Incidence and predictors of herpes zoster among antiretroviral therapy-naïve patients initiating HIV treatment in Johannesburg, South Africa

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Summary

Objectives—To describe the characteristics of HIV-infected patients experiencing herpes zoster after antiretroviral therapy (ART) initiation and to describe the incidence and predictors of a herpes zoster diagnosis.

Methods—Adult patients initiating ART from April 2004 to September 2011 at the Themba Lethu Clinic in Johannesburg, South Africa were included. Patients were followed from ART initiation until the date of first herpes zoster diagnosis, or death, transfer, loss to follow-up, or dataset closure. Herpes zoster is described using incidence rates (IR) and predictors of herpes zoster are presented as subdistribution hazard ratios (sHR) and 95% confidence intervals (95% CI).

Results—Fifteen thousand and twenty-five patients were included; 62% were female, the median age was 36.6 years, and the median baseline CD4 count was 98 cells/mm³. Three hundred and forty patients (2.3%) experienced herpes zoster in a median of 26.1 weeks after ART initiation.
Most (71.5%) occurred within 1 year of initiation, for a 1-year IR of 18.1/1000 person-years. In an adjusted model, patients with low CD4 counts (<50 vs. ≥200 cells/mm$^3$; sHR: 1.71, 95% CI: 1.21–2.47) and with a prior episode of herpes zoster (sHR: 1.53, 95% CI: 0.97–2.28) were at increased risk of incident herpes zoster.

**Conclusions**—While only 2% of patients were diagnosed with herpes zoster in this cohort, patients with low CD4 counts and those with prior episodes of herpes zoster were at higher risk for a herpes zoster diagnosis.

**Keywords**
Herpes zoster; HIV infection; Resource-limited settings; Shingles; Attrition

**Introduction**

While in immune competent populations, herpes zoster, also called shingles, is most often seen in elderly persons, it is also commonly reported among HIV-infected persons.1–5 After primary infection with varicella zoster virus (VZV), usually during childhood (chickenpox), the virus remains dormant in the sensory nerve roots. Reactivation of latent virus occurs in the elderly or immunocompromised and results in herpes zoster, a painful vesicular rash that is self-limited.2,6,7 In HIV-infected patients, herpes zoster can be more severe and prolonged, and may involve the eye or central nervous system.6

While data are lacking for low-resource settings, statistics from resource-rich environments suggest that while the lifetime risk of a herpes zoster episode in the general population is between 25% and 35%,8–10 the burden is substantially higher in HIV-infected populations.3 Although some studies have found that the incidence of herpes zoster has been decreasing since the scale-up of antiretroviral therapy (ART), the risk of a herpes zoster episode remains elevated in HIV-infected populations. In a recent study of HIV-infected patients conducted in Germany, the incidence of herpes zoster was 12/1000 person-years, while a cohort in the USA experienced herpes zoster at a rate of 9/1000 person-years.11,12 These estimates are both substantially higher than the incidence rate in the general population of resource-rich countries, which ranges from 2/1000 person-years to approximately 5/1000 person-years.10,13

To describe the characteristics of patients experiencing episodes of herpes zoster after ART initiation, we assessed the incidence of herpes zoster in a large cohort of ART-naïve HIV-infected patients initiating ART in Johannesburg, South Africa. We further sought to identify characteristics that were associated with an increased risk for a herpes zoster episode, and the timing of these episodes after initiation of ART.

**Methods**

**Study site**

The study was conducted at the Themba Lethu Clinic in Johannesburg, South Africa. Themba Lethu is a large outpatient, public sector HIV treatment clinic located within the Helen Joseph Hospital that receives non-governmental organization (NGO) support through
the President’s Emergency Plan for AIDS Relief (PEPFAR) program. ART at Themba Lethu has been provided in accordance with South Africa’s national treatment guidelines since it was first made available in the public sector in 2004 and currently follows the 2013 guidelines. Since 2004, approximately 30,000 patients have received HIV care at Themba Lethu and over 21,000 patients have initiated ART.

Prior to April 2010, patients were initiated on ART when they reached a CD4 count of <200 cells/mm$^3$ or if they experienced a World Health Organization (WHO) stage IV condition. The primary ART regimen was stavudine, lamivudine, and efavirenz, with options to substitute zidovudine for stavudine, emtricitabine for lamivudine, and nevirapine for efavirenz when indicated. After April 2010, tenofovir was chosen to replace stavudine in first-line regimens, and in August 2011 the ART eligibility threshold was raised to a CD4 count of ≤350 cells/mm$^3$.

Patient details including demographic information, laboratory test results, medications prescribed, clinical conditions, and other clinical details are captured in an electronic medical record system called TherapyEdge-HIV™. Data are entered into the database at the time of the clinical encounter by the treating clinician. Patients are typically seen every month for the first 6 months after ART initiation and then every 2 months thereafter for either antiretroviral medication pick-ups and/or medical visits. The CD4 count is assessed at ART initiation, 1 year after ART initiation, and yearly thereafter, while viral load is assessed 4–6 months after ART initiation, at 1 year, and then yearly thereafter.

While herpes zoster can be identified at regularly scheduled visits, it is often diagnosed at an unscheduled medical visit or retrospectively at the medical visit following the episode. Herpes zoster is diagnosed clinically, and treatment for the lesions is provided with acyclovir and pain medication. Start and stop dates of the episode are entered into TherapyEdge-HIV by the clinician.

**Study population**

We conducted a cohort analysis using data collected prospectively as part of routine patient care. We included all ART-naive adult patients (≥18 years old) who initiated any of the standard public sector first-line regimens listed above between April 2004 and September 2011 and had at least one visit after ART initiation at the Themba Lethu Clinic. Loss to follow-up was defined as ≥3 months late for a scheduled visit with no subsequent visit. Death was ascertained through patient tracing. In addition, for patients with a valid South African national identification number (61%), deaths were identified through linkage with the National Vital Registration System. The last linkage occurred in September 2011.

**Study variables**

Patients were followed from the date of ART initiation until the date of first herpes zoster diagnosis, or death, transfer, loss to follow-up, or dataset closure (September 6, 2012). Incident herpes zoster was defined as any herpes zoster episode occurring after the date of ART initiation.
We defined the baseline CD4 count to be the CD4 count conducted closest to the date of ART initiation, from 6 months prior to 7 days after ART initiation; this was categorized as <50 cells/mm$^3$, 50–99 cells/mm$^3$, 100–199 cells/mm$^3$, and ≥200 cells/mm$^3$. Classification by WHO stage was done by the clinician. If the clinician did not enter a classification, the WHO stage was determined according to the conditions present at ART initiation. Body mass index (BMI) was categorized according to standard categories (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m$^2$). Before defining anemia, recorded hemoglobin values were adjusted downward by 0.65 g/dl to account for the elevation of Johannesburg. Anemia was then defined using WHO guidelines as severe, moderate, mild, and none, which differ by sex (male: <8, 8–10, 11–12, ≥13 g/dl) and pregnancy status (female, pregnant: <7, 7–9, 10, ≥1 g/dl; female, not pregnant: <8, 8–10, 11, ≥12 g/dl). Finally, a prior episode of herpes zoster was defined as an episode that occurred prior to, or was present at, ART initiation.

**Statistical analysis**

The demographic and baseline characteristics of all patients included in the cohort are presented using frequencies for categorical variables and medians with corresponding interquartile ranges (IQR) for continuous variables. Incident herpes zoster rates per 1000 person-years and the corresponding 95% confidence intervals (95% CI) and predictors of herpes zoster within 12 months of ART initiation and herpes zoster ever on treatment are also presented.

Fine and Gray’s method was used for competing risks regression to estimate the subdistribution hazard ratios (sHR) of predictors of herpes zoster for each model, accounting for the competing event of mortality. Age, gender, and the baseline CD4 count were included as covariates in each model. Other potential confounding variables were included if they were plausible confounders based on prior knowledge and were associated with herpes zoster ($p < 0.2$) in the crude analyses.

In order to determine whether an incident herpes zoster diagnosis within 12 months of ART initiation had any impact on short-term treatment outcomes, we matched each patient with a herpes zoster diagnosis within 12 months of follow-up to eight patients without a herpes zoster diagnosis and compared attrition (death and loss to follow-up) 12 months after the date of diagnosis. Patients were matched on sex, age at ART initiation (± 5 years), baseline CD4 count category (<50, 50–99, 100–199, ≥200 cells/mm$^3$), and time on treatment. For each matched pair, the person-time accrued from the date of the incident herpes zoster diagnosis or the equivalent duration of follow-up for the matched subject who did not develop herpes zoster. We used a log-binomial model to assess the risk of attrition by incident herpes zoster status. Potential confounding variables that were plausible confounders based on prior knowledge and were associated with attrition ($p < 0.2$) in the univariate analyses were included in the adjusted model.
Results

Demographic and clinical characteristics

Between April 2004 and August 2011, 15,025 patients initiated a standard first-line ART regimen at the Themba Lethu Clinic and had at least one post-ART initiation follow-up visit. A further 2194 patients either did not initiate a standard first-line regimen or did not complete at least one follow-up visit and were excluded from the analysis. Among included patients, 62.2% were female and the median (IQR) age at ART initiation was 36.6 (31.4–43.1) years. Many patients were severely immunosuppressed upon ART initiation, with the median (IQR) baseline CD4 count being 98 cells/mm$^3$ (37–168 cells/mm$^3$); almost a third of patients (29.6%) had a baseline CD4 count <50 cells/mm$^3$. Just under half of the patients were moderately or severely anemic (48.2%) at ART initiation, and tuberculosis co-infection was common (14.2%). While patients who would go on to have an incident herpes zoster episode had a slightly lower median baseline CD4 count at ART initiation (77.5 cells/mm$^3$ vs. 99 cells/mm$^3$), other baseline demographic and clinical characteristics were similar between the groups (Table 1).

Incidence of herpes zoster

We identified 340 patients (2.3%) who had at least one episode of incident herpes zoster recorded after ART initiation. Of those, 6.8% ($n = 23$) had a record of herpes zoster prior to, or present at, ART initiation. The median (IQR) time to onset of herpes zoster after ART initiation was 26.1 weeks (9.9–61.9 weeks) and the majority of these cases ($n = 243; 71.5\%$) occurred within the first year on treatment. Among the 243 patients diagnosed with herpes zoster within 1 year of ART initiation, the median (IQR) time to diagnosis was 16.0 weeks (6.3–29.6 weeks). This corresponded to an overall incidence rate of 7.4/1000 person-years (95% CI 6.6–8.2) and a 1-year incidence rate of 18.1/1000 person-years (95% CI 15.9–20.5).

Among all patients who had a case of incident herpes zoster, 76.8% ($n = 261$) had a CD4 count recorded after ART initiation at the time of herpes zoster diagnosis (CD4 count date within ±3 months of the herpes zoster diagnosis date). The median (IQR) CD4 count at diagnosis was 231 cells/mm$^3$ (153–317 cells/mm$^3$), and of the 76.5% of patients with a viral load recorded within ±3 months of the date of herpes zoster diagnosis, 75.4% were virologically suppressed (viral load <400 copies/ml).

Predictors of incident herpes zoster within 12 months and any time after ART initiation

The CD4 count at ART initiation was a strong predictor of incident herpes zoster diagnosed within 12 months (Figure 1). Patients with a CD4 count <50 cells/mm$^3$ had a 1-year incidence rate of herpes zoster of 23.6/1000 person-years (95% CI 19.2–29.0), while patients with a CD4 count ≥200 cells/mm$^3$ experienced herpes zoster at half that rate (10.3/1000 person-years; 95% CI 6.6–16.2), corresponding to an increased risk of 2.02 for patients with CD4 counts <50 cells/mm$^3$ (95% CI 1.31–3.22). Those with a CD4 count between 50 and 99 cells/mm$^3$ (sHR 1.67, 95% CI 1.04–2.74) were also at increased risk for a herpes zoster diagnosis compared to patients with CD4 counts ≥200 cells/mm$^3$ (Table 2).
When extending the timeframe for a herpes zoster diagnosis to any time after ART initiation, a prior herpes zoster episode became an important predictor of incident herpes zoster on ART. Patients who had previously experienced herpes zoster were approximately 50% more likely to have an incident herpes zoster diagnosis than patients who had never experienced herpes zoster (sHR: 1.53, 95% CI: 0.97–2.28). CD4 count remained a predictor of incident herpes zoster diagnosis over this time period (Figure 1). Patients with a CD4 count <50 cells/mm\(^3\) were about 70% more likely to experience incident herpes zoster than patients with a CD4 count ≥200 cells/mm\(^3\) (sHR 1.71, 95% CI 1.21–2.47) (Table 2).

One-year treatment outcomes

Of the 243 patients who had a herpes zoster diagnosis recorded within 1 year of ART initiation, 237 (97.5%) were matched to 1896 patients who did not experience herpes zoster within 1 year, for a total of 2133 patients included in this sub-analysis. Among all 2133 patients, 295 (13.8%) died (4.5%) or were lost to follow up (9.3%). Patients who experienced herpes zoster were less likely to die or become lost to follow-up (9.7%) compared to non-herpes zoster patients (14.4%) (aHR 0.64, 95% CI 0.42–0.99) (Table 3). As death was similar across groups, the increase in attrition seen among patients who did not experience a herpes zoster episode was possibly due to increased monitoring of herpes zoster patients resulting in less loss to follow-up among that group.

Discussion

In this cohort of newly initiating HIV-infected patients, the overall burden of herpes zoster was low, with just 2% of patients experiencing herpes zoster after ART initiation. While this is lower than what has been found in other studies, ranging from 6.0% to 18.4%, the overall incidence rate of 7.4/1000 person-years was still greater than that seen in 60-year-old patients in the USA (5–6.5/1000 person-years) and similar to that seen in 70-year-old Americans (8–11/1000 person-years). This was true despite the fact that in our cohort the median age was <40 years. Further, the 1-year incidence rate was high at 18.1/1000 person-years and patients with low CD4 counts at ART initiation were consistently at higher risk for a herpes zoster diagnosis than patients with CD4 counts ≥200 cells/mm\(^3\). Likewise, our finding that having had a prior herpes zoster episode was predictive of having another herpes zoster episode after ART initiation is in line with the results from other studies. While in our study herpes zoster was not shown to be associated with an increased risk of attrition, clinicians should closely monitor patients at high risk for herpes zoster in order to provide effective treatment as soon as possible and thereby reduce the risk of complications associated with a herpes zoster episode.

While a recent study showed that the herpes zoster vaccine, Zostavax, was safe in HIV-infected patients with CD4 counts ≥200 cells/mm\(^3\), the majority of patients in our cohort initiated ART with baseline CD4 counts below that level, and patients who went on to develop incident herpes zoster initiated ART at CD4 counts well below 100 cells/mm\(^3\) (median 77.5 cells/mm\(^3\)). Patients also developed herpes zoster quickly after ART initiation and most experienced herpes zoster within 12 months of the date of initiation. Therefore, if vaccination was possible in immunocompromised patients, it would be needed either at the
time of initiation or shortly after, before the immune system recovered and CD4 counts increased. Due to the need to vaccinate patients while still in an immunosuppressed state, further research is needed to determine if a vaccine could be safe and effective in immunocompromised patients such as these.

This study should be viewed in light of several limitations. First, as patients may present with herpes zoster at a hospital or their local primary care facility, we are likely underestimating the true amount of herpes zoster experienced by patients in this cohort. While this would affect our incidence rates, our estimate of hazard ratios should be unaffected because we believe we likely had near perfect specificity of diagnosis of herpes zoster (very few false-positives). Second, data on complications of herpes zoster were unavailable, resulting in us being unable to quantify the number of patients who experienced post-herpetic neuralgia and/or any other complications of herpes zoster. Third, the last linkage to the South African National Vital Registration System was done in September 2011 and deaths occurring after then may not have been captured in our records. Fourth, routine viral load testing at baseline is not done in this cohort and thus, whilst patients were generally at highest risk for a zoster diagnosis early after ART initiation, we were unable to determine whether these episodes were immune reconstitution inflammatory syndrome as we were unable to assess an improvement in viral load from baseline. Finally, data on patients who have yet to initiate ART are limited in this cohort, rendering us unable to compare zoster incidence based on ART exposure history.

Despite these limitations, our study also has many strengths. Data can be entered into the electronic database retrospectively so a patient can report an episode of herpes zoster to their clinician at Themba Lethu and have the condition recorded even if they were not diagnosed on site. Similarly, due to the retrospective nature of diagnoses in the database, we were able to control for the effect of prior herpes zoster episodes, even those that occurred before a patient initiated ART, on the incidence of herpes zoster after initiation.

In conclusion, Herpes zoster is a painful condition that can be quite debilitating. As HIV-infected patients have been found to be at the same risk of developing herpes zoster as uninfected elderly adults, further research is needed to determine the safety and efficacy of the herpes zoster vaccine in such patients in order to reduce the morbidity associated with herpes zoster after ART initiation.

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References

1. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007; 44:S1–26. [PubMed: 17143845]

2. Arvin AM. Varicella-zoster virus. Clin Microbiol Rev. 1996; 9:361–81. [PubMed: 8809466]

3. Buchbinder SP, Katz MH, Hessol NA, Liu JY, O’Malley PM, Underwood R, et al. Herpes zoster and human immunodeficiency virus infection. J Infect Dis. 1992; 166:1153–6. [PubMed: 1308664]

4. Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. J Acquir Immune Defic Syndr. 2005; 40:169–74. [PubMed: 16186734]

5. Engels EA, Rosenberg PS, Biggar RJ. Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984–1997. J Infect Dis. 1999; 180:1784–9. [PubMed: 10558932]

6. Glesby M, Moore R, Chaisson R. Clinical spectrum of herpes zoster in adults infected with human immunodeficiency virus. Clin Infect Dis. 1995; 21:370–5. [PubMed: 8562746]

7. Cohen JI, Brunell PA, Straus SE, Krause PR. Recent advances in varicella-zoster virus infection. Ann Intern Med. 1999; 130:922–32. [PubMed: 10375341]

8. Van Hoek A, Gay N, Melegaro A, Opstelten W, Edmunds W. Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. Vaccine. 2009; 27:1454–67. [PubMed: 19135492]

9. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology. 2013; 81:928–30. [PubMed: 23999562]

10. Pinchinat S, Cebrián-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis. 2013; 13:170. [PubMed: 23574765]

11. Jansen K, Haastert B, Michalik C, Guignard A, Esser S, Dupke S, et al. Incidence and risk factors of herpes zoster among HIV-positive patients in the German competence network for HIV/AIDS (KompNet): a cohort study analysis. BMC Infect Dis. 2013; 13:372. [PubMed: 23937603]

12. Blank LJ, Polydefkis MJ, Moore RD, Gebo KA. Herpes zoster among persons living with HIV in the current antiretroviral therapy era. J Acquir Immune Defic Syndr. 2012; 61:203–7. [PubMed: 22766968]

13. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med. 1995; 155:1605–9. [PubMed: 7618983]

14. National Department of Health. National antiretroviral treatment guidelines. South Africa: National Department of Health; 2004.

15. National Department of Health. The South African antiretroviral treatment guidelines. South Africa: National Department of Health; 2013.

16. Fox MP, Maskew M, MacPhail AP, Long L, Brennan AT, Westreich D, et al. Cohort profile: The Themba Lethu Clinical Cohort, Johannesburg, South Africa. Int J Epidemiol. 2013; 42:430–9. [PubMed: 22434860]

17. National Department of Health. Circular on new criteria for initiating adults on ART at CD4 count of 350 cells/μl and below. South Africa: National Department of Health; 2011.

18. National Department of Health. Clinical guidelines for the management of HIV and AIDS in adults and adolescents. South Africa: National Department of Health; 2010.

19. Fox MP, Brennan A, Maskew M, MacPhail P, Sanne I. Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa. Trop Med Int Health. 2010; 15:405–13. [PubMed: 20180931]

20. World Health Organization. Vitamin and Mineral Nutrition Information System. Geneva: WHO; 2011. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. WHO/NMH/NHD/MMN/11.1 available at: http://www.who.int/vmnis/indicators/haemoglobin.pdf

21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94:496–509.
22. Song JY, Cheong HJ, Kim WJ, Lee JS, Jung MH, Jung HW, et al. Herpes zoster among HIV-infected patients in the highly active antiretroviral therapy era: Korean HIV Cohort Study. J Acquir Immune Defic Syndr. 2010; 53:417–9. [PubMed: 20190589]

23. Glesby MJ, Hoover DR, Tan T, Shi Q, Gao W, French AL, et al. Herpes zoster in women with and at risk for HIV: data from the Women’s Interagency HIV Study. J Acquir Immune Defic Syndr. 2004; 37:1604–9. [PubMed: 15577417]

24. Gilden D. Efficacy of live zoster vaccine in preventing zoster and postherpetic neuralgia. J Intern Med. 2011; 269:496–506. [PubMed: 21294791]

25. Glesby M, Moore R, Chaisson R. Zidovudine Epidemiology Study Group. Herpes zoster in patients with advanced human immunodeficiency virus infection treated with zidovudine. J Infect Dis. 1993; 168:1264–8. [PubMed: 8228361]

26. Benson, C.; Hua, L.; Andersen, J.; Jiang, J.; Bozzolo, D.; Annunziato, P., et al. Zostavax is generally safe and immunogenic in HIV+ adults virologically suppressed on ART: results of a phase 2, randomized, double-blind, placebo-controlled trial. Oral abstract 96. Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections; Seattle, USA. 2012.

27. Rothman, KJ.; Greenland, S.; Lash, TL. Modern epidemiology. 3. Philadelphia, PA: Lippincott Williams and Wilkins; 2008. Bias analysis; p. 359
Figure 1.
Cumulative incidence curves for (a) herpes zoster within 12 months of treatment initiation and (b) herpes zoster ever after ART initiation by baseline CD4 count among HIV-infected patients in Johannesburg, South Africa.
Patient demographics and clinical characteristics at treatment initiation and treatment outcomes for patients initiating ART at the Themba Lethu Clinic in Johannesburg, South Africa

| Variable                              | Exposure       | Incident Herpes Zoster Recorded | No Incident Herpes Zoster Recorded |
|---------------------------------------|----------------|-------------------------------|-----------------------------------|
| Total N                               | 340 (100%)     | 14685 (100%)                  |                                   |
| Sex                                   | Male           | 120 (35.3%)                   | 5558 (37.9%)                      |
|                                       | Female         | 220 (64.7%)                   | 9127 (62.2%)                      |
| Age, years                            | Median (IQR) N | 36.3 (31.7–44.3) 340          | 36.7 (31.4–43.1) 14685           |
|                                       | <30            | 68 (20.0%)                    | 2788 (19.0%)                      |
|                                       | 30–34.9        | 79 (23.2%)                    | 3385 (23.1%)                      |
|                                       | 35–39.9        | 64 (18.8%)                    | 3220 (21.9%)                      |
|                                       | 40–44.9        | 54 (15.9%)                    | 2350 (16.0%)                      |
|                                       | ≥55            | 75 (22.1%)                    | 2942 (20.0%)                      |
| CD4 count, cells/mm³                  | Median (IQR) N | 77.5 (27–144) 330             | 99 (38–169) 14243                |
|                                       | Missing        | 10 (2.9%)                     | 442 (3.0%)                        |
|                                       | <50            | 128 (37.7%)                   | 4320 (29.4%)                      |
|                                       | 50–99          | 64 (18.8%)                    | 2844 (19.4%)                      |
|                                       | 100–199        | 108 (31.8%)                   | 5111 (34.8%)                      |
|                                       | ≥200           | 30 (8.8%)                     | 1968 (13.4%)                      |
| WHO Stage                             | I/II           | 197 (57.9%)                   | 8535 (58.1%)                      |
|                                       | III/IV         | 143 (42.1%)                   | 6150 (41.9%)                      |
| BMI                                   | Median (IQR) N | 21.5 (19.5–24.3) 314          | 21.5 (19.1–24.8) 13307           |
|                                       | Missing        | 27 (7.9%)                     | 1437 (9.8%)                       |
|                                       | <18.5          | 55 (16.2%)                    | 2590 (17.6%)                      |
|                                       | 18.5–24.9      | 193 (56.8%)                   | 7515 (51.2%)                      |
|                                       | 25–29.9        | 49 (14.4%)                    | 2171 (14.8%)                      |
|                                       | ≥30            | 16 (4.7%)                     | 972 (6.6%)                        |
| Hemoglobin, g/dL                      | Median (IQR) N | 11.1 (9.5–12.5) 321           | 10.9 (9.4–12.4) 13716            |
| Anemia                                | Missing        | 19 (5.6%)                     | 971 (6.6%)                        |
|                                       | No Anemia      | 83 (24.4%)                    | 3396 (23.1%)                      |
|                                       | Mild Anemia    | 81 (23.8%)                    | 3231 (22.0%)                      |
|                                       | Moderate Anemia| 132 (38.8%)                   | 5700 (38.8%)                      |
|                                       | Severe Anemia  | 25 (7.4%)                     | 1387 (9.5%)                       |
| Co-infected with tuberculosis         | Yes            | 44 (12.9%)                    | 2093 (14.2%)                      |
|                                       | No             | 296 (87.1%)                   | 12592 (85.8%)                     |
| Pregnant                              | Yes            | 3 (0.9%)                      | 147 (1.0%)                        |
|                                       | No             | 337 (99.1%)                   | 14538 (99.0%)                     |
| Prior episode of herpes zoster recorded| Yes            | 23 (6.8%)                     | 626 (4.3%)                        |
|                                       | No             | 317 (93.2%)                   | 14059 (95.7%)                     |
| Final treatment outcome               | Alive          | 181 (53.2%)                   | 7283 (49.6%)                      |
|                                       | Dead           | 34 (10.0%)                    | 1528 (10.4%)                      |
|                                       | Lost to follow-up| 56 (16.5%)         | 3155 (21.5%)                      |
| Variable          | Exposure       | Incident Herpes Zoster Recorded | No Incident Herpes Zoster Recorded |
|-------------------|----------------|-------------------------------|-----------------------------------|
|                   | Transferred out| 69 (20.3%)                    | 2720 (18.5%)                      |

BMI, body mass index; IQR, interquartile range; WHO, World Health Organization
### Table 2

Unadjusted and adjusted subhazard ratios for incident herpes zoster within one year and ever after ART initiation among HIV-infected patients at the Themba Lethu Clinic in Johannesburg, South Africa

| Characteristic | Herpes zoster within 1 year of ART initiation | Herpes zoster ever after ART initiation |
|---------------|-----------------------------------------------|----------------------------------------|
|               | Rate per 1000 person-years | Unadjusted sHR (95% CI) | Adjusted sHR (95% CI) | Rate per 1000 person-years | Unadjusted sHR (95% CI) | Adjusted sHR (95% CI) |
| **Sex**       |                                |                          |                          |                                |                          |                          |
| Male          |                                | 18.56 (18.05–19.08)     | 1.03 (0.79, 1.33)        | 0.95 (0.72, 1.24)             | 120/16610.1              | 7.22 (6.04, 8.64)        | 0.92 (0.73, 1.14)        | 0.90 (0.71, 1.12)        |
| Female        |                                | 17.76 (17.38–18.14)     | Reference                | Reference                     | 220/29547.6              | 7.45 (6.52, 8.90)        | Reference                | Reference                |
| **Age at initiation, years** |                                |                          |                          |                                |                          |                          |
| <30           |                                | 16.48 (12.18–22.30)     | Reference                | Reference                     | 68/690.2                 | 7.82 (6.17, 9.92)        | Reference                | Reference                |
| 30–34         |                                | 20.48 (16.03–26.16)     | 1.24 (0.85–1.85)         | 1.24 (0.84–1.85)             | 79/11302.4               | 6.99 (5.61–8.71)         | 0.93 (0.67–1.29)         | 0.94 (0.68–1.30)         |
| 35–39         |                                | 13.80 (10.16–18.75)     | 0.83 (0.54–1.28)         | 0.84 (0.54–1.30)             | 64/10335.2               | 6.19 (4.85–7.91)         | 0.80 (0.57–1.12)         | 0.81 (0.57–1.14)         |
| 40–44         |                                | 18.65 (13.68–25.42)     | 1.12 (0.73–1.73)         | 1.15 (0.74–1.79)             | 54/7214.3                | 7.49 (5.73–9.77)         | 0.93 (0.65–1.33)         | 0.96 (0.67–1.38)         |
| ≥55           |                                | 20.97 (16.14–27.24)     | 1.26 (0.84–1.88)         | 1.32 (0.88–1.99)             | 75/8615.6                | 8.71 (6.94–10.92)        | 1.04 (0.75–1.45)         | 1.09 (0.78–1.53)         |
| **Baseline CD4+ count-cells/mm³** |                                |                          |                          |                                |                          |                          |
| <50           | 23.62 (19.21–29.04)            | 2.01 (1.31–3.19)        | 2.02 (1.31–3.22)         | 128/13740.5                | 9.32 (7.83–11.08)        | 1.67 (1.18–2.41)         | 1.71 (1.21–2.47)         |
| 50–99         | 19.05 (14.44–25.14)            | 1.69 (1.05–2.77)        | 1.67 (1.04–2.74)         | 64/95572.8                 | 6.69 (5.23–8.54)         | 1.26 (0.85–1.89)         | 1.27 (0.86–1.89)         |
| 100–199       | 16.30 (13.06–20.35)            | 1.46 (0.95–2.34)        | 1.46 (0.94–2.33)         | 108/16398.9                | 6.59 (5.45–7.95)         | 1.21 (0.85–1.75)         | 1.20 (0.84–1.74)         |
| ≥200          | 10.31 (6.58–16.16)             | Reference                | Reference                | 30/5313.0                  | 5.65 (3.95–8.08)         | Reference                | Reference                |
| **WHO Stage** |                                |                          |                          |                                |                          |                          |
| I/II          | 17.81 (15.11–21.00)            | 1.00 (0.78–1.30)        | --                       | 197/27168.4                | 7.25 (6.31–8.34)         | 0.99 (0.80–1.23)         | --                       |
| III/IV        | 18.40 (15.14–22.36)            | Reference                | --                       | 143/18989.3                | 7.53 (6.39–8.87)         | Reference                | --                       |
| **BMI-kg/m²** |                                |                          |                          |                                |                          |                          |
| <18.5         | 18.63 (13.73–25.21)            | 0.93 (0.66–1.30)        | 0.87 (0.61–1.21)         | 55/7499.8                  | 7.33 (5.63–9.55)         | 0.88 (0.65–1.17)         | --                       |
| 18.5–24.9     | 19.82 (16.79–23.41)            | Reference                | Reference                | 193/24676.4                | 7.82 (6.79–9.01)         | Reference                | --                       |
| 25–29.9       | 16.57 (11.84–23.19)            | 0.88 (0.60–1.26)        | 0.89 (0.60–1.28)         | 49/7178.1                  | 6.83 (5.16–9.03)         | 0.91 (0.66–1.22)         | --                       |
| ≥30           | 9.77 (5.08–18.77)              | 0.52 (0.25–0.96)        | 0.53 (0.25–0.99)         | 16/3170.4                  | 5.05 (3.09–8.24)         | 0.66 (0.38–1.06)         | --                       |
| **Anemia**    |                                |                          |                          |                                |                          |                          |
| None          | 16.41 (12.54–21.48)            | Reference                | --                       | 83/11240.5                 | 7.38 (5.95–9.16)         | Reference                | --                       |
| Mild          | 18.77 (14.48–24.33)            | 1.18 (0.83–1.69)        | --                       | 81/10534.1                 | 7.69 (6.18–9.56)         | 1.06 (0.79–1.42)         | --                       |
| Characteristic                     | Herpes zoster within 1 year of ART initiation | Herpes zoster ever after ART initiation |
|-----------------------------------|-----------------------------------------------|-----------------------------------------|
|                                   | Herpes zoster/person-years                    | Rate per 1000 person-years | Unadjusted sHR (95% CI) | Adjusted sHR (95% CI) | Herpes zoster/person-years | Rate per 1000 person-years | Unadjusted sHR (95% CI) | Adjusted sHR (95% CI) |
| Moderate                          | 102/5144.2                                    | 19.83 (16.33–24.08)          | 1.22 (0.90–1.67)        | --                     | 132/17565.1                | 7.51 (6.34–8.91)              | 1.00 (0.77–1.29)        | --                     |
| Severe                            | 19/1155.5                                     | 16.44 (10.49–25.78)         | 0.95 (0.56–1.56)        | --                     | 25/3813.0                  | 6.56 (4.43–9.70)              | 0.80 (0.51–1.22)        | --                     |
| Tuberculosis                      |                                               |                             |                         |                         |                          |                          |                           |                         |
| Yes                               | 35/1895.0                                     | 18.47 (13.26–25.72)         | 1.01 (0.70–1.43)        | --                     | 44/7180.8                  | 6.13 (4.56–8.23)              | 0.86 (0.62–1.17)        | --                     |
| No                                | 208/11564.9                                   | 17.99 (15.70–20.60)         | Reference               | --                     | 296/3976.8                 | 7.59 (6.78–8.51)              | Reference               | --                     |
| Prior episode of zoster           |                                               |                             |                         |                         |                          |                          |                           |                         |
| Yes                               | 12/590.2                                      | 20.33 (11.55–35.80)         | 1.15 (0.61–1.96)        | --                     | 23/2492.6                  | 9.23 (6.13–13.89)             | 1.51 (0.96–2.25)        | 1.53 (0.97–2.28)       |
| No                                | 231/12869.8                                   | 17.95 (15.78–20.42)         | Reference               | --                     | 317/43665.1                | 7.26 (6.50–8.10)              | Reference               | Reference              |

BMI-body mass index; CI-confidence interval; sHR-subdistribution hazard ratio; WHO-world health organization
Table 3
Unadjusted and adjusted risk ratios for attrition among HIV-infected patients at the Themba Lethu Clinic in Johannesburg, South Africa

| Characteristic                        | Attrition/N (%) | Unadjusted RR (95% CI) | Adjusted RR (95% CI) |
|---------------------------------------|-----------------|------------------------|----------------------|
| Herpes zoster within 1 year of ART initiation |                 |                        |                      |
| Yes                                   | 23/237 (9.7%)   | 0.68 (0.45–1.01)       | 0.64 (0.42–0.99)     |
| No                                    | 272/1896 (14.4%)| Reference              | Reference            |
| Sex                                   |                 |                        |                      |
| Male                                  | 136/819 (16.6%) | 1.37 (1.11–1.70)       | 1.35 (1.05–1.73)     |
| Female                                | 159/1314 (12.1%)| Reference              | Reference            |
| Age at Initiation, years              |                 |                        |                      |
| <30                                   | 48/374 (12.8%)  | Reference              | Reference            |
| 30–34                                 | 90/579 (15.5%)  | 1.21 (0.87–1.68)       | 1.04 (0.74–1.47)     |
| 35–39                                 | 38/353 (10.8%)  | 0.84 (0.56–1.25)       | 0.75 (0.49–1.14)     |
| 40–44                                 | 57/349 (16.3%)  | 1.27 (0.89–1.82)       | 1.02 (0.69–1.50)     |
| ≥55                                   | 62/478 (13.0%)  | 1.01 (0.71–1.44)       | 0.90 (0.62–1.30)     |
| Baseline CD4 count, cells/mm³         |                 |                        |                      |
| <50                                   | 143/810 (17.7%) | 1.26 (0.84–1.88)       | 0.94 (0.61–1.45)     |
| 50–99                                 | 54/450 (12.0%)  | 0.86 (0.55–1.34)       | 0.76 (0.47–1.22)     |
| 100–199                               | 74/702 (10.5%)  | 0.75 (0.49–1.15)       | 0.70 (0.44–1.10)     |
| ≥200                                  | 24/171 (14.0%)  | Reference              | Reference            |
| Baseline WHO Stage                    |                 |                        |                      |
| I/II                                  | 141/1218 (11.6%)| Reference              | Reference            |
| III/IV                                | 154/915 (16.8%) | 1.45 (1.18–1.80)       | 1.21 (0.96–1.53)     |
| Baseline BMI, kg/m²                   |                 |                        |                      |
| <18.5                                 | 80/405 (19.8%)  | 1.51 (1.18–1.94)       | 1.19 (0.92–1.54)     |
| 18.5–24.9                             | 150/1150 (13.0%)| Reference              | Reference            |
| 25–29.9                               | 26/296 (8.8%)   | 0.67 (0.45–1.00)       | 0.80 (0.53–1.19)     |
| ≥30                                   | 13/121 (10.7%)  | 0.82 (0.48–1.41)       | 1.00 (0.58–1.73)     |
| Anemia at ART Initiation              |                 |                        |                      |
| None                                  | 54/515 (10.5%)  | Reference              | Reference            |
| Mild                                  | 59/484 (12.2%)  | 1.16 (0.82–1.65)       | 1.08 (0.75–1.55)     |
| Moderate                              | 126/824 (15.3%) | 1.46 (1.08–1.97)       | 1.35 (0.97–1.89)     |
| Severe                                | 45/209 (21.5%)  | 2.05 (1.43–2.95)       | 1.85 (1.24–2.77)     |
| Tuberculosis co-infection             |                 |                        |                      |
| Yes                                   | 49/330 (14.9%)  | 1.09 (0.82–1.45)       | --                   |
| No                                    | 246/1803 (13.6%)| Reference              | --                   |

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; RR, risk ratio; WHO, world health organization