 mg Efavirenz EFV, 200 mg emtricitabine FTC, and 245 mg Tenofovir disoproxil TDF) two weeks after the start of antituberculosis treatment.

The patient's condition has improved under treatment, with the disappearance of symptoms. Treatment adherence is good, the CD4 count has been above 500 cells/mm^3 between 2006 and 2022, and the viral load has been undetectable with less than 50 copies/ml of blood since 2018.

The current story dates back to March 2024, with the onset of vaginal discharge associated with pelvic pain.

Vaginal discharge is unusual and abundant. They are white in color, sometimes foul-smelling with a strong, unpleasant "rotten fish" odor, and have a curdled milk appearance. They are accompanied by itching, burning during urination, and slight swelling of the vulva.

Pelvic painare located in the lower abdomen. They are dull and constant of varying intensity, with persistent temporality, like a sensation of heaviness, pressure, cramps, or tension sometimes radiating into the back.

The case warrants a consultation with the internal medicine department from the Army Central Hospital "Pierre MOBENGO" to Brazzaville.

Clinical examination reveals redness, scratch marks, and ulcerations upon inspection of the vulva and perineum; speculum examination reveals small, fragile ulcerations that bleed easily upon insertion of the speculum, and confirms abundant vaginal discharge, white in color, with a strong unpleasant odor of "rotten fish", resembling curdled milk; bimanual vaginal examination reveals adnexal pain and painful uterine mobility.

The samples are taken for biological testing (urine culture with antibiogram, vaginal swab with antibiogram) and reveal 3 germs, namely: Candida albicans, Gardnerella vaginalis, and Trichomonas vaginalis. The CD4 count is 510 cells/mm^3; the viral load is 200copies/ml of blood. The pelvic ultrasound shows no cervical masses, no increase in cervical volume, and no change in its echogenicity. The patient is put on antimicrobials, and counseling on adherence to antiretroviral therapy is provided.

The evolution under treatment is marked by an intermittent symptomatology that necessitates a new gynecological exploration in January 2025.

The speculum examination will reveal a budding, ulcerated, irregular, friable lesion and exophytic bleeding on contact.

Lugol's colposcopy allows for better visualization of the appearance of the odor-negativity of the bud. The cervix remains yellow, contrasting sharply with the rest of the cervix, which is dark brown (due to glycogen deficiency). Atypical, disorganized neovascularization is present. Biopsies are performed.

Histological examination shows the Tumor cells that cross the basement membrane and infiltrate the dermis and underlying tissues; there is cytological atypia and keratinization with horny globes: this is a grade II squamous cell carcinoma.

There are no palpable lymph nodes, and the MRI is still pending.

The CD4 count is 56 copies/mm^3. The viral load is 9,332 copies/ml of blood. The genotypic resistance test shows:

Embarrassed	Mutation sought	Associated resistance	Impact on ACRIPTEGA
Reverse Transcriptase (RTI)	M184V	No resistance to Lamivudine (3TC)	No failure
Reverse Transcriptase (RTI)	K65R	Tenofovir resistance (TDF)	Major failure(TDF component compromised)
Integrase Inhibitor (INI)	N155H + Q148H/R/K	High resistance to Dolutegravir (DTG)	Total failure(inactive EFV component)

Case 2

This is a 62-year-old divorced retired civil servant living in Brazzaville. She is HIV-positive and receives regular follow-up care with good treatment adherence. She avoids contaminated water and food and practices good hand hygiene.

She is menopausal and reports having used protection during sexual intercourse until the onset of her current symptoms. She has no family history of chronic bowel disease or gastrointestinal tumors. She doesn't consume alcohol or smoke.

The early history dates back to 2009 with the occurrence of an altered state of consciousness in a feverish context. The clinical picture begins with intense, band-like headaches without any aggravating factors, temporarily relieved by paracetamol, followed by fever. The fever is persistent, accompanied by chills, sweating, and dizziness. Insomnia is also present.

The clinical picture justifies self-medication. The progressive onset of diffuse pain, physical asthenia, and anorexia prompted a consultation at an integrated health center; a diagnosis of malaria was made based on a rapid diagnostic test (RDT), and the patient was put on treatment.

The occurrence of early postprandial food vomiting episodes, without diarrhea or abdominal pain, not preceded by nausea, not calming the headaches with an alteration of consciousness ranging from obnubilation to drowsiness justifies his admission to the internal medicine department of the Army Central Hospital "Pierre MOBENGO" to Brazzaville, where after clinical and paraclinical exploration, the diagnosis of cerebral toxoplasmosis due to retroviral infection by HIV-1 is made.

The CD4 count is 190 cells/mm^3; viral load measurement is not yet available in Brazzaville. The patient was started on high-dose Cotrimoxazole and triple antiviral therapy (600 mg Efavirenz EFV, 200 mg emtricitabine FTC, and 245 mg Tenofovir disoproxil TDF) two weeks after the start of treatment for cerebral toxoplasmosis.

The patient's condition has improved under treatment, with the disappearance of symptoms. Treatment adherence is good, the CD4 count has been above 500 cells/mm^3 between 2010 and 2022, and the viral load has been undetectable with less than 50 copies/ml of blood since 2018.

The current story dates back to February 2025, with the onset of intermittent, watery diarrhea.

The diarrhea consists of loose stools, occurring 6 to 7 times a day, and is associated with...Cramps, spasms, abdominal pain, and sensations of bloating and urgency to defecate are common. Nausea, vomiting, and intense fatigue are also present. There is no mucus, blood, or undigested food.

The onset of intense thirst, dryness of the mouth and lips, dizziness with decreased urine volume (oliguria), which has become dark in color, and a tendency towards drowsiness warrants admission to the internal medicine department from the Army Central Hospital "Pierre MOBENGO" of Brazzaville.

Clinical examination reveals gastroenteritis complicated by severe dehydration; the etiology to be investigated is HIV-1 retroviral infection.

Parasitological examination of stool samples shows oval oocysts measuring 26 to 29 µm x 13-18 µm, appearing fuchsia red on a blue background with modified Ziehl-Neelsen staining, and which are characteristic of: *Isospora belli. The stool culture is negative.*

*The complete blood count shows leukopenia and eosinophilia; the CRP is 65*mg/L. The *sedimentation rate is 100 mm in the first hour.* The serum creatinine level is 13 mg/dL with a Glomerular Filtration Rate (GFR) of 45 mL/min/1.73 m^2; the blood urea level is 130 mg/dL, and the blood ionogram shows hypokalemia at 2.5mmol/L.

The CD4 count is 82 copies/mm^3. The viral load is 4,800 copies/ml of blood. The genotypic resistance test shows:

Embarrassed	Mutation sought	Associated resistance	Impact on ACRIPTEGA
Reverse Transcriptase (RTI)	M184V	No resistance to Lamivudine (3TC)	No failure
Reverse Transcriptase (RTI)	K65R	Tenofovir resistance (TDF)	Major failure(TDF component compromised)
Integrase Inhibitor (INI)	Q148H/K/R + G140S/A/C	High resistance to Dolutegravir (DTG)	Total failure(inactive DTG component)

The abdominal ultrasound is normal.

Discussion

Discussion of Case 1

Commentary on case 1

Overall interpretation: The case of this 62-year-old patient, living with HIV, highlights the challenges of aging with a chronic infection and the risk of cancers associated with human papillomavirus (HPV), even in the absence of a reported active sex life. Although therapeutic adherence ensures good control of HIV, menopause, and chronic immunosuppression (despite treatment) increase susceptibility to precancerous lesions of the cervix.

The lack of awareness of HPV infection and the absence of vaccination highlight a common preventive gap, even though high-risk HPV can persist for years. Abstaining from sexual intercourse, while protective against new infections, does not eliminate previous infections, making cervical cancer screening crucial for this patient group.

Until 2022, the therapeutic outcome of this patient illustrates the success of the integrated management of TB/HIV co-infection in Brazzaville, despite the initial diagnostic challenges related to the availability of viral load.

Therapeutic strategy and initiation timing before the transition: The choice to start antiretroviral (ARV) treatment two weeks after the initiation of quadruple antituberculosis therapy (RHZE) is in perfect accordance with international recommendations [4-6].

In a patient with 340 CD4/mm^3, a two-week delay allows for a reduction in bacillary load and improved digestive tolerance before the introduction of ARVs, while limiting the risk of Immune Reconstitution Inflammatory Syndrome (IRIS), which is more frequent when CD4 is below 50 cells/mm^3.

The use of Efavirenz (EFV) 600 mg was appropriate here. Although rifampicin is a potent cytochrome P450 enzyme inducer, EFV remains one of the few NNRTIs whose efficacy is maintained when co-administered with antituberculosis treatment, without the systematic need for dose adjustment in many patients [7].

Immunological and virological evolution before the transition: The 16-year trend (2006-2022) demonstrates robust and sustained immune restoration. The increase from 340 to over 500 cells/mm^3 testifies to the excellent efficacy of the TDF/FTC/EFV combination.

This immune response explains the rapid disappearance of tuberculosis symptoms and the absence of relapses or secondary opportunistic infections. Although viral load (VL) testing was only available from 2018 onwards, the confirmed undetectable viral load (<50 copies/ml) retrospectively validates the therapeutic strategy.

This also underlines the importance of the late but crucial access to molecular biology tools in Brazzaville for monitoring the "third target" of UNAIDS 95-95-95 goals.

Compliance and long-term monitoring before the transition: The success of this case is mainly due to exemplary therapeutic adherence. Maintaining an undetectable viral load for more than four years (2018-2022) under a treatment line including EFV requires strict adherence, as Efavirenz has a lower genetic barrier to resistance than newer integrase inhibitors (such as Dolutegravir) [8].

Clinicopathological correlation and diagnostic delay after the transition: The case presented illustrates the critical interaction between HIV infection and the natural history of cervical cancer, classifying this pathology as a defining disease of AIDS.

The period of intermittent symptoms (March 2024 - January 2025) underlines the difficulty of early diagnosis.

The vaginal discharge and pelvic pain were initially mistaken for common infections. The iodine-negative appearance with Lugol's solution (positive Schiller test) confirms the absence of glycogen, a characteristic of neoplastic cells.

The presence of disorganized neovascularization is a strong marker of invasive malignancy. Grade II (moderately differentiated) with keratinized globes confirms a keratinization process, typical of invasive squamous cell carcinomas.

Impact of immunosuppression (CD4 at 56/mm^3) after the transition: A CD4 count < 200/mm^3 is a major risk factor for HPV persistence and rapid progression to invasive carcinoma. A high HIV viral load (9,332 copies/ml) suggests either a lack of antiretroviral (ARV) therapy due to non-adherence or treatment failure, promoting a permissive tumor microenvironment.

Severe immunosuppression complicates tolerance to cancer treatments (radiotherapy/chemotherapy) and increases the risk of opportunistic infectious complications [9].

Challenges of staging and therapeutic perspectives: The absence of palpable lymphadenopathy is reassuring, but pelvic MRI is essential to assess parametrial and lymph node involvement (FIGO classification). Management must be twofold: oncological, according to the MRI stage (concurrent radiotherapy and chemotherapy or surgery), and immunological, for the urgent restoration of immunity with optimized triple antiretroviral therapy to limit tumor progression.

Commentary on the transition

The patient's clinical course, marked by a diagnosis of HIV/Tuberculosis in 2002 and the emergence of cervical cancer in 2024, illustrates the challenges of long-term HIV management. The critical point here lies in the major therapeutic failure during the transition to the TLD (Acriptega) protocol.

Analysis of the Genotypic Resistance Profile:

The resistance test reveals a complex pharmacological situation:

- K65R (TDF): This mutation directly compromises Tenofovir, the mainstay of the Atripla (TDF/FTC/EFV) regimen and Acriptega (TDF/3TC/DTG).

- M184V (3TC/FTC): Although noted without immediate resistance in the genotypic record, it is classically associated with resistance to Lamivudine, but increases sensitivity to TDF (resensitization phenomenon), which makes the simultaneous presence of K65R and M184V particularly deleterious to the INTI skeleton.
- N155H + Q148H/R/K (DTG): This is the most alarming element. The combination of these mutations on the integrase confers high resistance to Dolutegravir, rendering Acriptega completely ineffective.

Impact of the Atripla to Acriptega transition: The switch from Atripla (containing Efavirenz, an NNRTI) to Acriptega aimed to improve tolerance and genetic barrier function. However, in this specific case, this transition was likely carried out under an unsuppressed viral load or with pre-existing archived resistances.

The total failure of the DTG component (Dolutegravir) suggests that the patient has developed cross-resistance or that the selective pressure of prior treatment has promoted the emergence of multi-resistant strains.

Comorbidities and immunosuppression: A diagnosis of cervical cancer in 2024, a condition classified as AIDS-related, indicates persistent or uncontrolled immunosuppression. The interaction between virological failure and HPV-induced carcinogenesis is evident here.

Treatment must now include third-line triple therapy (potentially including boosted Darunavir or Etravirine, depending on remaining sensitivities) alongside the oncological protocol.

Limitations and perspectives: This study underscores the critical need for genotypic testing before any major therapeutic transition in patients with a long history of antiretroviral therapy (since 2002). The choice of Acriptega, while recommended by public health authorities, proved inadequate given the already complex resistance profile.

Summary of the discussion on case 1

This case illustrates a complex situation of long-term HIV management, characterized by major virological failure under third-line treatment (Acriptega/DTG) and oncological comorbidity (cervical cancer). The patient's long history since 2002 suggests potential treatment exhaustion, confirmed by genotypic resistance testing.

The resistance profile shows the persistence of the M184V mutation (conserved 3TC sensitivity) but, more importantly, the presence of K65R, compromising Tenofovir (TDF). The critical element is the double mutation in the integrase gene (N155H + Q148H/R/K), resulting in high-level resistance to Dolutegravir (DTG), the cornerstone of current antiretroviral therapy. This profile of complete failure (major TDF failure + INI resistance) drastically limits therapeutic options.

The occurrence of cervical cancer in 2024, despite regular monitoring, underscores the need for enhanced oncological surveillance in women living with HIV for a long time, even those on treatment. Virological failure leads to chronic immunosuppression, which promotes oncogenic progression.

Management requires multidisciplinary consultation, combining an urgent change in antiretroviral strategy towards molecules with a high genetic barrier and appropriate oncological care.

In conclusion, this case highlights the challenge of managing multi-resistance (particularly to integrase inhibitors) associated with non-communicable comorbidities, requiring more robust surveillance strategies and last-line therapeutic alternatives.

Discussion of case 2

Comment on case 2

Evolving profile before the transition: The profile of this 62-year-old patient, living with HIV and under regular follow-up care, highlights the challenges of aging with HIV in sub-Saharan Africa. The progression from an initial febrile syndrome (misinterpreted as simple malaria) to a syndrome of intracranial hypertension (headache, projectile vomiting without nausea) and altered consciousness (confusion, drowsiness) is pathognomonic of central neurological involvement.

In the context of HIV-1 infection, toxoplasmosis is the most frequent cause of intracranial mass lesions. Diagnosis at the "Pierre MOBENGO" Central Military Hospital in Brazzaville is generally based on clinical presentation (fever, headache, and localizing signs or altered mental status) and imaging, particularly CT/MRI (typical presence of abscesses with target-like contrast enhancement surrounded by perilesional edema).

In malaria-endemic areas like Brazzaville, parasitemia can coexist with other serious illnesses. The failure of antimalarial treatment and the worsening neurological symptoms should have raised concerns about a co-infection earlier. Self-medication temporarily masked the signs, delaying specialized care.

Standard care treatment for cerebral toxoplasmosis relies on the combination of Sulfadiazine and Pyrimethamine (or high-dose Cotrimoxazole as an alternative) along with corticosteroids to reduce cerebral edema. The prognosis depends on the speed with which treatment is initiated and on immune reconstitution with antiretroviral therapy.

Commentary on the transition

Despite good therapeutic adherence guaranteeing a probably controlled viral load and rigorous lifestyle, the

occurrence of gastrointestinal symptoms unexplained by classic risk factors (fecal exposures, family history) requires a thorough diagnostic approach.

Chronic HIV infection, even under antiretroviral therapy, induces a state of chronic inflammation and intestinal dysbiosis, increasing the risk of degenerative or opportunistic infectious gastrointestinal diseases, even in the absence of apparent risk behavior [10].

The context of menopause adds a component of hormonal dysregulation that can affect mucosal health. The absence of tobacco and alcohol limits confounding factors, suggesting an etiology related to premature immune senescence or long-term side effects of treatment, rather than environmental or hygiene-related causes.

Host profile and post-transition opportunism: The diagnosis of isosporiasis (or cystoisosporiasis) in this case is typically associated with advanced HIV infection. With a CD4 lymphocyte count of 82 cells/mm^3, the patient is in a stage of profound immunodeficiency (AIDS), which promotes the emergence of opportunistic protozoa such as Cystoisospora belli. The detectable viral load (4,800 copies/mL) indicates active viral replication, explaining the patient's vulnerability to chronic intestinal infections.

Analysis of the clinical and biological picture: The digestive symptoms, marked by intermittent watery diarrhea since February 2025, are characteristic of isosporiasis. In immunocompromised patients, this parasitic infection is not limited to an acute episode but tends towards chronicity, leading to malabsorption and major fluid and electrolyte imbalances.

Severe hypokalemia (2.5 mmol/L) is a direct consequence of gastrointestinal losses. It constitutes a metabolic emergency that can be life-threatening due to cardiac arrhythmias. Elevated urea (130 mg/dL) and creatinine (13 mg/dL), associated with a decreased eGFR (45 mL/min/1.73 m^2), suggest prerenal (functional) renal insufficiency secondary to severe dehydration.

The elevated ESR (100 mm) and CRP at 65 mg/L confirm a systemic inflammatory state, possibly exacerbated by HIV infection and possible co-infections.

Contribution of parasitology: The definitive diagnosis was made using modified Ziehl-Neelsen staining, the reference technique for highlighting Apicomplexa oocysts. The observed dimensions (26-29 µm x 13-18 µm) and staining affinity (fuchsia red on a blue background) are pathognomonic for Cystoisospora belli.

Eosinophilia noted in the complete blood count, although nonspecific, is a leading biological sign often associated with tissue or intestinal protozoan infections in immunocompromised hosts.

Analysis of the immunovirological status: The patient presents with severe immunosuppression (CD4=82 cells/mm^3), classifying the case as AIDS. The viral load of 4800 copies/ml, although moderate, confirms active virological failure under treatment. This correlation between persistent viremia and a very low CD4 count drastically increases the risk of opportunistic infections.

Impact of Reverse Transcriptase (RTI) Mutations: The K65R mutationis critical because it confers high-level resistance to tenofovir (TDF). It reduces enzymatic susceptibility and decreases the virus's replicative capacity, but it renders the TDF component completely ineffective.

The absence of the M184V mutation. It is important to note that in clinical practice, M184V normally induces high-level resistance to lamivudine (3TC). However, it increases sensitivity to TDF through a compensatory mechanism (resensitization), which is here overridden by the presence of K65R [11].

Resistance to Integrase Inhibitors (INIs): The most concerning point is the association of the Q148H/K/R and G140S/A/C mutations. This profile is the most deleterious for second-generation INIs: The Q148 pathway, combined with secondary mutations (G140), confers total and high-level cross-resistance to Dolutegravir (DTG).

The residual efficacy of DTG, the mainstay of ACRIPTEGA, is zero, which explains the lack of control of viral replication [12].

Analysis of resistances and therapeutic impact: The presence of Q148H/K/R mutations combined with G140S/A/C is critical. Although DTG is known for its high genetic barrier function, this specific combination confers high resistance to second-generation integrase inhibitors. Acriptega thus loses its primary therapeutic driver.

The K65R mutation induces cross-resistance to Tenofovir (TDF), the mainstay of Atripla and Acriptega. While the M184V mutation appears to be absent here (although it is classically associated with lamivudine), the loss of sensitivity to TDF completely disrupts the triple therapy.

Consequences of the Atripla transition towards Acriptega: The switch to Acriptega in 2021, although standardized, appears to have been made in this patient despite a history of pre-existing or acquired resistance to Atripla (particularly via K65R). Failure with Dolutegravir suggests prior uncontrolled exposure to integrase inhibitors or, more likely, functional monotherapy with DTG following established resistance to the other components of the regimen.

With a CD4 count < 200 copies/mm^3, the patient is at the stage of clinical AIDS, at risk of major opportunistic infections.

The persistence of a detectable viral load under DTG-containing therapy, despite resistance mutations, confirms the urgent need for a change in treatment regimen.

The genotypic profile demonstrates multidrug resistance affecting both NRTIs and INIs. The simplified transition strategy of 2021 has reached its limits for this profile. Third-line treatment, potentially including molecules with even higher genetic barriers or new classes (boosted Darunavir), is imperative.

Summary of the discussion on case 2

The case presented illustrates a classic and successful management of a major opportunistic infection, revealing the AIDS stage. The diagnosis of cerebral toxoplasmosis in this patient, with a CD4 count of 190 cells/mm^3, is consistent with data in the literature, which generally places the risk of Toxoplasma gondii reactivation below the threshold of 200 cells/mm^3.

The initiation of treatment with high-dose Cotrimoxazole (in the absence of sulfadiazine-pyrimethamine) remains consistent with international recommendations for resource-limited settings, demonstrating robust clinical efficacy.

A crucial point of this observation is the two-week delay between the start of anti-infective treatment and the initiation of triple antiretroviral therapy (ART).

This timing is optimal: it reduces the risk of developing neurological immune reconstitution inflammatory syndrome (IRIS), which is particularly dangerous in central nervous system disorders, while rapidly restoring cellular immunity. The use of the TDF/FTC/EFV combination reflects the first-line protocols in effect at that time, demonstrating excellent long-term tolerability.

The patient's immunovirological evolution (2010-2022) is exemplary in two respects:

- The increase from 190 to over 500 cells/mm^3 confirms an effective reconstitution of adaptive immunity, ruling out the risk of relapse of toxoplasmosis.
- Sustained viral suppression (<50 copies/ml) since 2018 underscores the importance of rigorous treatment adherence. It also demonstrates the effectiveness of care provided at the Army Central Hospital in Brazzaville, despite initial technical challenges (unavailability of viral load testing in 2009).

This case highlights the evolution of access to healthcare in Brazzaville. While in 2009, monitoring was limited to CD4 counts, the subsequent availability of viral load testing confirmed virological success. This shift from immunological to virological monitoring aligns with UNAIDS' 95-95-95 targets. However, the transition requires... already, resistance genotyping to prevent similar situations.

Understanding the role of SIRT1 modulation in interaction with specific classes of antiretrovirals [13]

SIRT1 mechanism in HIV infection:

SIRT1 acts primarily as an intrinsic restriction factor. It deacetylates the HIV Tat protein, a necessary step for Tat recycling and maintaining efficient transcriptional elongation of the virus.

In case of high SIRT1 activity, Viral replication is slowed down (latency is maintained).

In case of low SIRT1 activity: Viral transcription goes into overdrive, but the cell experiences increased oxidative stress and inflammation.

Interaction with INNTI

Before Acriptega, many patients used Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). NNRTIs are known to induce mitochondrial stress and ROS (reactive oxygen species) production. This chronic stress depletes NAD+ stores, reducing SIRT1 activity.

The patient may exhibit low-grade inflammation (inflammaging) even if the viral load is undetectable. The chromatin architecture around the HIV promoter (LTR) becomes unstable.

Interaction with Integrase Inhibitors

Acriptega contains dolutegravir (DTG). The switch from NNRTIs to INSTIs critically alters SIRT1 dynamics. DTG interferes with divalent metal ions. Some studies suggest this may influence magnesium-dependent pathways that indirectly regulate the NAD+/NADH ratio, impacting SIRT1 efficiency. Unlike NNRTIs, which block DNA synthesis, DTG blocks integration. If SIRT1 is under-activated during the switch, latent reservoirs can be more readily reactivated, creating competition between blocked integration and increased residual transcription.

Analysis of the failure during the transition to Acriptega

In your case study, therapeutic failure could be explained by these two mechanisms related to SIRT1:

Case A: Epigenetic decompensation syndrome: If the patient had very low SIRT1 activity (due to age or long exposure to NNRTIs), the switch to Acriptega suddenly releases the metabolic pressure exerted by the old drugs. Without the "bridle" of SIRT1, the virus can initiate aborted but inflammatory transcription cycles, promoting the emergence of mutations if DTG concentrations are not optimal at the tissue level.

Case B: SIRT1 polymorphism and genetic barrier: SIRT1 modulates autophagy. Transition to DTG requires efficient clearance of defective viral components. Inadequate modulation of SIRT1 prevents the degradation of unintegrated pre-integration complexes (PICs). These PICs can persist as episomal DNA loops (2-LTRs), prolonging immune system exposure and promoting immunological failure despite initial apparent virological suppression.

Discussion of the feasibility, standardization, and clinical utility of measuring plasma SIRT1 levels in routine practice [14]

The integration of SIRT1 (Sirtuin 1) measurement into the monitoring of patients on Acriptega (Dolutegravir/Lamivudine/Tenofovir) in case of therapeutic failure raises major challenges in terms of feasibility, standardization, and clinical utility.

Feasibility and accessibility: Currently, SIRT1 testing is not a routine examination in medical biology laboratories. Its measurement relies primarily on research techniques such as ELISA or RT-PCR (for mRNA), which require specific equipment and reagents not available in most HIV care centers. The high cost of these analyses limits their widespread use, particularly in settings where Acriptega is used as a first-line treatment on a large scale.

Standardization of measurements: There is currently no international consensus on normal reference ranges for plasma SIRT1. SIRT1 levels vary according to age, sex, and metabolic comorbidities, making the interpretation of a single result complex. Without an ISO 15189 standard specifically applied to this biomarker, results lack reproducibility between different laboratories.

Clinical utility in Acriptega failure: In a case study on therapeutic failure, SIRT1 has theoretical interest but still limited practical utility because SIRT1 interacts with the HIV Tat protein to regulate viral transcription.

Failure under Acriptega could be associated with SIRT1 dysregulation, but genotypic resistance testing remains the standard to guide treatment change, and low SIRT1 levels are correlated with chronic inflammation as well as premature aging in HIV+ patients, which could help identify patients at risk of non-virological complications, but not necessarily explain pharmacological failure.

The main causes of failure under Acriptega remain non-compliance with therapy and areas where the measurement of SIRT1 does not provide a direct answer compared to the classic pharmacological assessment.

Conclusion

The analysis of these two clinical cases highlights a paradoxical but instructive situation: the occurrence of a virological failure when switching from a stable combination (Atripla) to a modern regimen based on Dolutegravir (Acriptega), despite prior viral suppression.

There has been a break in virological success. When the viral load was undetectable under Atripla, the switch to Acriptega acted as a revealer of pre-existing or acquired vulnerabilities. Resistance testing confirmed that the failure was not solely due to poor adherence, but to the presence of specific mutations compromising the efficacy of the new treatment line. These cases suggest the possible presence of historical mutations (often M184V/I), which, although "silent" under Atripla, weakened the genetic barrier to the new treatment, thus exposing Dolutegravir to selective pressure.

This study also highlights that the transition to Acriptega, while recommended due to its better tolerability, is not without risk in patients with a long history of treatment. It reminds us of the importance of:

- Therapeutic history: Carefully check for any history of failures under NRTIs before any transition.
- Close monitoring: Strengthen viral load monitoring in the 6 months following a change of strategy ("Switch"), even if the patient was undetectable.
- Access to genotyping: Introduce the stress test as an essential tool to guide the transition and selection of a robust third line.

Ethics and consent

The patient's free and informed consent was obtained in writing, ensuring respect for his dignity, autonomy, and the confidentiality of his personal data, in accordance with the Declaration of Helsinki.

This process ensured that the patient understood the nature, objectives, potential risks, and benefits of this case study, as well as their right to withdraw their consent at any time without prejudice. Consent is documented and retained, confirming the ethical compliance of this publication.

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