Timely HIV Diagnosis and HIV/TB Comanagement Among California Patients in 2008

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ABSTRACT

Objective. National guidelines highlight the roles of early HIV diagnosis and effective comanagement for HIV and tuberculosis (TB) to prevent mortality and morbidity from HIV-related TB. We assessed HIV diagnosis timing and HIV/TB comanagement for California HIV/TB patients.

Methods. We reviewed and analyzed public health charts for California HIV/TB patients reported during 2008. HIV diagnoses fewer than three months before TB diagnosis were considered new HIV diagnoses. We determined the proportion of patients with new HIV diagnoses, risk factors for new HIV diagnoses, and proportion of patients receiving recommended CD4 cell count measurements, supervised TB therapy, and antiretroviral therapy (ART).

Results. Of 130 HIV/TB patients, 51% had new HIV diagnoses. Foreign-born patients were more likely than U.S.-born patients to have new HIV diagnoses. Supervised TB therapy and CD4 cell count measurements followed national recommendations for 91% and 74% of patients, respectively. At least 73% of patients started ART before completing TB therapy. Compared with patients who had previous HIV diagnoses, patients with new HIV diagnoses started ART later and had lower CD4 cell counts and higher viral loads at TB diagnosis.

Conclusions. Although most HIV/TB patients received the recommended treatment, half had new HIV diagnoses. Compared with patients who had previous HIV diagnoses, patients with new HIV diagnoses had greater immunosuppression at TB diagnosis. A new diagnosis indicates that HIV could have been diagnosed earlier and ART or treatment for latent TB infection could have been initiated to prevent TB development.

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Human immunodeficiency virus (HIV) infection is a potent risk factor for death among tuberculosis (TB) patients.¹⁻⁵ In the United States during 2006, HIV-infected patients comprised 12% of TB patients with known HIV status but 30% of patients who died during TB therapy.¹ Among all states, California reported the largest number of TB patients and the second-largest number of patients diagnosed with HIV infection in 2009.^{6,7} A field assessment in California found that 132 TB patients had HIV in 2008,⁸ accounting for 14% of all TB patients with HIV in the U.S.⁹

Timely HIV diagnosis is an important step in preventing TB disease and HIV/TB mortality. Early HIV diagnosis informs patients of their risk for developing TB disease and triggers opportunities to prevent TB through isoniazid prophylaxis and antiretroviral therapy (ART).¹⁰ Isoniazid prophylaxis effectively reduces the risk of progression to TB disease among HIV-infected patients with latent TB infection (LTBI).¹¹ ART restores immune function and is estimated to reduce the risk of TB in HIV-infected patients by 65%.¹² ART even reduces the TB risk in people without a positive tuberculin skin test, suggesting a possible protective effect against establishment of infection by *Mycobacterium tuberculosis*.^{13,14}

Even when LTBI progresses to TB disease in patients unaware of their HIV infection, HIV diagnosis is still critical because providers are alerted to patients' need for ART, which can reduce the risk of death.⁴ Providers can also make referrals to HIV services and coordinate HIV/TB comanagement. Therefore, HIV status determination is recommended for all TB patients.²

Once TB patients with HIV infection are identified, effective HIV/TB comanagement is needed to optimize patient outcomes. Recommendations from the Office of AIDS Research Advisory Council (OARAC) help TB clinicians ensure effective comanagement.¹⁵ TB clinicians should obtain cluster of differentiation 4 (CD4) cell counts to monitor HIV progression and determine the timing of ART. Clinicians should also ensure supervision of TB therapy to enhance adherence and prevent acquired TB drug resistance. At the time of the 2008 OARAC recommendations, there was insufficient evidence to determine the optimal timing of ART initiation during TB therapy. Although the 2008 guidelines did not make formal recommendations, they suggested that ART be started two weeks after TB treatment initiation for patients with <100 CD4 cells/millimeter cubed (mm³), eight weeks after TB treatment initiation for patients with 100–200 CD4 cells/mm³, and based on clinical judgment for patients with >200 CD4 cells/mm³.

U.S. guidelines highlight the need for early HIV

identification and effective HIV/TB comanagement, but little is known about the actual timing of HIV identification or strength of elements of HIV/TB comanagement practices for patients in California. Therefore, we conducted a review of TB patients with HIV (henceforth referred to as HIV/TB patients) reported in California during 2008 to assess the timing of HIV diagnosis and adherence to the 2008 OARAC HIV/TB comanagement recommendations.

METHODS

Study population

We conducted a retrospective review of public health records for all TB patients reported in 2008 from California to identify HIV/TB patients. Public health records included patient charts and databases maintained by local TB programs to monitor and manage TB cases. HIV/TB patients had any of the following before TB therapy completion: (1) positive HIV test results, (2) self-report of positive HIV status, (3) provider report of a positive HIV status, or (4) report of patient receiving ART medication. Public health records of HIV/TB patients underwent a second review to assess the timing of HIV testing and HIV/TB comanagement parameters. We collected information on HIV diagnosis timing, supervision of TB therapy, ART initiation, CD4 cell counts, viral loads, and mortality. These data were then merged with individual demographic and clinical data from the state TB registry.

Definitions

Patients were classified according to the relative timing of their HIV and TB diagnoses. The TB diagnosis date was defined as the earliest of the TB case report date, collection date of the first positive sputum culture, or TB therapy start date. Patients with an HIV diagnosis more than three months before TB diagnosis were classified as having a previous HIV diagnosis; all others were classified as having a new HIV diagnosis. This classification scheme allowed us to identify patients diagnosed with HIV infection during TB diagnosis, assuming the TB diagnostic period could take up to three months.

We also classified patient providers according to their association with local health department TB programs. TB provider type was associated with TB programs if patient care was delivered by local health department TB programs or by clinics associated with local TB programs. All other providers, including some county hospital clinicians not related to local TB programs, were unassociated with TB programs. Overall TB management was dichotomized as either

associated with TB programs (having any management by providers associated with TB programs) or completely unassociated with TB programs. Calendar weeks when patients were hospitalized for at least one day were considered hospitalization weeks. If the first and second calendar weeks of TB therapy were hospitalization weeks, the patient was considered hospitalized during TB diagnosis.

We also examined CD4 cell count and viral load measurements at TB diagnosis. The measurement at TB diagnosis was defined as the test result closest to the TB diagnosis date and within 90 days of it. When measurements were before and after TB diagnosis and were also an equal amount of time from the TB diagnosis date, the earliest test result was used as the measurement at TB diagnosis. Measurements within 90 days of TB diagnosis but on an unknown day of the month were considered to have occurred on the 15th day of the specified month.

We assessed initial supervision of TB therapy and ART initiation during TB therapy. Patients who initiated directly observed therapy (DOT) within the first 56 days of TB therapy and patients who were hospitalized, jailed, or in rehabilitation facilities for the first 56 days of TB therapy were considered to have initially supervised TB therapy. Patients who received at least one antiretroviral dose during TB therapy were considered to have received ART during TB therapy.

When analyzing patient characteristics associated with a new HIV diagnosis, we identified patients with a previous TB episode. Patients with another TB diagnosis more than 12 months before their current one were considered to have a previous TB episode.

Statistical analysis

We calculated the proportion of HIV/TB patients with a new HIV diagnosis and examined specific demographic and clinical characteristics of this group, including age; sex; race/ethnicity; foreign birth; site of TB disease; previous TB episode; history of incarceration, homelessness, excess alcohol use, or illicit drug use; and provider of TB management. We used bivariate logistic regression to identify factors associated with a new HIV diagnosis and to calculate odds ratios (ORs) and 95% confidence intervals (CIs). We used Fisher's exact test to calculate *p*-values when sample sizes were small. Factors with *p* < 0.20 were included in a multivariate model. We then used backwards-stepwise hierarchical selection to identify independently significant factors using multivariate logistic regression and calculate adjusted ORs (AORs).

To measure adherence to the 2008 OARAC guidelines, we determined the proportion of patients with

initially supervised TB therapy and CD4 cell counts at TB diagnosis. We also determined the proportion of patients who started ART before TB therapy completion and when ART was started.

We compared differences in hospitalization, death, and CD4 cell counts and viral loads at TB diagnosis between patients with a new HIV diagnosis and patients with a previous HIV diagnosis using a Chi-square test. All analyses were conducted using SAS® version 9.2.¹⁶

RESULTS

Timing of HIV status

Of 2,667 TB patients reported in California in 2008, 1,752 (65.7%) had a known HIV status, including 132 (5%) with HIV/TB. We were able to review public health records and assess HIV diagnosis timing for 130 (99%) of the 132 HIV/TB patients. Of these patients, 64 (49%) had a previous HIV diagnosis and 66 (51%) had a new HIV diagnosis (Table 1). Among the 64 patients with a previous HIV diagnosis, 51 (80%) were diagnosed with HIV more than 12 months before TB diagnosis, nine (14%) were diagnosed with HIV 3–12 months before TB diagnosis, and four (6%) had a previous HIV diagnosis, but the exact timing of HIV diagnosis was unclear. Among the 66 patients with a new HIV diagnosis, 12 (18%) were diagnosed with HIV 0.5–3 months before TB diagnosis, 45 (68%) were diagnosed with HIV within 0.5 months of TB diagnosis, two (3%) were diagnosed with HIV 0.5–1 month after TB diagnosis, and seven (11%) had a new HIV diagnosis, but the exact timing of HIV diagnosis was unclear (data not shown).

Risk factors for having a new HIV diagnosis

Race/ethnicity, foreign birth, and previous TB episode were associated with a new HIV diagnosis. Compared with white people, Hispanic and Asian people were more likely to have a new HIV diagnosis. Foreign-born patients were also more likely to have a new HIV diagnosis compared with U.S.-born patients (62% vs. 33%). Race and foreign birth were collinear. All 10 Asian patients and 65 (85%) of 77 Hispanic patients in our evaluation were foreign-born. No patient with a previous TB episode had a new HIV diagnosis (Table 1).

Sex, previous TB episode, age, and foreign birth were included in the initial multivariate model for new HIV diagnosis. Because race and foreign birth were collinear, only foreign birth was included in multivariate analyses. Through backwards-stepwise hierarchical selection, we identified foreign birth as the only significant independent risk factor for having a new HIV diagnosis (Table 1).

Table 1. Characteristics of all HIV/TB patients in California, 2008 (n=130)

Characteristic	Previous HIV diagnosis (n=64)	New HIV diagnosis (n=66)	Bivariate results	
	N (percent)	N (percent)	OR (95% CI)	P-value
Overall TB management				
Completely unassociated with TB programs	17 (26.6)	23 (34.9)	Ref.	0.279
Associated with TB programs	46 (71.9)	41 (62.1)	0.66 (0.31, 1.40) ^a	
Unknown	1 (1.6)	2 (3.0)	NA	
Age (in years)				
15–29	7 (10.9)	13 (19.7)	Ref.	0.289
30–44	33 (51.6)	35 (53.0)	0.57 (0.20, 1.61)	
45–59	20 (31.3)	16 (24.2)	0.43 (0.14, 1.33)	
≥60	4 (6.3)	2 (3.0)	0.27 (0.04, 1.86)	0.151 ^b
Sex				
Male	49 (76.6)	59 (89.4)	Ref.	0.057
Female	15 (23.4)	7 (10.6)	0.39 (0.15, 1.03)	
Previous TB episode				
No	57 (89.1)	66 (100.0)	Ref.	0.006 ^b
Yes	7 (10.9)	0 (0.0)	NA ^c	
History of homelessness, incarceration, drug abuse, or alcohol abuse				
No	38 (59.4)	41 (62.1)	Ref.	0.749
Yes	26 (40.6)	25 (37.9)	0.89 (0.44, 1.80)	
Site of disease				
Pulmonary only	32 (50.0)	39 (59.1)	Ref.	0.299
Extrapulmonary	32 (50.0)	27 (40.9)	0.69 (0.35, 1.39)	
Race/ethnicity				
White	13 (20.3)	4 (6.1)	Ref.	0.441
Black	17 (26.6)	9 (13.6)	1.72 (0.43, 6.85)	
Hispanic	31 (48.4)	46 (69.7)	4.82 (1.44, 16.17)	0.011
Asian	3 (4.7)	7 (10.6)	7.58 (1.31, 43.92)	0.022 ^b
Nativity				
U.S.-born	33 (51.6)	16 (24.2)	Ref.	0.002
Foreign-born	31 (48.4)	50 (75.8)	3.33 (1.58, 7.02)	
Nativity and race/ethnicity				
U.S.-born				
White	13 (39.4)	4 (25.0)		
Black	14 (42.4)	6 (37.5)		
Hispanic	6 (18.2)	6 (37.5)		
Asian	0 (0.0)	0 (0.0)		
Foreign-born				
White	0 (0.0)	0 (0.0)		
Black	3 (9.7)	3 (6.0)		
Hispanic	25 (80.7)	40 (80.0)		
Asian	3 (9.7)	7 (14.0)		

^aExcluding patients without a known provider^bDetermined using Fisher's exact test^cAll people in stratum have a previously known HIV status.

HIV = human immunodeficiency virus

TB = tuberculosis

OR = odds ratio

CI = confidence interval

Ref. = reference group

NA = not applicable

HIV/TB comanagement

Of 127 patients who started TB therapy, 94 (74%) had CD4 cell counts and 65 (51%) had viral load measurements at TB diagnosis, 115 (91%) had initially supervised TB therapy, and at least 93 (73%) started ART before TB therapy completion (Table 2). There were no significant differences in these practices between patients with a new HIV diagnosis and patients with a previous HIV diagnosis.

Of 63 patients who had a previous HIV diagnosis, 38 (60%) started ART before TB therapy initiation. Of the 64 patients who had a new HIV diagnosis, only seven (11%) started ART before TB therapy initiation ($p<0.001$) (Table 2). Of the 23 patients who did not receive ART during TB therapy, 15 had at least one documented reason why it was not given. Reasons for not receiving ART included death ($n=4$), loss to follow-up ($n=4$), nonadherence to TB therapy ($n=3$), homelessness ($n=2$), substance abuse ($n=2$), and concerns about immune reconstitution inflammatory syndrome ($n=2$) (data not shown).

Providers unassociated with TB programs played a major role in initial TB care for HIV/TB patients. Among the 127 patients starting TB treatment, providers unassociated with TB programs diagnosed TB in

121 (95%) patients and initiated TB treatment in 101 (80%) patients. However, there was no difference in initiating ART between providers associated with TB programs and providers unassociated with TB programs (data not shown).

Immune function, hospitalization, and death

Among patients who started TB therapy, those with a previous HIV diagnosis had less advanced immunosuppression at TB diagnosis than those who had a new HIV diagnosis, as measured by CD4 cell count and viral load (Table 3). Hospitalization at TB diagnosis was more likely among patients with a new HIV diagnosis than among patients with a previous HIV diagnosis, but this difference was not statistically significant.

There was no difference between patients with a new HIV diagnosis and patients with a previous HIV diagnosis in the proportion of patients dying before TB treatment completion. We also examined deaths by CD4 cell count. Death occurred for seven (16%) of 44 patients with <100 CD4 cells/mm³ and for three (5%) of 59 patients with ≥ 100 CD4 cells/mm³ ($p=0.073$). Five additional patients died, but they did not have CD4 cell count information (data not shown).

Table 2. Documentation of HIV/TB comanagement among patients (n=127) starting TB treatment in California, 2008

Characteristic	Previous HIV diagnosis (n=63) N (percent)	New HIV diagnosis (n=64) N (percent)	P-value
CD4 cell count documented within 90 days of TB diagnosis			0.579
No	15 (23.8)	18 (28.1)	
Yes	48 (76.2)	46 (71.9)	
Viral load documented within 90 days of TB diagnosis			0.788
No	30 (47.6)	32 (50.0)	
Yes	33 (52.3)	32 (50.0)	
Initially supervised TB therapy			0.563
No	5 (7.9)	7 (10.9)	
Yes	58 (92.1)	57 (89.1)	
Timing of ART start			<0.001 ^a
Did not start ART	8 (12.7)	15 (23.4)	
Before TB treatment	38 (60.0)	7 (10.9)	
During TB treatment weeks 1–2	0 (0.0)	7 (10.9)	
During TB treatment weeks 3–8 ^b	5 (7.9)	10 (15.6)	
During TB treatment week 9 to end of TB treatment ^c	6 (9.5)	20 (31.3)	
Timing cannot be determined	6 (9.5)	5 (7.8)	

^aCompares the proportion of patients starting ART before TB treatment initiation among those who started ART

^bIncludes patients whose ART start was inexact but before TB treatment week 9

^cIncludes patients whose ART start was inexact but during TB treatment

HIV = human immunodeficiency virus

TB = tuberculosis

CD4 = cluster of differentiation 4

ART = antiretroviral therapy

Table 3. Immune function and outcomes during TB treatment for HIV/TB patients in California, 2008

Characteristic	Previous HIV diagnosis N (percent)	New HIV diagnosis N (percent)	P-value
CD4 cell count at TB diagnosis for those starting TB treatment (in cells/mm ³) (n=94)			0.008 ^b
<100	14 (29.2)	25 (54.4)	
100–200	9 (18.8)	12 (26.1)	
201–350	8 (16.7)	6 (13.0)	
351–500	9 (18.8)	3 (6.5)	
>500	7 (14.6)	0 (0.0)	
Unable to categorize	1 (2.1) ^a	0 (0.0)	
Viral load at TB diagnosis for those starting TB treatment (copies/mL) (n=65)			0.007
≤1,000	14 (42.4)	2 (6.3)	
1,001–10,000	2 (6.1)	2 (6.3)	
10,001–100,000	10 (30.3)	10 (31.3)	
100,001–500,000	5 (15.2)	10 (31.3)	
>500,000	2 (6.1)	8 (25.0)	
Deaths (n=130)	8 (12.5)	7 (10.6)	0.83
Hospitalization for first 2 weeks of TB treatment (n=127)			0.092
Yes	28 (44.4)	38 (59.4)	
No	35 (55.6)	26 (40.1)	

^aCD4 count listed as <200 cells/mm³

^bExcludes patient whose CD4 cell count could not be categorized

TB = tuberculosis

HIV = human immunodeficiency virus

CD4 = cluster of differentiation 4

mm³ = millimeter cubed

mL = milliliter

DISCUSSION

Our findings suggest a need for earlier HIV diagnosis and treatment initiation to prevent TB. It is concerning that nearly half of California HIV/TB patients in 2008 had new HIV diagnoses. Such patients were unaware of their HIV infection and, thus, might have missed opportunities to prevent TB through ART and isoniazid prophylaxis. Delayed HIV diagnosis has been recognized as a major problem in the U.S. An estimated 20% of HIV-infected people were undiagnosed in 2008,¹⁷ and 33% of people diagnosed with HIV in 2008 developed acquired immunodeficiency syndrome (AIDS) within a year.⁶ In California, 61% of AIDS patients diagnosed from 2000 to 2006 had their first HIV diagnosis within a year of AIDS diagnosis.¹⁸ In California, like the rest of the country, there is a need to address this gap by improving HIV testing outreach and education efforts in addition to HIV prevention activities.

Because foreign-born people are at increased risk for TB in the U.S.,¹⁹ it is especially important to target HIV testing efforts toward this population. Although the U.S. Centers for Disease Control and Prevention recommended testing all people aged 13–64 years in health-care settings for HIV in 2006,²⁰ this population is

still unreached. In our evaluation of HIV/TB patients, foreign-born people (100% of Asian and 85% of Hispanic people) were more likely to have a new HIV diagnosis. This finding is consistent with national findings that foreign birth is a strong predictor of late HIV testing in the U.S.^{21–24} Research has shown that undocumented status, lack of health insurance, perceived lack of risk, and stigma contribute to delayed HIV testing among foreign-born people.^{22,25,26} Foreign-born people often have limited access to care.²⁷ Low-cost HIV testing outside of traditional health-care settings, education on HIV risks, and promotion of early testing and care may increase early HIV diagnosis among foreign-born patients. Because previous research on HIV testing among foreign-born patients has focused largely on Hispanic populations, additional studies are needed to identify barriers and potential interventions for foreign-born Asian people.

Early HIV diagnosis and care in patients at risk for TB present opportunities to prevent TB. ART, LTBI testing, and isoniazid prophylaxis are highly effective TB prevention measures and are key strategies to mitigate epidemics of HIV-associated TB.^{28,29} ART soon after HIV infection is essential because the risk of TB decreases as

CD4 cell counts increase.³⁰ Effective strategies exist to prevent HIV-associated TB, but gaps in HIV detection may hinder their effective implementation.

Although early HIV diagnosis was associated with improved immune function at TB diagnosis, our evaluation may have been underpowered to identify an association with improved outcomes. Patients with previous HIV diagnoses had higher CD4 cell counts at TB diagnosis than patients who had new HIV diagnoses. Other studies have shown that higher CD4 cell counts have been associated with improved TB survival,^{31–33} but we did not observe improved survival among patients with previous HIV diagnoses. However, our evaluation included only 15 deaths. We also found that patients with previous HIV diagnoses were less likely to be hospitalized at TB diagnosis, but this difference was not statistically significant.

Once HIV infection was identified, most TB patients received recommended HIV/TB comanagement based on measures we examined. Of the patients starting TB therapy, 74% had CD4 cell count measurements and 91% had initially supervised TB therapy. However, there is room for improvement, as only 73% of HIV/TB patients initiated ART before TB therapy completion. Some patients did not receive ART due to substance abuse, homelessness, and nonadherence to treatment. Yet, social support can address ART adherence concerns in drug-abusing and homeless populations.^{34,35} And although the 2008 OARAC guidelines noted insufficient evidence regarding the timing of ART during TB treatment, recent studies demonstrate that ART during TB therapy reduces TB mortality among the most immunocompromised individuals in developing country settings.^{36–39} As a result, OARAC released updated guidelines in 2012 formally recommending ART initiation within two weeks of TB treatment initiation for patients with <50 CD4 cells/mm³, 2–4 weeks after TB treatment initiation for those with severe clinical disease, and 8–12 weeks after TB treatment initiation for those without severe clinical disease.⁴⁰ These new guidelines should prompt providers to attempt the provision of lifesaving ART treatment for all HIV/TB patients.

Public health TB programs can initiate and direct improvements in HIV/TB comanagement among providers outside of TB programs, who play a major role in TB diagnosis and initial TB care. TB programs are responsible for linking HIV/TB patients to HIV care and coordinating TB therapy accordingly. To facilitate optimal care, TB programs should (1) ensure measurement and documentation of CD4 cell counts for all HIV/TB patients and (2) ensure administration and documentation of DOT and ART. Gaps in monitoring

CD4 cell counts, supervising TB therapy, or initiating ART should stimulate interventions such as provider education.

Limitations

This study was subject to several limitations. First, if patients lacked documentation of recommended care, we could not distinguish whether it was because care was truly inadequate or because receipt of adequate care was incompletely documented. Incomplete documentation in the public health record would have caused misclassification, especially among patients managed outside of TB programs. Secondly, the small sample size limited our multivariate and outcome analysis. Lastly, our evaluation included patients from 2008 only. Therefore, estimates may not reflect the most recent practices. However, they were the most recent data available at the time of study initiation, and these data provide an important baseline for practices among HIV/TB cases in California.

CONCLUSIONS

Based on our evaluation, there is likely a need for earlier HIV diagnosis and care, particularly among foreign-born people at risk for TB in California. Almost half of California's HIV/TB patients had new HIV diagnoses and missed opportunities for TB prevention. These patients started ART later and had more advanced immunosuppression than patients who had previous HIV diagnoses. Outreach and education should target foreign-born people at risk for TB to identify HIV infection earlier and link them to HIV care and TB preventative care. Public health TB programs should continue to monitor HIV/TB comanagement data to ensure adherence to guidelines.

This evaluation was reviewed and approved by the California Health and Human Services Agency Institutional Review Board and all relevant local review boards. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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