Warfarin-induced skin necrosis in HIV-1-infected patients with tuberculosis and venous thrombosis

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Background. At the turn of the century, only 300 cases of warfarin-induced skin necrosis (WISN) had been reported. WISN is a rare but potentially fatal complication of warfarin therapy. There are no published reports of WISN occurring in patients with HIV-1 infection or tuberculosis (TB).

Methods. We retrospectively reviewed cases of WISN presenting from April 2005 to July 2008 at a referral hospital in Cape Town, South Africa.

Results. Six cases of WISN occurred in 973 patients receiving warfarin therapy for venous thrombosis (0.62%, 95% CI 0.25 - 1.37%). All 6 cases occurred in HIV-1-infected women (median age 30 years, range 27 - 42) with microbiologically confirmed TB and venous thrombosis. All were profoundly immunosuppressed (median CD4+ count at TB diagnosis 49 cells/μl, interquartile range 23 - 170). Of the 3 patients receiving combination antiretroviral therapy, 2 had TB-IRIS (immune reconstitution inflammatory syndrome). The median interval from initiation of antituberculosis treatment to venous thrombosis was 37 days (range 0 - 150). The median duration of parallel heparin and warfarin therapy was 2 days (range 1 - 6). WISN manifested 6 days (range 4 - 8) after initiation of warfarin therapy. The international normalised ratio (INR) at WISN onset was supra-therapeutic, median 5.6 (range 3.8 - 6.6). Sites of WISN included breasts, buttocks and thighs. Four of 6 WISN sites were secondarily infected with drug-resistant nosocomial bacteria (methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter*, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*) 17 - 37 days after WISN onset. In 4 patients, the median interval from WISN onset to death was 43 days (range 25 - 45). One of the 2 patients who survived underwent bilateral mastectomies and extensive skin grafting at a specialist centre.

Conclusion. This is one of the largest case series of WISN. We report a novel clinical entity: WISN in HIV-1 infected patients with TB and venous thrombosis. The occurrence of 6 WISN cases in a 40-month period may be attributed to (*i*) hypercoagulability, secondary to HIV-1 and TB; (*ii*) short concurrent heparin and warfarin therapy; and (*iii*) high loading doses of warfarin. Active prevention and appropriate management of WISN are likely to improve the dire morbidity and mortality of this unusual condition.

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Warfarin-induced skin necrosis (WISN) is a rare complication of warfarin therapy, with an estimated prevalence of 0.01 - 0.1% in individuals receiving warfarin.[1,2] WISN is associated with high morbidity, often necessitating aggressive surgical intervention, and may be fatal in the absence of early accurate diagnosis and treatment. Originally described in 1943, WISN was first associated with oral anticoagulants in 1954.[3] By 2000, only 300 cases had been reported internationally.[4] Most cases occur in patients receiving treatment for venous thrombo-embolism (VTE); 25% of WISN occurs in patients with cardiac indications for therapy (e.g. atrial fibrillation, valve replacement) or cerebrovascular insufficiency.[2] To date, published reports do not associate WISN with HIV-1 infection or tuberculosis (TB). We describe 6 cases of WISN with poor outcome occurring in HIV-1-infected patients receiving treatment for TB.

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Methods

Setting

We retrospectively reviewed 6 cases of WISN seen at G F Jooste Hospital (Cape Town, South Africa) from April 2005 through July 2008. G F Jooste Hospital is a 200-bed adult (>15 years) public hospital that receives referrals from primary care clinics serving a catchment population of 1.3 million high-density, low-income people. We have previously described national guidelines for antituberculosis treatment and antiretroviral therapy in South Africa.[5,6] The Research Ethics Committee of the University of Cape Town approved the study (REF: 182/2009).

Definitions

We defined venous thrombosis as either visualisation of a non-compressible thrombus with Doppler ultrasound (popliteal or femoral venous thrombosis) or a venous filling defect with radio-contrast during computed tomography (CT) (inferior vena cava or superior sagittal sinus thrombosis). A radiologist performed sonography and interpreted the CT findings. WISN was defined as a characteristic drug eruption on the skin, occurring shortly after starting warfarin therapy for a venous thrombosis and progressing to skin and subcutaneous tissue loss. We defined the following: microbiologically confirmed TB as *Mycobacterium tuberculosis* cultured or acid-fast bacilli (AFB) seen in sputum or a lymph node aspirate; TB-IRIS (immune reconstitution inflammatory syndrome) using the consensus clinical case definition of paradoxical TB-IRIS for resource-limited settings;[7] extended-spectrum beta-lactamase (ESBL)-producing bacteria as bacteria having clavulanate-inhibited transferable enzymes able to hydrolyse third- and fourth-generation cephalosporins as tested by the disc diffusion (fishtail) method; and methicillin-resistant *Staphylococcus aureus* (MRSA) as having an oxacillin minimum inhibitory concentration of >4 mg/l.

Materials

We obtained clinical information from hospital notes, laboratory reports and communication with attending physicians. The following data were reviewed: patient demographics, HIV-1 status, CD4+ counts (nadir and post-ART where available), TB episode (microbiological confirmation, drug susceptibility testing), site of venous thrombosis, anticoagulation therapy, site of WISN, international normalised ratio (INR) at WISN onset, antibiotic treatment, and outcome (e.g. death, surgical intervention). All patients admitted to G F Jooste Hospital from 2005 through 2008 were managed using a standardised venous thrombosis protocol. Following diagnosis of venous thrombosis, low-molecular-weight (LMW) heparin (enoxaparin 1 mg/kg twice daily by deep subcutaneous injection) was prescribed for a maximum of 5 days. Warfarin was started 2 days after heparin initiation to minimise the risk of warfarin-induced skin necrosis. If the patient was receiving TB treatment for 10 days or longer, the loading dose of warfarin was adjusted from 5 mg to 10 mg.

Results

Baseline characteristics

Nine hundred and seventy-three patients were diagnosed with venous thromboses and received warfarin therapy at G F Jooste Hospital over the 40-month study period. WISN occurred in 6 HIV-1-infected women receiving treatment for microbiologically confirmed TB (Table I). The prevalence of WISN in our study population was 0.62% (6/973) (95% CI 0.25 - 1.37%). The median age was 33 years (range 27 - 42). The median CD4+ count at TB diagnosis was 49 cells/µl (interquartile range 23 - 170). Three patients received ART (regimens specified in Table I). Two patients (cases 2 and 3) were diagnosed with TB-IRIS. The median interval from

Table I. Baseline characteristics and site of venous thrombosis in 6 HIV-1-infected patients with warfarin-induced skin necrosis

Previous TB	Age (yrs), gender	TB site, TB result	Duration: TB treatment to ART	ART regimen	TB-IRIS	CD4+ at TB diagnosis (cells/µl)	CD4+ at TB-IRIS (cells/µl)	Duration: ART to venous thrombosis	Duration: TB treatment to venous thrombosis	Venous thrombosis site
Yes	42, F	Pulmonary, drug-sensitive *M.tb*	*	AZT/3TC/ EFV	–	396	-	28 months	0 days†	L popliteal vein
No	36, F	Cervical node, smear positive	4 weeks	D4T/3TC/ EFV	Yes	41	199	1 month	65 days	R SFV, R popliteal vein
No	30, F	Pulmonary, drug-sensitive *M.tb*	2 weeks	D4T/3TC/ EFV	Yes	10	91	1 month	50 days	IVC, into L renal vein
Yes	28, F	Pulmonary, drug-sensitive *M.tb*	–	–	–	56	–	–	0 days†	L popliteal and femoral veins
No	27, F	Pulmonary, smear positive	–	–	–	17	–	–	152 days	Superior sagittal sinus
No	35, F	Pulmonary, drug-sensitive *M.tb*	–	–	–	208	–	–	24 days	L common femoral vein

F = female; ART = combination antiretroviral treatment; AZT = zidovudine 300 mg twice daily, D4T = stavudine 30 mg twice daily, 3TC = lamivudine 150 mg twice daily, EFV = efavirenz 600 mg nocte; smear positive = acid-fast bacilli seen with Ziehl-Neelsen stain; drug-sensitive *M.tb* = *Mycobacterium tuberculosis* cultured sensitive to rifampin and isoniazid; TB treatment = antituberculosis treatment; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome; L = left; R = right; SFV = superficial femoral vein; IVC = inferior vena cava; * = ART preceded TB treatment by 28 months, 0 days; † = tuberculosis and venous thrombosis diagnosed on the same day.

initiation of antituberculosis therapy to venous thrombosis was 37 days (range 0 - 150). Venous thrombosis sites included popliteal and femoral veins, the inferior vena cava, and the superior sagittal sinus. Only patient 3 was an inpatient at the time of venous thrombosis (and received LMW heparin prophylaxis); the remaining patients were admitted to hospital as a result of venous thrombosis. No patient had a personal or family history of previous venous thrombosis.

Clinical features at WISN and outcomes

The warfarin loading dose was 5 mg or 10 mg (Table II). The median duration of parallel heparin and warfarin therapy was 2 days (range 1 - 6) and the median interval from initiation of warfarin therapy to WISN was 6 days (range 4 - 8). The INR at WISN onset was supra-therapeutic, median 5.6 (range 3.8 - 6.6). Activated partial thromboplastin times (aPTT) were not measured. Sites of WISN included the breasts, buttocks and thighs (Fig. 1). Skin biopsy was performed in 1 patient (Fig. 1). After WISN diagnosis, warfarin was stopped and LMW heparin was used to manage anticoagulation. Wound cultures from infected WISN sites produced the following drug-resistant nosocomial organisms: *Escherichia coli* (ESBL), *Klebsiella pneumoniae* (ESBL), *S. aureus* (MRSA), *Acinetobacter baumannii* and *Serratia marcescens*. Antimicrobial sensitivities of each organism are listed in Table II.

Four patients died, and no autopsies were performed. All 4 patients were profoundly immunosuppressed at TB diagnosis. The median interval from WISN onset to death was 43 days (range 25 - 45). The two surviving patients' CD4+ counts at TB diagnosis exceeded 200 cells/µl. Patient 1 was referred to a specialist centre for aggressive surgical management (Fig. 1, D - F). Patient 6 recovered with appropriate wound care and prophylactic broad-spectrum intravenous antibiotics (a third-generation cephalosporin).

Discussion

This is one of the largest case series of WISN. We report a novel clinical entity: WISN occurring in HIV-1-infected patients with TB and venous thrombosis.

All 6 patients were chronically ill women of reproductive age with venous thromboses. WISN typically occurs in obese, perimenopausal women who are receiving anticoagulant therapy for a deep-vein thrombosis or pulmonary embolism.[2] Women are affected more frequently than men (4:1)[2] – the reason for this predilection is unclear. In women, the breast is most commonly affected, followed by the buttocks and thighs;[8] our patients were similarly affected. It is postulated that local tissue factors contribute to the development of WISN at these sites, and that such factors include trauma and variation in local temperature and perfusion.[9,10]

About 90% of affected patients develop symptoms between the 3rd and 6th day of warfarin therapy,[2,4,11] which is similar to our experience. The clinical presentation of WISN is characteristic (Fig. 1, A - C); all our patients demonstrated these clinical features. Widespread disease may result in deep tissue necrosis, secondary infection and multi-organ failure.[2]

Mortality within 3 months of WISN onset is substantial (15%), even with appropriate treatment.[2] Four of our 6 patients died within 45 days of onset. All deaths were probably due to a sepsis syndrome complicating wound infection. All wound cultures were taken from infected wounds. These were not surveillance cultures. Prior rifampicin, trimethoprim-sulfamethoxazole and cephalosporin use in our patients may have favoured the selection of highly antibiotic-resistant organisms. In South Africa, more than 50% of *S. aureus* isolates from public hospitals are resistant to rifampicin and/or trimethoprim sulfamethoxazole.[12] Failure of effective infection control measures, lack of appropriate antimicrobial chemotherapy,[6] delayed referral to a specialist centre for surgical debridement, and profound immunosuppression at TB diagnosis probably contributed to the 4 deaths. In contrast, the superior immune function at TB diagnosis of patients 1 and 6 may account for their survival. Pulmonary emboli may have also complicated warfarin cessation and contributed to death. We were unable to determine the exact cause of death, as the patients' relatives declined consent to perform autopsies. It is important to note that despite prompt referral to a specialist centre, patient 1 had considerable morbidity including bilateral mastectomies, an impaired gait due to a contracture of her left thigh, and the associated psychosocial stigma.

Classic histological features of WISN include full-thickness epidermal necrosis and thrombosed vessels in the dermis. While the underlying pathophysiological mechanisms remain unclear, it is postulated that WISN results from an imbalance between intrinsic pro- and anticoagulant factors during the first few days of warfarin therapy.[2,11] Warfarin is a vitamin K antagonist and reduces serum levels of vitamin K-dependent factors, which include factors II, VII, IX and X, protein C and protein S. Serum levels of factor VII (a procoagulant factor), and proteins C and S (anticoagulant factors) decline more rapidly than serum levels of factors II, IX and X (procoagulant factors) on warfarin therapy.[2,11] This results in an initial hypercoagulable state, which, especially in the presence of additional risk factors such as protein C and/or S deficiency, may predispose to WISN.[4] The INR is factor VII-dependent, so patients will have a raised INR, but a relative protein C deficiency will nonetheless result in a hypercoagulable state.[13] Screening for these conditions before warfarin initiation is not recommended, however, as they lack the necessary sensitivity and specificity to accurately predict the risk of developing WISN.[2,4] Owing to the retrospective nature of our study, serum levels of protein C, protein S and antithrombin III were not measured. The lack of genetic testing and coagulation work-up is a limitation of our study.

The prevalence of WISN in our study population is 0.62% (6/973), which is six times higher than that reported in HIV-uninfected patients.[1,2] The occurrence of 6 WISN cases in a 40-month period at one centre is unusual. It may be a result of the short duration of parallel heparin and warfarin therapy (median 2 days) observed in our patients. Parallel heparin and warfarin therapy is postulated to prevent the development of WISN, and should be continued until the vitamin K-dependent clotting factors have been consumed (72 - 96 hours).[2,4,8,11] In our patients, premature cessation of heparin during the initial hypercoagulable period of warfarin therapy may have exacerbated an underlying hypercoagulable disorder (such as a protein C or S deficiency) and culminated in WISN. In our

Table II. Clinical features of warfarin-induced skin necrosis and outcomes

Case	Initial warfarin dosage (daily)	Duration of heparin + warfarin overlap	Duration from warfarin treatment to WISN onset	INR at WISN onset	Antibiotics at WISN onset	Site of WISN	Duration from WISN onset to wound infection	Wound culture from WISN site	Antimicrobial sensitivities	WISN to death
1	5 mg	2 days	6 days	6.6	ART, HRZES, TMP-SMX, ceftriaxone	Breasts, L thigh	21 days	*S. aureus* (MRSA) *A. baumannii*	Clindamycin, erythromycin, vancomycin Colistin	Alive
2	10 mg	3 days	4 days	6.2	ART, HRZE	R buttock	26 days	*K. pneumoniae* (ESBL) *E. coli*	Amikacin, ertapenem, imipenem, meropenem Amikacin, cefotaxime, ceftriaxone, cefuroxime, ciprofloxacin, co-amoxyclav, gentamicin	44 days
3	10 mg	1 day	4 days	4.9	ART, HRZE, ampicillin, amikacin	Buttocks	17 days	*E. coli* (ESBL) *A. baumannii*	Amikacin, imipenem, meropenem, piperacillin-tazobactem Amikacin, colistin, tobramycin	25 days
4	10 mg	2 days	8 days	4.5	HRZE	L breast	37 days	*S. marcescens* *K. pneumoniae* (ESBL)	Imipenem, meropenem, piperacillin-tazobactem Amikacin, imipenem, meropenem	42 days
5	-	6 days	6 days	6.4	HRZE	L breast, L hip	-	Not requested		45 days
6	5 mg	3 days	8 days	3.8	HRZE, metronidazole, TMP-SMX	L thigh	-	Not requested (wound not infected)		Alive

WISN = warfarin-induced skin necrosis; ART = combination antiretroviral treatment; HRZES = antituberculosis treatment: H: isoniazid, R: rifampicin, Z: pyrazinamide, E: ethambutol, S: streptomycin; TMP-SMX = trimethoprim-sulfamethoxazole; INR = international normalised ratio; L = left; R = right; MRSA = methicillin-resistant *Staphylococcus aureus*; ESBL = extended-spectrum beta-lactamase-producing organism.

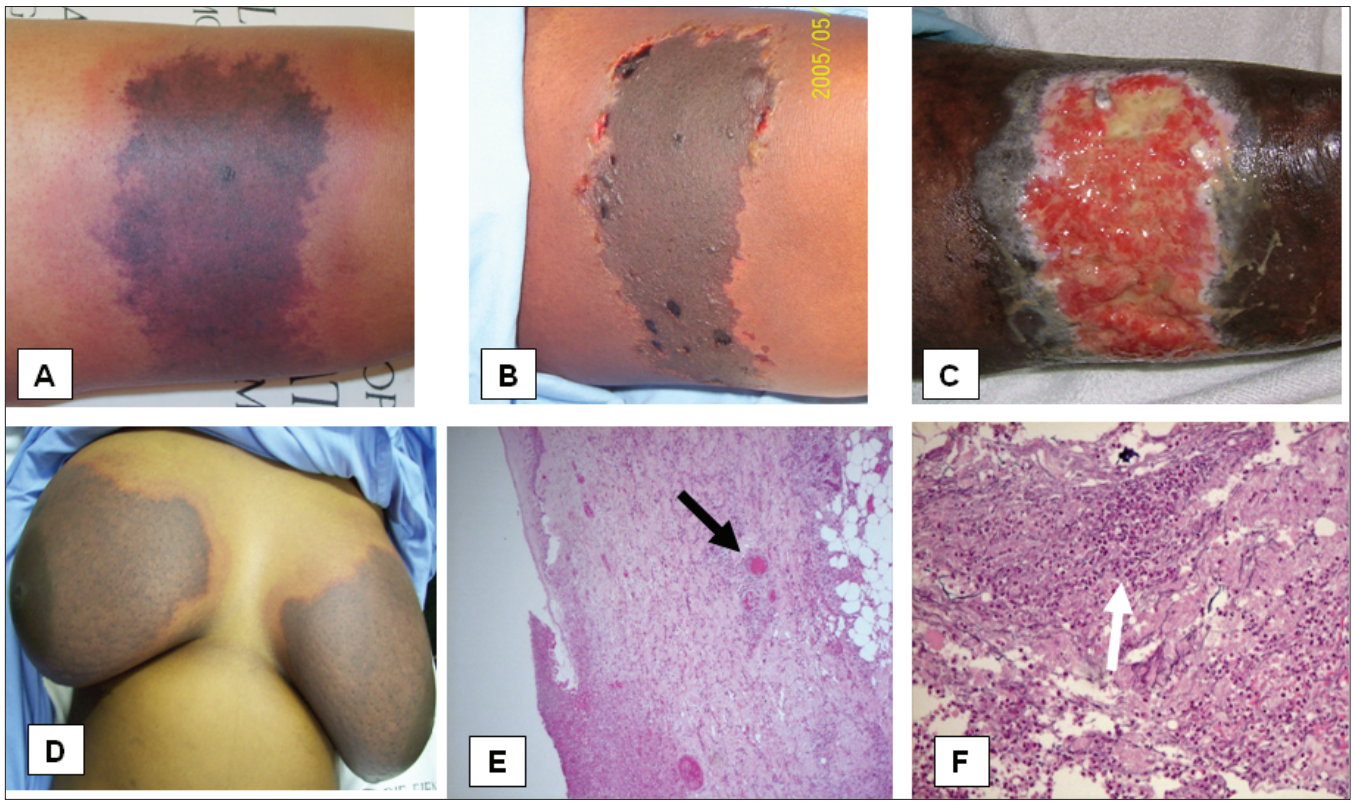

Fig. 1, A - C: Left thigh of patient 6 showing typical macroscopic features of warfarin-induced skin necrosis. A painful, well-localised purplish lesion with a poorly demarcated erythematous flush[9] developed 6 days after commencing warfarin therapy (A). Oedema formed in the dermis and subcutaneous tissues, which elevated and further demarcated the lesions from unaffected skin (B). Petechiae and haemorrhagic bullae were also observed; such bullae signified irreversible damage and ensuing full-thickness skin necrosis.[3,4,9] Sloughing of the eschar revealed deep defects that extended into the subcutaneous tissue (C). D - F: WISN in an HIV-1-infected woman with tuberculosis and venous thrombosis (patient 1). A 42-year-old HIV-infected woman was admitted to hospital in June 2008. She was compliant with antiretroviral treatment (ART), and her CD4 count was 396 cells/µl. Drug-sensitive Mycobacterium tuberculosis *was cultured from her sputa. Ultrasound examination confirmed a left popliteal thrombosis. Six days after starting warfarin therapy she developed skin lesions on her breasts and left thigh, consistent with WISN (D). Sixteen days after WISN onset, a punch biopsy of her left thigh was performed. Histological examination showed full-thickness epidermal necrosis with numerous thrombosed vessels in the superficial dermis (E, arrowed), consistent with WISN. She received antibiotics for wound infection according to microbial sensitivities. Forty-four days after WISN onset, plastic surgeons performed a bilateral mastectomy and extensive tissue excision from the left thigh. Split-thickness skin grafts were used to cover the defects. Microscopy of tissue excised from the left thigh showed extensive necrosis of subcutaneous fat, numerous foreign body-type giant cells and focal suppuration (F, arrowed). There were fresh thrombi in vessels, and some vessels showed recanalisation. No organisms were seen on Brown and Brenn (modified Gram stain) or Ziehl-Neelsen stains. Ten months after WISN, she has an impaired gait due to a contracture of her left thigh.*

setting, we routinely prescribe a loading dose of 5 or 10 mg of warfarin in TB patients with venous thromboses, as rifampicin induces the rate of warfarin clearance by cytochrome p450 (CYP) 2C9.[14] This dose of warfarin with a short window of parallel heparin and warfarin therapy may have contributed to the high prevalence of WISN (0.62%).

HIV infection is a widely acknowledged risk factor for VTE.[15-17] Some reports cite a tenfold increase in the incidence of deep-vein thrombosis (DVT) in HIV/AIDS as opposed to the general population.[15] The following independent risk factors have been identified for VTE in HIV-positive patients: low CD4 count, high viral load, advanced stage of immunocompromise, opportunistic infections, AIDS-related neoplasms, HIV-associated auto-immune disorders (e.g. auto-immune haemolytic anaemia), hospitalisation in the past 3 months, and central venous catheter use in the past 3 months.[16-18] Exposure to antiretroviral therapy (ART) has not been associated with VTE.[16,17] HIV-positive patients are also more likely to demonstrate multiple acquired and persistent thrombophilic abnormalities; the frequency of these abnormalities increases with progression to AIDS, and their presence may contribute to the high prevalence of venous and arterial thrombosis in patients with HIV infection.[19] These abnormalities include antiphospholipid antibodies, lupus anticoagulant, anticardiolipin antibodies, increased von Willebrand factor, increased d-dimers, and deficiencies of protein C, protein S, antithrombin and heparin cofactor II.[20] The acquired protein S and protein C deficiencies seen in acutely ill patients may be reversible following treatment for opportunistic infections and/or ART.[18]

M. tuberculosis infection may present clinically as DVT; 2 of our patients (patients 1 and 4) were diagnosed with TB and DVT simultaneously. DVT usually occurs shortly after initiating antituberculosis therapy (about 2 weeks).[21] Rifampicin-based regimens have a fivefold increased risk of DVT (relative risk = 5), so DVT prevention is recommended in patients on rifampicin.[21] DVT is also associated with advanced HIV infection and PTB. The following thrombogenic factors probably contribute to this association: acquired protein C and protein S deficiencies, elevated plasma fibrinogen, impaired fibrinolysis, depressed ATIII, reactive thrombocytosis, increased platelet aggregation, and antiphospholipid antibodies.[22] These parameters may improve with antituberculosis treatment.[22]

It is not known whether IRIS predisposes to venous thrombosis. A single case is reported of IRIS manifesting as disseminated TB, myelopathy, encephalopathy and DVT;[23] with appropriate treatment, IRIS resolved and no adverse drug effects occurred. We report the first 2 cases of TB-IRIS and WISN occurring simultaneously. The 2 patients diagnosed with TB-IRIS were profoundly immunosuppressed, had a short duration from starting antituberculosis treatment to initiation of ART, and presented with recurrence of TB symptoms soon after initiating ART.[7]

Active prevention and appropriate management of venous thromboses are likely to alleviate the dire morbidity and mortality associated with WISN. Prophylactic heparinisation of acutely ill hospital patients with HIV-1 infection and/or TB will reduce the incidence of venous thrombosis. In patients with venous thrombosis, parallel heparin therapy for at least the first 4 days of warfarinisation[2,4,8,11] may limit the occurrence of WISN. WISN should be considered in all newly warfarinised patients with new skin lesions. Effective infection control measures and expedited referral to specialist centres for surgical review may reduce mortality.

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