HIV, Cardiovascular Diseases, and Chronic Arsenic Exposure co-exist in a Positive Synergy

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Abstract

Recent epidemiological evidences indicate that arsenic exposure increases risk of atherosclerosis, cardiovascular diseases (CVD) such as hypertension, atherosclerosis, coronary artery disease (CAD) and microangiopathies in addition to the serious global health concern related to its carcinogenic effects. In experiments on animals, acute and chronic exposure to arsenic directly correlates cardiac tachyarrhythmia, and atherogenesis in a concentration and duration dependent manner. Moreover, the other effects of long-term arsenic exposure include induction of non-insulin dependent diabetes by mechanisms yet to be understood. On the other hand, there are controversial issues, gaps in knowledge, and future research priorities of accelerated incidences of CVD and mortalities in patients with HIV who are under long-term anti-retroviral therapy (ART). Although, both HIV infection itself and various components of ART initiate significant pathological alterations in the myocardium and the vasculature, simultaneous environmental exposure to arsenic which is more convincingly being recognized as a facilitator of HIV viral cycling in the infected immune cells, may contribute an additional layer of adversity in these patients. A high degree of suspicion and early screening may allow appropriate interventional guidelines to improve the quality of lives of those affected. In this mini-review which have been fortified with our own preliminary data, we will discuss some of the key current understating of chronic arsenic exposure, and its possible impact on the accelerated HIV/ART induced CVD. The review will conclude with notes on recent developments in mathematical modeling in this field that probabilistically forecast incidence prevalence as functions of aging and life style parameters, most of which vary with time themselves; this interdisciplinary approach provides a complementary kernel to conventional biology.

ABBREVIATIONS: As₂O₃, arsenic trioxide; AsV, arsenate; AsIII, arsenite; CAD, coronary artery disease; CVD, cardiovascular disease; EC, endothelial cell; NO, nitric oxide; NOS, nitric oxide synthase; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species.
Introduction

The World of Arsenic

The knowledge of medicinal and homicidal use of arsenic can be traced back to the early days of human civilization. The poisonous and carcinogenic properties of arsenic compounds, or “Arsenicals”, have been known for more than 2000 years [2, 3]. In the west, much of the current awareness can be traced back to the 1944 comedy movie Arsenic and Old Lace (http://www.imdb.com/title/tt0036613/). Emperors, kings, arctic explorers, heirs and commoners have been treated with arsenicals for both legitimate and homicidal purposes. A popular myth suggests that in 55 AD, the infamous Roman emperor Nero poisoned his stepbrother Britannicus with arsenic before his 14\textsuperscript{th} birthday. Conversely, Hippocrates used arsenicals to treat ulcers.

In the course of time, Arsenicals made their place in medicine for treating sleeping sickness, syphilis, tuberculosis and certain skin diseases. In the early 1800s, Arsenic exposure was linked to cancer leading to a progressive diminution in its medicinal use. Arsenical have widespread use in embalming during and after the American Civil War, and today, Arsenic leaching from old cemeteries is a known groundwater pollutant in the Unites States. Arsenic has been used widely in the United States as a wood preservative until the year 2004 [4]. Eventually, as wood comes into contact with soil and water, it releases Arsenic to the environment. This is a major source of Arsenic in the environment, in particular in children playgrounds. In addition, Arsenic plays an important role in the semiconductor industry in the form of gallium arsenide, a compound used in a wide range of electronic devices [5].

Sources of Occupational Exposure to Arsenic

1. Semi-conductors industry, notably of fast chips based on gallium arsenide often involving the toxic gas ARSINE, AsH\textsubscript{3}.
2. Glass manufacturing.
3. Mining operations and purification of metal ores and metals. Specifically, sulfide base ore processing (iron pyrite, lead sulfide)
4. Manufacturing of certain drugs, Cattle and poultry food additives (some anti-cancer drugs, e.g. Roxarsone).
5. Manufacturing and use of pesticides and insecticides which contain Arsenic.
6. Wood Treatment
7. Rat and animal poisons.
8. Old paints

N.B. Although in most countries the use of Arsenic and its compounds for Applications 5, 6, 7 and 8 has been banned or discontinued, there are still many products that contain Arsenic which were manufactured before the ban took effect. This includes:

- Old paints
- Wood treatment
- Manufacturing of certain drugs
- Rat and animal poisons
- Semi-conductors industry
Most Arsenic in the terrestrial environment is found in rocks and soils. Arsenic in surface and ground water is mostly a mixture of arsenite and arsenate. Arsenic is widely distributed in food; particularly high levels are found in seafood [6]. The major man-made sources of Arsenic include coal combustion, nonferrous metal smelting, and the burning of agricultural wastes. Arsenic compounds have been widely used as herbicides, fungicides, wood preservatives, desiccants, cattle and sheep dips, and as coloring agents. Arsenic continues to be widely used in agriculture, in glass and ceramics, as a metal alloy, and in semiconductors and other electronic devices. In the past, Arsenic containing rodenticides and ant poisons were responsible for many exposures. Suicidal and homicidal poisonings continue to be reported. Bacteria within soils and sediments can transform arsenate to arsenite, which can be converted into methylarsenic acid. Also within the soils and sediments, bacteria can transform methylarsenic acid into dimethylarsinic acid. All these arsenic compounds are then sublimated through rain and thereby percolate into drinking water. Molds can convert methylarsenic acid into trimethylarsine, which can then also be available within water. In addition, molds and bacteria can convert dimethylarsinic acid into both trimethylarsine and dimethylarsine in water. Once in water, trimethylarsine and dimethylarsine can volatilize into the atmosphere. Therefore, different forms of Arsenic can be found in the soil, sediments, water, atmosphere and the food chain. (Reviewed in:[7]).

Non-occupational human exposure to arsenic in the environment is primarily through the ingestion of food and water [8, 9]. Arsenic has been detected in groundwater in several countries of the world, with concentration levels exceeding the WHO drinking water guideline value of 10 µg/L (WHO) as well as the national regulatory standards (e.g. 50 µg/L in India and Bangladesh)[10, 11]. Arsenic in groundwater is often associated with geologic sources. Today, arsenic contamination of drinking water is a major worldwide public health problem. A very large number of people in India and in different parts of the world (countries like Bangladesh, Chile, Taiwan, Mexico, Thailand, Germany and parts of China) are being highly affected due to the intake of arsenic contaminated ground water [8, 10-12]. A significant fraction of the population living in the Indian districts of West Bengal (e.g. Maldaha, Murshidabad, Nadia, Bardhaman, Hooghly, 24-Parganas, and Kolkata) are also under heavy environmental exposure to arsenic and suffer from the effects of chronic arsenic toxicities initiating an alarmingly high incidence of skin, bladder and lung and also ‘Blackfoot’ disease (arsenic induced oxidative stress, microvascular damage and gangrene of foot)[13-16].

The daily intake of total arsenic from food and beverages is generally between 20 and 300 µg/day. Foodstuffs such as meat, poultry, dairy products and

| Sources of Exposure to Arsenic in Daily Life. |
|------------------------------------------------|
| 1. Most drinking water contains small amounts of Arsenic. Natural water leaches small amounts of Arsenic from rocks and sand. Some industrial operations sometimes contaminate water with Arsenic. |
| 2. Arsenic was found in items such as wine, juice, syrup, glues and pigments. |
| 3. Arsenic is found in many foods both as organic compounds such as methyl arsines, and as inorganic arsenates and arsinates. The organic compounds are less toxic than the inorganic compounds. |
| 4. Inorganic arsenic compounds were found in apple juice, orange and grapefruit juice, in vinegars and salad dressings, in milk and dairy products, beef, pork, poultry and in cereal. |
| 5. Arsenic is found in most unshelled rice but also in shelled rice and in its products. |

**Roxarsone** is an organoarsenic compound that is widely used in the poultry, pork, and cattle industry as a food additive to increase weight gain and improve feed efficiency. The drug was also approved in the United States for use in pigs. Roxarsone is marketed** as 3-Nitro by Zoetis, a former subsidiary of Pfizer. In 2006, approximately **one million kilograms** of Roxarsone were produced in the U.S. **Use of Roxarsone was discontinued in the US since 2011**
cereals have higher levels of inorganic Arsenic [17]. Pulmonary exposure may contribute up to approximately 10 µg/day in a smoker and about 1 µg/day in a non-smoker, and more in polluted areas. The concentration of metabolites of inorganic arsenic in urine ranges from 5 to 20 µg of Arsenic/liter, but may even exceed 1000 µg/liter. In workplaces with up-to-date occupational hygiene practice, exposure generally does not exceed 10 µg/m³ (8-h time-weighted average). Concentrations as low as 0.5 ppm Arsenic may trigger the initial symptoms of exposure [18].

The symptoms of small-to-moderate exposure to arsenic may appear immediately or only after several hours include headaches, vertigo and nausea. Subsequently, problems related to oxygen transfer in the body due to interferences with the hemoglobin, along with possible impairment of renal functions.

Exposure to small doses of Arsenic compounds over a long period of time can result in lung, skin or liver cancer, or cancer of the lymphatic system [19], including damage to organs, such as the esophagus, as also confusion and disorientation. Arsenic mainly enters via drinking water or food that has been eaten but it can also penetrate into the body through the skin or the lungs [20].

Most Arsenic compounds are soluble in water to some extent and thus are easily transported in the blood stream and assimilated by the body. The water solubility also helps remove some of the Arsenic via the urine and the excrement. The urine and other excrements may change to darker red-brown or even greenish color [21]. Notably, a significant portion of the ingested Arsenic is absorbed by various bodily tissues and is retained over an extended period of time. Some of the Arsenic that enters the body is excreted out of the body rather rapidly but a fraction of it accumulates in various organs including the blood vessels in addition to the hair and the nails. The fraction of Arsenic that is retained in the body depends on the specific Arsenic compound that entered, the portal that it entered through, i.e. ingestion or inhalation, and other components present in the food that were consumed together. While such arsenic based toxic wastes are liberated very slowly, nevertheless they cause physiological damage in various organ systems [22].
Recent clinical research has shown that arsenic trioxide, administered intravenously, could induce cancer remission in some people with refractory acute promyelocytic leukemia [23, 24]. Although the highly suggestive but inconclusive epidemiological evidences support the Arteriosclerotic lesions, ischemic heart disease and thereby increased mortality risk was increased among arsenic-exposed persons [25, 26]. Arsenic can trigger multiple abnormal electrocardiographic patterns not limited to ventricular tachyarrhythmia [27, 28]. While the carcinogenic and cancer therapeutic potentials of arsenic have widely been studied, there is a relatively smaller attention to arsenic induced CVDs [29].

**Arsenic and Cardiovascular diseases**

Being long considered a potent human health hazard due to its neoplastic outcomes, Arsenic also shows increasing epidemiological evidence of links between Arsenic exposure and risks of CAD and CVDs. As mentioned earlier, Arsenic is a major risk factor for the endemic peripheral artery disease characterized by severe arteriosclerosis and subsequent gangrene of affected extremities, so-called “Blackfoot” disease (BFD) [30, 31]. In addition, systemic vascular disease have been epidemiologically linked to chronic Arsenic exposure. High mortality from ischemic heart disease was first reported in copper smelter workers who were exposed to arsenic [32]. In the United States epidemiological studies correlations between standard mortality ratios for cardiovascular diseases and arsenic levels in food and drinking water [33, 34]. In our experimental system acute exposure of inorganic arsenic induced tachycardia in isolated amphibian hearts similar to adrenalin that could have been blocked by a beta blocker (Figure 1). Ischemic heart disease and cerebral infarction are considered late clinical manifestations of generalized atherosclerotic process and ultrasound studies in the superficial carotid artery indicated a dose response relationship between carotid atherosclerosis and chronic exposure to arsenic [33, 35, 36]. In the aforementioned studies, a significant biological links have been observed after careful adjustment of the statistical data for major CVD risk factors, signifying arsenic exposure as a potential independent risk factor for atherosclerosis, CAD, and increased incidences of cardiovascular morbidity, mortality.
Chronic low dose exposure to Arsenic induce endothelial dysfunction

The endothelium, being most sensitive to systemic or micro-environmental stress, is one of the prime target of chronic arsenic toxicity. Naturally occurring and highly toxic inorganic form arsenic rapidly induces reactive oxygen species (ROS) formation and thereby induce proliferation response in vascular smooth muscle cells. The net effect of such activity is attenuation of endothelium-dependent conduit artery dilation via downregulation of endothelial NO synthase, events that are temporally matched to the accumulation of oxidants across the vessel wall. Reduced expression of endothelial nitric oxide synthase (eNOS) leading to diminished bioavailability of vasodilating nitric oxide (NO) is a hallmark of endothelial dysfunction.

A number of earlier publications indicate that Arsenic imposes serious threats to cardiovascular health and co-morbidity. Reports of chronic arsenic exposure induced CVD related mortality, endothelial dysfunction, dysregulated lipid metabolism, and some other detailed mechanistic studies are also starting to emerge [1, 37-41]. Moreover, in a recent study it was shown that even habitual fish intake, although generally reflect healthier dietary habits with favorable effects on the endothelial function, can actually increase the chronic exposure levels of Arsenic and subsequent deleterious alteration in the arterial flow mediated dilation (FMD) – a clinical indicator of endothelial dysfunction [42]. Chronic low exposure to arsenic induce Cyclin D1 dependent NFκB/BCL3 mediated pathways leading to cellular proliferation [43]. In addition, other associated deleterious effects of chronic Arsenic exposure includes generation and persistence of proactive platelet, induction of dyslipidemia and increase endothelial adhesion of activated monocytes initiating a pro-atherogenic condition [38, 44].

Our recent studies indicate that a range of ultra-low concentrations of Arsenic (10nM – 10µM) exposure significantly down-regulate the mRNA levels of eNOS in addition significantly diminished expression of Krüppel-like Factor 2 (KLF2) and Krüppel-like Factor 4 (KLF4) in HUVEC (not shown), and in primary human aortic endothelial cells respectively. Krüppel-like factors 2 and 4 are pivotal laminar flow inducible transcription factors that modulate several genes critical for maintaining an antithrombotic endothelial surface [45, 46]. KLF2 is a key determinant of the anti-inflammatory and anti-atherogenic vascular environment [47-49], and a potent inducer of endothelial nitric oxide synthase (eNOS) [50]. KLF2 blocks expression of the procoagulant Tissue Factor [51] and also inhibits thrombin-induced activation of endothelial cells by decreasing expression of the thrombin-activated protease activated receptor type 1 (PAR-1), conversely, TNF-α, IL-1β, and oxidative stress, repress KLF2 expression in the endothelial cells (EC) [52]. KLF4 is also an independent regulator of EC function, and is protective against atherosclerosis [53]. According to reports, Krüppel-like factors (KLFs) are important mediators of monocyte differentiation and activation as well. KLF2 is a negative regulator of proinflammatory genes both in the ECs and monocytes and expression of KLF2 in monocytes is reduced following exposure to TNF-α or LPS and in monocytes from patients with coronary artery disease [54]. Krüppel-like factor 4 is also involved in myeloid cell differentiation [55] and is a critical regulator of macrophage polarization; in vitro exposure of mouse macrophages to LPS, proinflammatory
cytokines, or oxLDL, results in decreased KLF4 levels [53, 56]. Mouse macrophages deficient in KLF4 have enhanced foam cell formation in response to oxLDL [53]. Our preliminary observations shows brief exposure of inorganic Arsenic in nanomolar concentration induce significant down-regulation of several other endothelial regulator genes including increased expression of VCAM-1, and E-selectin (unpublished observations, not shown) in HUVEC (Human Umbilical Vein Endothelial Cell).

To determine whether the reduced eNOS expression in Arsenic exposed endothelial cells and other peripheral blood mononuclear cells (not shown), could be linked to a reduced expression of endothelial KLF4 (and KLF2: not shown), we examined nuclear KLF4 levels by immunofluorescence microscopy, normalizing the digitized nuclear KLF4 fluorescence to nuclear DNA (as measured by DAPI fluorescence). We observed significantly reduced KLF4 expression in Arsenic exposed primary human aortic endothelial cells when compared to the KLF4 expression in untreated control cells (Figure 2a. ***p < 0.001).

Interestingly, when the nuclear levels of histone H3, as an internal control, was measured using identical parameters no such dose or time dependent effect of Arsenic exposure on in the endothelial cells was observed (Figure 2b.). We confer, the vascular micro-environment during Arsenic exposure is pathologically modified characterizing a diminished expression of the anti-inflammatory and anti-atherogenic transcriptional regulator KLF2 and KLF4 in addition to significant reduction in eNOS production and increased expression of endothelial adhesion molecules, like VCAM-1 and E-selectin. Here, we provide a comprehensive set of data showing the effects of low dose Arsenic exposure (10µM) at different time point on cultured primary human aortic endothelium from descending thoracic aorta (Figure 2).

Figure 2: Arsenic exposure reduce Krüppel-like Factor 4 expression in human aortic endothelial cells in a time and dose dependent manner. Human primary aortic endothelial cells were grown in sterile chamber slides, and exposed to 10mM of Arsenic at the indicated time points. The cells were subsequently immunostained and digital images were recorded by epi-fluorescence microscopy (EVOSÒFL, Life Technologies) using a 100X objective (20X images for large scale data acquisition and analyses) for the detection and analysis of nuclear KLF4 (Panel a) and Histone H3 (Panel b.) as internal control. Quantitative fluorescence intensity ratio (KLF4:DAPI) data of 100 cells at each time point from 3 independent experiments are presented to the right of each panel. The data were compared using a two tailed Mann Whitney test. ***p<0.001.
Arsenic-induced molecular and cellular events related to atherogenesis: In vitro studies cultured human endothelial cell indicate that arsenic can initiate oxidative damage, activation of transcription factors, and gene expression relevant to endothelial dysfunction and CVDs (Figure 3). Chronic exposure to Arsenic is also a potential risk factor for type 2 diabetes. Exposure to inorganic Arsenic induces pre-diabetic effects by altering deregulating lipid metabolism, gluconeogenesis and insulin secretion in healthy individuals, and worsens glucose metabolism in established diabetics although insulin resistance might be not the sole reason of diabetic effects caused by inorganic Arsenic [57].

**Arsenic exposure, cardiovascular diseases and global HIV incidences:** Cardiovascular abnormalities are common in HIV-infected individuals but often go unrecognized or untreated, which results in increased cardiovascular-related morbidity and mortality and reduced quality of life. Clinicians may mistakenly attribute signs of cardiovascular abnormalities to pulmonary or infectious causes, an error that can delay appropriate treatment. Despite a dramatic improvement in survival in the antiretroviral therapy (ART) era, there remains an increased risk of thromboembolic and cardiovascular co-morbidities in these treated [58-60]. The core mechanism(s) that contribute to this increased risk of CVD in HIV disease have not been fully elucidated, but may be partially related to chronic immune activation [61, 62]. Systemic indices of inflammation and coagulation have been linked to cardiovascular risk in HIV infection [63] and PET CT scans have demonstrated metabolic evidence of aortic inflammation in treated HIV infection [64].

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**Figure 3:** Schematic view of plausible arsenic induced oxidative damage and endothelial dysfunction. Arsenic interacts with G Protein Coupled Receptors (GPCR) to initiate signal amplification schemes regulating NOX-dependent redox signaling. Downstream signaling for dysfunction was (partially adapted from: States JC, et al., Toxicol Sci. 2009.[1]).
Endothelium is a highly reactive surface, responding to a myriad of micro-environmental stress-inducing factors resulting from infection tissue injury, and inflammation [65]. ECs serve as selective micro environmental barriers for the exchange of fluid and macromolecules from the vascular compartment to the tissue. In addition, the bidirectional relationship that follows between the coagulation pathways and vascular inflammation modulating endothelial homeostasis is widely recognized [66, 67].

We showed in one of our recent reports that eNOS and KLF2 are significantly downregulated inducing endothelial dysfunction along with a dramatic increase in the subendothelial migration of CD8 T cells and inflammatory monocytes in the aortic endothelium of *Rhesus macaque* who are acutely infected with simian immunodeficiency virus (SIV)- the HIV homologue infecting non-human primates [68]. How such downregulation affects the formation and sustenance of the immunological synapse bond is of extreme importance in defining the immune lifeline of an affected individual. An immediate future extension of our present line of research in this field is to analyze such effects based on mathematical and probabilistic models that will also highlight the quantitative importance of all affecting factors.

Chronic low dose exposure to inorganic Arsenic and Arsenicals, endothelial dysfunction, CVD, and an association of endemic HIV infections opens up future avenues of research into, what is a relatively poorly understood topic with major implications for human health. While the data acquisition on the world prevalence of HIV and cardiovascular diseases is thorough, the data on chronic exposure to Arsenic is still incomplete for most part of the world. But, we know a large sum of the world population, mostly unknowingly, is exposed to Arsenic irrespective of the socioeconomic status or geographical location of their country. This is a fact which generally indicate that the HIV infected population who are on continued anti-retroviral therapy (ART) with controlled viremia, are also exposed...
to low, moderate or high levels of environmental Arsenic that might be an additional trigger in initiating their accelerated endothelial dysfunction and atherosclerotic lesions. Determination of the true risk of CVD in HIV and measuring the synergistic effects of Arsenic exposure that further complicates the pathogenesis of CVD will become increasingly important in the long-term management of HIV-infected patients receiving antiretroviral therapy.

**Arsenic Modelling and Transport**

As described above, Arsenic is now widely accepted to have a dual role as a causative and a curative agent primarily in non-infectious disease proliferation [69] but also as a secondary instigator of population infection [70]. While conventional biology is typically a first resort, probabilistic prediction of affectation and disease proliferation often stretch beyond the realms of experimental data, especially in predicting what levels of fluctuation of the affecting parameters could instigate a certain threshold of arsenic inflicted persecution. As an example, if the water arsenic toxicity factor increases by 5% over the next 3 years while the glutathione depletion factor decreases by 7% leading to an overall protein inactivation increase by 8% (considering only a few token factors) during the same time span, what will be the increase in arsenic afflicted atherosclerosis and CVD during this time? To address such questions in a non-invasive procedure, computer based data analysis and statistical modeling is the new genre of science in this interdisciplinary arena.

Techniques from statistical mechanics, thermodynamics and nonlinear mechanics, together with native computer simulation, has started unearthing lots of features that have so far remained outside the conventional research purview. In a recent ensemble modeling approach, a mathematical model has been studied that predicts intracellular arsenic flow rates under varying mutant conditions, focusing on the toxicity mechanism of arsenic. This data based analyzes clearly highlight an array of important conclusions like a) protein based arsenic profiles have short-termed exposure while glutathione based arsenic compounds have longer termed ramifications; b) arsenic dynamics is mostly a transient mechanism that probabilistically escapes the vacuole via natural export mechanism, etc. While this work was studied on a yeast substrate, more indicative suggestions towards the protein-versus-glutathione debate have been advised. While this line of modeling directly assesses the microbiological origin of its affectation, secondary infections in the form of (Buruli) ulcerous swellings, believed to be arsenic inflicted, have recently been studied using data from chosen African countries [70]. The results from this study indicate without confirming as much the importance of environmental implication of arsenic disease propagation. Similar results were obtained a while ago by a South African modeling group who studied the optimal control of arsenic transmission dynamics targeting *mycobacterium ulceran* infection [71]. While the data analysis results [70] indicated the roots of the proliferation mode, this more recent kinetic equation based nonlinear modeling [71] traced the mitigation
mechanism as an optimal combination of environmental and health education together with water purification protocols.

Modeling attempts at arsenic retention processes in wetland areas is another line of complementary research that focuses on the role of trace elements in arsenic effect proliferation. Analyzing a model representing arsenic propagation dynamics in constructed wetlands targeting a quantitative prediction of the mutual relationship between iron and arsenic retention efficiency increase, the model results indicate a maximum arsenic retention efficiency of 85-95\% [72]. What all such effects ultimately culminate at is in the population response to exposure of chemical carcinogens at low to high exposure levels often leading to a mutation of a single-cell DNA, hastening a terminal illness. A consummate detailing of such “carcinogenesis modeling” can be availed from a self-sufficient overview by Vineis, et al. [73]. Of the five models discussed here, only Model 4 indirectly alludes to arsenic affectation of carcinoma, another indication of insufficient research in this field.

The above highlighted areas are only the tips of the proverbial iceberg. More concerted efforts combining complementary inter- and cross-disciplinary efforts are needed to tackle this problem, an approach that has taken pace off late.

**Concluding Remarks**

Studies summarized in this mini-review suggest that chronic Arsenic exposure induces pathophysiological events relevant to the atherogenic potential including impaired vascular nitric oxide homeostasis, low Krüppel-like factor 2, 4 expression, and enhanced expression endothelial adhesion molecule like VCAM-1. These detrimental changes in the endothelial microenvironment, collectively expressed as endothelial dysfunction are the key molecular events in the cardiovascular system which are surprisingly common to Arsenic exposure and in the HIV infected patients on long-term ART. Based on the accumulating epidemiological evidences and experimental data, we conclude, arsenic exposure could be considered as an important modifying factor in the understating and intervention strategies of atherosclerosis and related cardiovascular diseases in virologically controlled HIV patients on ART, at least under certain circumstances (including genetic background, diet, co-exposure and geographical location). Also, we would argue that the considerable overlap with the worldwide exposure of Arsenic, incidences of HIV infection positively reinforce the initiation, persistence, and progress of HIV infection itself and the pathogenesis of related cardiovascular complications. While mathematical modeling of arsenic poisoning, infection and its impact on carcinogenesis is a vital and newly adopted line of research, the sheer paucity of material in gelling together known biological observations against data and mathematical models clearly indicates the need for more detailed and target driven studies. Over the next couple of years, such cross-platform research is expected to hold center stage in leading the light in this field.
Conflict of Interest Statement:
All other authors declare that they have no competing interests.

Authors' contribution:
AP and SP designed, performed, analyzed experiments, and SP, AKC, and AP wrote the manuscript with collaborations from GP, and AKC. All authors contributed to general design and discussion of the project and reviewed and approved the manuscript.

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