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Review

Mechanisms of Arrhythmia and Sudden Cardiac Death in Patients With HIV Infection

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ABSTRACT

Long-term survival of HIV-infected patients has significantly improved with the use of antiretroviral therapy (ART). As a consequence, cardiovascular diseases are now emerging as an important clinical problem in this population. Sudden cardiac death is the third leading cause of mortality in HIV patients. Twenty percent of patients with HIV who died of sudden cardiac death had previous cardiac arrhythmias including ventricular tachycardia, atrial fibrillation, and other unspecified rhythm disorders. This review presents a summary of HIV-related arrhythmias, associated risk factors specific to the HIV population, and underlying mechanisms. Compared with the general population, patients with HIV have several cardiac conditions and electrophysiological abnormalities. As a result, they have an increased risk of developing severe arrhythmias, that can lead to sudden cardiac death. Possible explanations may be related to non-ART polypharmacy, electrolyte imbalances, and use of substances observed in HIV-infected

RÉSUMÉ

La survie à long terme des patients infectés par le VIH s'est considérablement améliorée grâce à la thérapie antirétrovirale (TAR). En conséquence, les maladies cardiovasculaires sont en voie de devenir un problème clinique important dans cette population. La mort subite d'origine cardiaque se classe au troisième rang des causes de mortalité chez les patients vivant avec le VIH. Vingt pour cent des patients vivant avec le VIH qui sont décédés de mort subite d'origine cardiaque présentaient déjà des arythmies cardiaques comme la tachycardie ventriculaire, la fibrillation auriculaire et d'autres troubles du rythme non précisés. Cet article de synthèse présente un résumé des arythmies liées au VIH, des facteurs de risque associés propres à la population vivant avec le VIH et des mécanismes sous-jacents. Par rapport à la population générale, les patients infectés par le VIH ont davantage de conditions cardiaques et d'anomalies électrophysiologiques. Par conséquent, ils présentent un risque accru de développer des arythmies sévères qui peuvent mener à la

With the introduction of more effective treatments for persons infected with HIV, a larger number of patients survive much longer and develop new complications.[1-3] As a consequence, HIV-related heart disease, which—in the earlier years—was not a major complication of HIV infection, is now emerging as an important clinical problem.[4-6] Although we do recognize that the spectrum of cardiovascular diseases in patients with HIV is broad and includes coronary heart diseases and heart failure, this review will focus on sudden cardiac death and cardiac arrhythmias. Mechanistic insight will also be described and most likely involve complex interactions between risk factors, drug treatment, and effects related to immunologic consequences of HIV infection and associated inflammation (Figure 1).

Causes of death in patients with HIV-1 treated with antiretroviral therapy (ART) between 1996 and 2006 in Europe and North America was retrospectively studied in 13 different cohorts.[7] A specific cause of death was found in 85% of the 1,597 patients studied who died during this period. Of the patients in whom the cause of death could be determined, half were due to AIDS and AIDS-related malignancies. Among the non–AIDS-related causes, cardiovascular disease ranks third (7.9%) behind non–AIDS-related malignancies (11.8%) and non–AIDS-related infection (8.2%). Of the 126 deaths from cardiovascular disease, 51 (40%) were coronary heart disease, 23 (18%) were stroke, and 52 (41%) were classified as other heart diseases. It is important to note that cause of death was unknown in 15% of cases and could mask sudden cardiac death.

Cardiac Rhythm Disturbances

Sudden cardiac death

From 2000 to 2009, Tseng et al conducted a retrospective study of 2860 outpatients with HIV, treated or not with

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patients; many of these conditions are associated with alterations in cardiac electrical activity, increasing the risk of arrhythmia and sudden cardiac death. However, clinical and experimental evidence has also revealed that cardiac arrhythmias occur in HIV-infected patients, even in the absence of drugs. This indicates that HIV itself can change the electrophysiological properties of the heart profoundly and cause cardiac arrhythmias and related sudden cardiac death. The current knowledge of the underlying mechanisms, as well as the emerging role of inflammation in these arrhythmias, are discussed here.

mort subite d'origine cardiaque. Ce phénomène pourrait s'expliquer par la polypharmacie s'ajoutant à la TAR, les déséquilibres électrolytiques et l'utilisation de substances que l'on observe chez les patients infectés par le VIH; bon nombre de ces facteurs sont associés à une altération de l'activité électrique cardiaque, augmentant ainsi le risque d'arythmie et de mort subite d'origine cardiaque. Toutefois, les données probantes tant cliniques qu'expérimentales ont également révélé que même en l'absence de médicaments, des arythmies sont présentes chez les patients infectés par le VIH. Autrement dit, le VIH lui-même est capable de causer de profondes modifications des propriétés électrophysiologiques du cœur et d'entraîner des arythmies cardiaques et la mort subite d'origine cardiaque. Les connaissances actuelles au sujet des mécanismes sous-jacents et le rôle émergent de l'inflammation dans ces arythmies sont analysés dans le présent article.

ART, to examine all causes of death in this population.[8] They reported that sudden cardiac death was the third leading cause of death (13%) after AIDS (57%) and overdoses/suicides/unknown causes (19%). Remarkably, sudden cardiac death accounted for 86% of all cardiac deaths and was 4.5 times higher than in the general population. HIV-positive patients who died from sudden cardiac death had more previous hypertension, heart failure/cardiomyopathies, myocardial infarction and arrhythmias (including atrial fibrillation, ventricular tachycardia, and other unspecified rhythm disorders) than persons with HIV who died of AIDS and natural causes.[8]

In the general population, prevalence of sudden cardiac death increases with age and is more common in men than women. This parallels the risk factor for coronary heart disease, which is thought to be the most common cause underlying sudden cardiac death, followed by other structural heart disease such as heart failure and cardiomyopathy. In young adults (< 40 years), 10% of sudden cardiac death is thought to occur in the absence of structural heart disease and is associated with conduction system abnormalities.[9] Non-structural heart diseases associated with sudden cardiac death may include Brugada syndrome, Wolff-Parkinson-White syndrome, idiopathic ventricular fibrillation, as well as congenital or drug-induced long QT syndrome.[10-12] Both forms (congenital and acquired) of long QT syndrome are associated with the development of torsades de pointes, a well-recognized cause of sudden cardiac death.[13,14]

QTc prolongation and torsades de pointes

Acquired long QT syndrome. Torsades de pointes is a life-threatening polymorphic ventricular tachycardia associated with delayed ventricular repolarization reflected on the electrocardiogram (ECG) as a prolonged QTc interval.[14] In the last decade, several groups have reported higher prevalence of prolonged QTc interval in patients with HIV.[15-18] Several studies showed that hospitalized patients with HIV had prolonged QTc intervals: 1.6 to 4 times more than uninfected hospitalized controls.[5,19,20] Table 1 summarizes results of 8 prevalence studies conducted between 1997 and 2017. The reported prevalence of prolonged QTc in HIV populations varied between 7.4% and 37.6%, with a weighted average (by number of patients) of 18.9%. Four of these studies included HIV-negative controls. The prevalence of prolonged QTc in these control populations varied between 7.0% and 16.6%, with a weighted average (by number of patients) of 7.2%.

Compared with the congenital long QT syndrome, the acquired form is a more common cause of QTc prolongation. It refers to the impact of some conditions (hypokalemia or drugs, for example) on ventricular repolarization, mainly via the blockade of the rapidly activating delayed rectifier potassium current (I_{Kr}), encoded by the human ether-a-go-go–related gene (*hERG*).[21,22] A review of monographs and postmarketing studies was conducted to determine whether ART drugs currently prescribed in Canada for HIV-infected patients could prolong the QTc interval. The most preferred initial ART regimen in Canadian HIV-positive patients comprise a combination of nucleotide reverse transcriptase inhibitors (NtRTI: eg, tenofovir), nucleoside reverse transcriptase inhibitors (NRTI: eg, emtricitabine, lamivudine, abacavir), non-nucleoside reverse transcriptase inhibitors (NNRTI: eg, efavirenz) and protease inhibitors (eg, ritonavir, atazanavir).[23] The majority of these drugs do not present clinically significant risks of QTc interval prolongation based on a threshold of 500 ms[24] (or even a lower threshold of 440 ms for some studies or a change of more than 10 ms).[25-31] There is 1 case report of QT prolongation with efavirenz[32] as well as QT prolongation with this same drug in CYP2B6*6*6 allele carriers.[33] On the other hand, a case-control study showed no association between QTc prolongation and this drug.[25] Protease inhibitors (atazanavir, lopinavir and saquinavir)[34-36] have also been pointed out as QTc interval-prolonging drugs (CredibleMeds.org), and *in vitro* studies showed that HIV protease inhibitors block hERG channels.[37] However, this does not seem to translate into a clinical risk for users of protease inhibitors. Indeed, Soliman et al showed a similar and minimal effect on the QTc interval of different protease inhibitor-based regimens (including atazanavir, lopinavir, and saquinavir) compared with NNRTI regimens.[38] In fact, the QTc interval was 1.5 ms lower in patients taking protease inhibitors than in the NNRTI group.[38] The unadjusted mean QTc intervals for users of atazanavir/ritonavir, lopinavir/ritonavir, and saquinavir/ritonavir were 414 ms, 413 ms, and 422 ms, respectively.

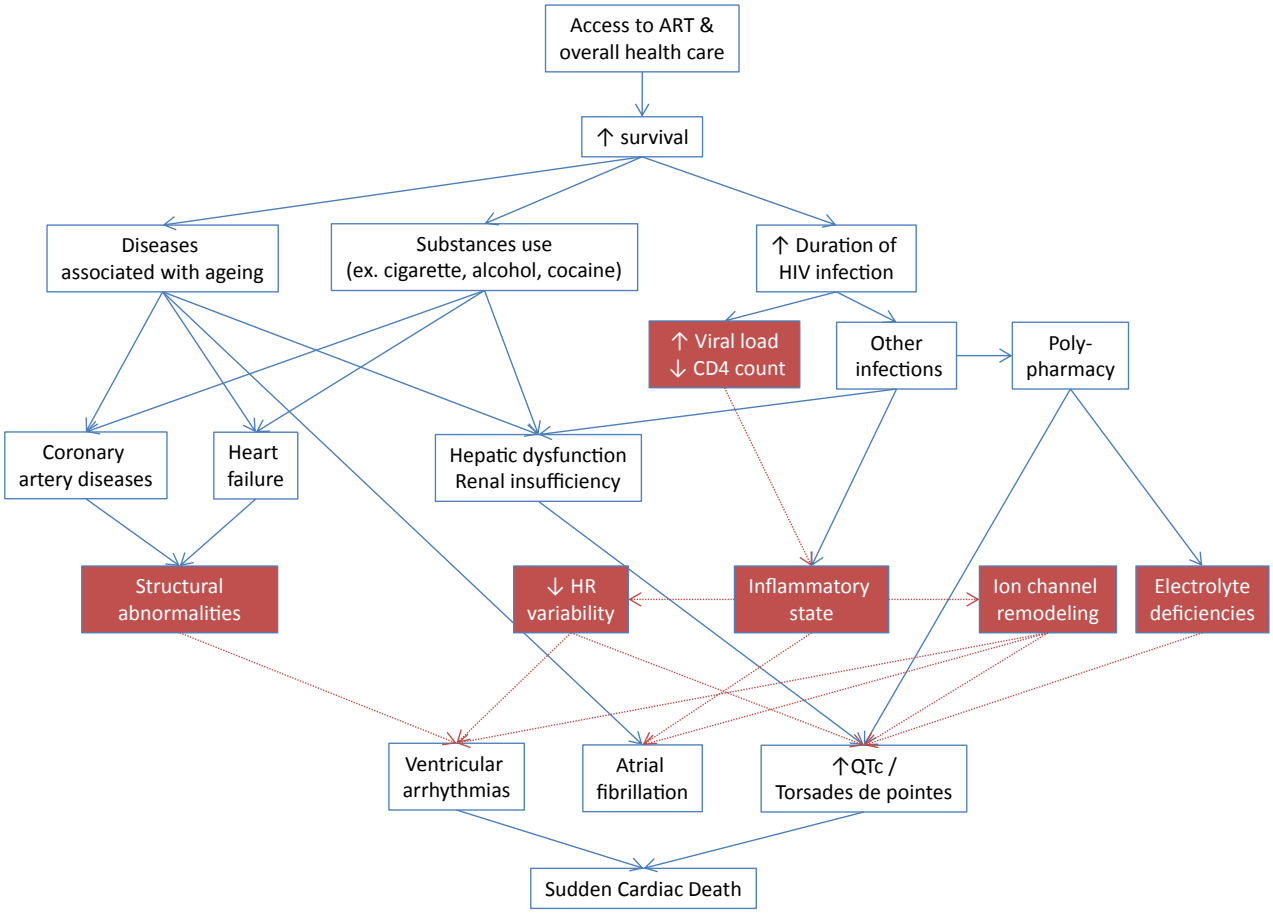

Figure 1. Representation of the complex links between non-exhaustive risk factors, underlying physiopathological mechanisms (**red boxes**), cardiac arrhythmias and sudden cardiac death in HIV population. ART, antiretroviral therapy; HR, heart rate.

Of note, the QTc interval difference between saquinavir/ritonavir users and non-protease inhibitor users has disappeared after adjusting for race. Indeed, more Asians have been treated with saquinavir, and the Asian population is associated with prolonged QTc intervals.[38] None of the 815 patients treated with either atazanavir/ritonavir, lopinavir/ritonavir or saquinavir/ritonavir had QTc intervals greater than 500 ms. Overall, the data presented here suggest that ART regimen in Canadian patients with HIV do not appear to have a clinical impact on the QTc interval.

Polypharmacy. Non-ART medications commonly prescribed to HIV-infected patients—such as macrolides, pentamidine, antifungals, fluoroquinolones, or methadone—may cause greater QTc prolongation concerns than ART. Cases of QTc prolongation and torsades de pointes in patients with HIV receiving high doses of methadone have been reported.[39,40] We recognize that methadone maintenance therapy is recommended as a safe and effective treatment to reduce illicit consumption of opioids and has undoubtedly great benefits in reducing overall morbidity. However, it would be advisable to

Table 1. Summary of prolonged QTc prevalence studies in HIV-infected populations

	Prevalence of QTc prolongation				QTc prolongation threshold	
Reference	HIV+	n	HIV−	n	Men	Women
Kocheril et al[19]	28.6%	42	7.0%	34,181	> 440 ms	
Sani and Okeahialam[5]	37.6%	178	10.0%	80	> 440 ms	
Nordin et al[106]	20.5%	816	16.6%	832	> 470 ms	
Njoku et al[20]	17.4%	166	10.5%	38	> 440 ms	> 460 ms
Reinsch et al[17]	19.8%	776			> 440 ms	> 460 ms
Qaqa et al[18]	17.0%	135			> 440 ms	> 460 ms
Moreno et al[15]	12.4%	194			> 440 ms	> 450 ms
Gili et al[16]	7.4%	351			> 450 ms	> 470 ms

Bazett's formula was used in all studies for heart rate QT correction.
n, total number of patients included in the study; QTc, corrected QT.

limit the number of drugs with known effects on the QTc interval in HIV-infected patients (for example, choose another equivalent antibiotic if available). Moreover, as patients with HIV are often treated with polypharmacy,[41] they have a higher risk of pharmacodynamics and pharmacokinetics interactions.[42-44] Finally, comorbidities such as renal and hepatic insufficiency may be associated with increased plasma concentration of liable drugs.[45-49]

Electrolyte imbalances. Electrolyte disturbance is another factor that can contribute to the increased risk of QTc prolongation in HIV-infected patients. In fact, more than half of the patients infected with HIV complain of gastrointestinal symptoms, especially diarrhea.[50] Acute diarrhea is estimated to be 4 times more prevalent in patients with HIV infection than in seronegative controls, even after adjusting for multiple factors (age, sex, and race).[51] This may be due to the virus itself, opportunistic infections in response to the weak immune system of these patients, ART, or other drug treatments used in HIV-infected patients.[52] As a consequence, electrolyte deficiencies—such as hypokalemia, hypocalcaemia, and hypomagnesaemia—are often reported in this population.

Electrolyte imbalances due to diarrhea, vomiting, use of diuretics, hospitalizations, or nutritional deficiencies also reported in HIV patients become particularly problematic when they cause hypokalemia, a known risk factor for QTc prolongation. Because external potassium ions interact with the pore and influence the rapid inactivation of the channel,[53] low extracellular potassium concentration reduces the outward current generated by hERG channel, even if an increased gradient could theoretically do the opposite.[54] This is of clinical significance because hypokalemia caused by diarrhea or other mechanisms increases the QTc interval and may exacerbate the effects of hERG-blocking drugs. Therefore, electrolyte imbalances—specifically, hypokalemia—represent an important risk factor for torsades de pointes and sudden cardiac death in patients with HIV.

Primary association with HIV infection. Although polypharmacy or electrolyte imbalances, such as hypokalemia, are likely contributors of QTc prolongation in HIV-infected patients, clinical and experimental evidence also indicate a primary association with HIV infection itself.[5,16,20,55,56] Indeed, QTc prolongation and torsades de pointes have been described in HIV-infected patients, even in the absence of drugs. Sani and Okeahialam studied 255 hospitalized patients who were not taking medications known to cause QTc prolongation.[5] Among seropositive but asymptomatic patients, the prevalence of QTc prolongation (greater than 440 ms) was 22 of 78 (28%) and, as they developed AIDS, it reached 45 of 100 (45%). In contrast, prolonged QTc interval was present only in 8 of 80 (10%) of HIV-negative persons. Their study shows that HIV patients had a prolonged QTc interval that was not due to drug treatment, demonstrating that HIV infection itself is associated with prolongation of the QTc interval. In a recent study, Njoku et al showed that the prevalence of QTc prolongation, defined as QTc interval greater than 440 ms in men and 460 ms in women, was 18.2% in HIV-infected patients on ART, 16.4% in HIV-positive ART-naive patients, both greater than the 10.5% reported in controls ($P < 0.01$).[20] These findings support the view that the effects of ART on QTc interval are negligible, as mentioned above. In a retrospective study, Gili et al found that 26 of 351 (7.4%) HIV patients had prolonged QTc interval (defined as $>$ 450 ms in men and $>$ 470 ms in women) regardless of ART.[16] A more advanced state of the HIV infection, defined by a nadir of the $CD4^+$ cell count below 200 cells/mm^3, was the only independent predictor of QTc prolongation in this population (odds ratio [OR] 5.8, 95% confidence interval [CI], 1.3-26.4). Overall, these studies strongly suggest that an underlying feature of HIV affects the electrical properties of the heart.

Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is associated with an increased risk of stroke, heart failure, and overall mortality. The prevalence of AF is approximately 1% to 2% in the general population and increases to nearly 10% in the elderly.[57] Perhaps because of the younger age of those infected with HIV, AF seems to be relatively rare in HIV-positive patients. Accordingly, AF remains largely unexplored in HIV-infected patients with only 2 studies, to our knowledge, that have examined potential association between HIV and development of AF.[58,59] Using a large cohort of American HIV-infected veterans, Hsu et al was the first group to report a significant association between markers of HIV severity and AF.[58] Of the 30,533 HIV-infected patients who participated in the study, 780 (2.6%) developed AF over a median duration of HIV infection of 6.8 years. A low number of CD4+ T cells ($<$ 200 cells/mm^3) and a high HIV viral load ($>$ 100,000 copies/mL) were both independently associated with the development of AF, even after adjusting for traditional AF risk factors. As the HIV registry used by Hsu et al included HIV-infected patients only, this study did not have a comparison group. Recently, Sanders et al compared occurrence of AF and atrial flutter (AFL) between HIV positive and uninfected matched patients.[59] Patients with HIV were frequency-matched 1:2 on age, sex, race, ZIP code, and clinic location with uninfected persons. They reported that AF/AFL were more common in HIV-infected people, with 101 confirmed AF/AFL cases (2.0%) among 5,052 HIV-positive patients and 159 confirmed AF/AFL cases (1.6%) among 10,121 uninfected controls. However, this difference was attenuated by adjustment for AF risk factors.[59] Similar to the findings reported by Hsu et al, a lower CD4+ cell count ($<$ 200 cells/mm^3) was associated with approximately a 2-fold increased risk for AF/AFL, even after adjustment for demographics and cardiovascular risk factors. On the other hand, in this cohort there was no association between high HIV viral load and AF/AFL susceptibility.

Adaptive immune system changes and persistent inflammation have been proposed to be associated with increased risk of AF in HIV-infected individuals. Low CD4+ cells count and high HIV viral load have both been associated with chronic inflammation with high levels of proinflammatory cytokines.[60,61] Previous reports have shown that similar inflammatory markers are also elevated in AF.[62,63] Of note, in their study, Sanders et al reported that each additional year on ART was associated with a reduction of the AF risk.

Moreover, many of the inflammatory markers decrease with ART, suggesting that the increased susceptibility to AF among HIV-infected patients could be through an inflammatory mechanism. Future studies will be required to elucidate the underlying mechanisms by which HIV increases risk of AF. However, based on findings in the ventricle showing profound changes in ionic currents induced by HIV and proinflammatory cytokines,[55,56,64,65] it is tempting to speculate that similar electrophysiological remodelling could also occur in the atrium, which may contribute to the higher incidence of AF in HIV.

With the benefits of ART, the life expectancy of people living with HIV will continue to improve, and the incidence of AF will likely increase, as older age favours AF.[66] In addition to the risk associated with AF, a higher prevalence of cerebrovascular events has been reported in HIV-infected patients.[67] Given that ischemic stroke is one of the main complications of AF, this represents an additional concern for this population.

Autonomic Dysfunction (Reduced Heart Rate Variability)

Compared with the general population, HIV-infected patients have a higher prevalence of autonomic dysfunction, as measured by heart rate variability (HRV).[68-71] Indeed, patients with HIV have decreased HRV, with a shift of cardiac sympathovagal balance that may contribute to predisposition to lethal cardiac arrhythmias. Furthermore, as QTc prolongation is associated with parasympathetic and sympathetic dysfunction,[72] it is not surprising to see that autonomic dysfunction in HIV-infected patients is often associated with prolonged QTc interval that can also lead to severe ventricular arrhythmias.[25] Although sympathovagal balance changes have been correlated with the severity of HIV disease progression,[73] they are already present in the early stages.[69]

The mechanisms underlying autonomic dysregulation in HIV-infected patients are still poorly understood. Recent studies reported greater levels of inflammation in HIV patients with lower HRV.[71,74] Other studies suggest that neurological complications of HIV may also be implicated.[71] Indeed, it has been suggested that at least the regulatory protein transactivator of transcription (Tat) could be associated with changes in cardiac autonomic control as it has been shown to impair cardiac vagal neurons.[75,76] However, ART does not seem to be involved.[77] Further studies are still needed to determine if other mechanisms are implicated.

Mechanisms Underlying HIV-Related Rhythm Disturbances

Cardiac electrical remodelling

The HIV genome consists of at least 9 genes. Among them, *nef* has been shown to be a major determinant for the pathogenicity of HIV. In support of this notion, it has been reported that a cohort of patients infected with a strain of HIV-1 harbouring a *nef* deletion remained asymptomatic for several years without ART.[78] Similarly, strains of simian immunodeficiency virus (SIV) lacking the *nef* gene have also been shown to be less pathogenic in macaques.[79] Small-animal models of HIV infection have been developed to help study HIV-related pathologies. One model of interest is the CD4C/HIV transgenic mouse. The gene *nef* of the HIV-1 genome is expressed in CD4C/HIV transgenic mice under the control of regulatory sequences (CD4C) comprising the murine CD4 gene enhancer and the promoter elements of the human CD4 gene.[80,81] CD4C/HIV transgenic mice develop a severe AIDS-like disease. Their symptoms are similar to those observed in human patients with HIV/AIDS. Using the CD4C/HIV transgenic mouse model, our group has made significant progress in understanding the mechanisms underlying cardiac arrhythmias associated with HIV. We first showed rhythm disturbances associated with severe ventricular electrophysiological remodelling that occurred in the absence of any pharmacological intervention.[55,56,64,65] Notably, the QTc interval and the ventricular action potential duration (APD) were significantly prolonged in CD4C/HIV transgenic mice compared with littermate controls. The 2-fold increase in APD was attributable to a 50% reduction in the major repolarizing outward potassium currents present in mouse ventricular myocytes: the transient outward K^+ current (I_{to}), the ultrarapid delayed rectifier K^+ current (I_{Kur}) and the steady-state K^+ current (I_{ss}).[55] In addition, the depolarizing sodium currents (I_{Na}) were also reduced by 30% in these mice.[64] Thus, the net effect was an alteration in conduction velocity and repolarization, 2 risk factors for arrhythmias. It is interesting that all these effects involved no changes in cardiac function or morphology as assayed by echocardiography.[55] Although we recognize that direct extrapolation of animal data to humans is difficult and that mice and humans share some components of ventricular repolarization K^+ currents but not all,[82] this study clearly shows that HIV had a similar physiological effect on the duration of the QTc interval in both species. These data provided the first experimental evidence that HIV itself might be directly implicated in inducing cardiac electrical remodelling in HIV.

Subsequently, using pharmacological tools, other groups examined the impact of another HIV-1 encoded protein, Tat, on HIV-related QTc prolongation.[83,84] Tat is important for HIV transcription and pathogenicity.[85] Bai et al first reported that a 24-hour incubation with 200 ng/mL of Tat protein significantly reduced hERG current in HEK293 cells through increasing ROS generation.[83] In addition, they also reported that *in vivo* treatment with Tat protein reduced I_{Kr} currents and prolonged the APD of guinea pig ventricular myocytes. Recently, Tat transfection in COS-7 cells has been reported to decrease hERG current by 50% and the KCNE1-KCNQ1 current (the slowly activating delayed rectifier K^+ current, I_{Ks}) by 69% through reduction in availability of phosphatidylinositol-(4,5)-bisphosphate (PIP2).[84] Concurrently, the authors reported that a 24-hour incubation of hiPSC-CM with Tat protein (200 ng/mL) reduced I_{Kr} by 31% and led to a prolongation of ventricular-like APD at 70% and 90% of repolarization. Given the importance of *nef* and *tat* in the pathogenicity of HIV, these cellular effects may contribute to the higher prevalence of QTc prolongation and increased sudden cardiac death risk in patients with HIV.

Known risk factors for QTc prolongation/torsades de pointes	General/control population	HIV+ population
Older age	53.8% < 40 years old*	60.5% < 40 years old †
Female sex	0.99 male : 1 female‡	4.5 male : 1 female[107]
Congenital long QT syndrome	Equal risk in both populations	
Underlying heart disease	1x	1.5x[108, §]
Electrolyte imbalance (eg, ↓ K^+)	~ < 2%[108]	19%[109]
Increased inflammatory status¶	-	56% (HIV+ on ART) 26% (HIV+ ART naïve)[110]
Polypharmacy	11.6%	24.4%[41]

Lower prevalence in the HIV compared with the general/control population
Equal prevalence in the HIV compared with the general/control population
Increased prevalence in the HIV compared with the general/control population

Figure 2. Comparison of risk factors for QTc prolongation/torsades de pointes between the general/control and HIV-infected populations. ART, antiretroviral therapy; QTc, corrected QT. *United States Census Bureau: Profile of General Population and Housing Characteristics: 2010: https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=DEC_10_DP_DPDP1&src=pt. †Center for Disease Control and Prevention: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2016-vol-28.pdf. ‡United Nations Population Division: http://data.un.org/en/iso/ca.html. §The incidence in HIV-infected patients is approximately 1.5 times higher than in the general/control population. ¶Reported as % of patients with level of high-sensitivity C-reactive protein above 3 mg/dL, the cut-off point for increased risk of cardiovascular complications.

Implication of Cytokines in Electrical Remodelling

As it is well known that cytokines mediate HIV-related pathologies, we examined serum levels of proinflammatory cytokines in CD4C/HIV mice and found a significant increase in the concentrations of tumor necrosis factor α (TNFα) and interleukin-1β (IL1β), both at the top of the inflammatory cascade.[86] To distinguish the specific roles of each cytokines, we examined the effects of TNFα and IL1β on ventricular ionic currents.[56,65] Results demonstrated that long-term exposure to clinically relevant concentrations of proinflammatory cytokines reduced the current density of several ionic currents. Specifically, IL1β decreases the calcium currents, whereas TNFα reduces potassium and sodium currents without affecting calcium currents. The net effect of the decrease in these ionic currents in response to cytokines may be detrimental. Indeed, by affecting conduction velocity, prolonging repolarization, and decreasing calcium currents, the risk of arrhythmia is significantly increased. Together, these results may contribute to explain the role played by inflammation and proinflammatory cytokines in the development of electrical remodelling and associated cardiac arrhythmias in the setting of HIV infection. Nevertheless, this question warrants further investigations.

Other Possible Mechanisms Increasing the Risk of Arrhythmia in HIV Patients

Recreational drugs

People living with HIV have a greater prevalence of substance use than the general population.[87-94] The negative effects of tobacco smoking, alcohol,[95] and illicit drugs (eg, cocaine and heroin) have been documented on outcomes of HIV such as ART nonadherence.[88-91] Beyond these effects, tobacco smoking,[96] alcohol,[97] and cocaine[98] are well known for their cardiac toxicity and put patients at risk for coronary heart disease, heart failure, and arrhythmias. Moreover, reports suggest that at least some of these substances can directly block the hERG channel.[99-104] This may contribute to increase the risk of QTc prolongation and torsades de pointes; however, further studies are required to clearly determine the impact of these substances on the electrical properties of the heart.

Conclusion

Sudden cardiac death is now the third leading cause of death in patients with HIV.[8] The complex medical, pharmacological, and environmental profiles of this population are

associated with several known risk factors of arrhythmias and sudden cardiac death (Figs. 1 and 2). Although it is generally recognized that arrhythmias can occur as a result of drug treatments, substance use, or electrolyte imbalances, accumulating evidence also supports the involvement of HIV in itself.[5,16,20,55,64] Transgenic mouse models helped to provide a better understanding of the pathophysiological mechanisms of HIV-related arrhythmia and strongly support a role for inflammation and proinflammatory cytokines on cardiac ion channels and associated pathologic electrical remodelling.[55,56,64,76,85,105] Additional studies are needed to better understand the complex links between modifiable risk factors of arrhythmias in patients with HIV and to determine if pathological electrophysiological processes can be reversed if they are corrected.

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The authors have no conflicts of interest to disclose.

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